As to the first question, the crucial element of patentability for most biological inventions in the United States, as shown in the *Chakrabarty* case, will be the fact that the substance was in some way changed from the naturally occurring substance by human intervention. For example, although genes and regulatory sequences may be obtained from natural sources, it is the removal of the DNA sequences from their natural habitat and their joining to other DNA sequences that provides the human-made requirement of the *Chakrabarty* case. Thus, it is not the sequence that is new, but the environment, such as the host or flanking DNA regions (44).*

As to the second question, it should be noted that U.S. law, in contrast to the laws of most foreign countries, provides a 1-year grace period between the date of any publication by the inventor relating to the invention and the filing of a patent application. This grace period in the United States is generally viewed as favorable to the rapid dissemination of new scientific knowledge, because knowledge pertaining to an invention can be published without the inventor's foregoing the opportunity to file for a patent. Most countries other than the United States require the patent application to have been filed before the invention is disclosed, for example, in a scientific paper. This requirement is known as "absolute novelty" and will be discussed in greater detail in the section comparing and contrasting U.S. and foreign law.**

UTILITY

The utility standard in the United States is generally not a difficult standard for an invention to meet to qualify for a U.S. patent. There is one potential problem, however, with regard to biological inventions. Since the courts have held that an invention must show some practical or commercial utility (12,32,33), certain results of research that may be very important for research purposes (e.g., a new DNA probe or even certain organisms) may not meet the utility standard. This problem can generally be avoided by describing some practical use of the invention in the patent application, even if that use will not be the one that is of ultimate commercial value to the company.

NONOBVIOUSNESS

The nonobviousness standard that inventions must meet to qualify for a U.S. patent pertains to the degree of difference between the invention and the "prior art." An invention that would have been obvious at the time it was made to a person with ordinary skill in the relevant field of technology is not patentable (35 U.S.C. §103). The U.S. patent law requirements for nonobviousness and novelty together represent a policy that a patent should not take from the public something that it already enjoys or potentially enjoys as an obvious extension of current knowledge.

Given the fact that many of the basic techniques in biotechnology are well known and straightforward to competent scientists, how can the various inventions meet the nonobviousness standard? The answer is that biotechnology is still in many respects a very inexact science. Many of the various manipulations of genetic material, for example, will give unexpected results. Difficulty in the isolation or preparation of materials and the unexpected or superior nature of results are some of the criteria that would be used to show nonobviousness.

It is interesting to note that some scientists view hybridoma technology as more straightforward than rDNA technology. If this is true, patents may be more difficult to obtain for hybridoma technology than for rDNA inventions, necessitating a greater reliance on trade secrets. However, there are still many problems associated with human-human hybridomas, so broad patents may be able to be secured for inventions in that area. (See *Box D.—Patents on Hybridoma Inventions* for further information on patenting hybridoma technology.)

The nonobviousness requirement may present another problem for biotechnology. The rapid

*In a companion case to *Chakrabarty*, a lower court, the Court of Customs and Patent Appeals (now the Court of Appeals for the Federal Circuit), held that a purified culture of naturally occurring bacteria was patentable subject matter (3). For procedural reasons, the Supreme Court did not rule on this issue.

**Japan provides for a limited 6-month grace period for: 1) experimentation, publication, and papers presented before scientific organizations by the applicant; 2) unauthorized disclosure by third parties; and 3) displays at authorized exhibits. Otherwise, it is considered an absolute novelty country.

Box D.—Patents on Hybridoma Inventions*

Many scientists and others unfamiliar with the patent law have questioned how a technology invented by Kohler and Milstein in the mid-1970's and well known to practitioners in the field could give rise to patentable inventions. It is important to remember, however, that hybridoma technology has many technical problems associated with it—anyone who solves any one or more of those problems will likely be able to obtain a patent on that improvement in the state of the art. The following improvements, for example, would be potentially patentable (17):

- new myeloma cell lines that offer improvements over existing myeloma cell lines,
- new culture media that offer improved growth,
- new methods of fusion that offer significant improvement over those currently employed,
- new and improved selection procedures,
- new hybridomas that are more stable and consistent in the production of MAbs,
- new MAbs that react to antigens different from those that prior patented MAbs react to, or
- new methods of using MAbs whether for diagnostic kits, cell sorting, tissue typing, purification, or other uses.

There may be some problems with respect to patenting hybridoma technology. One relates to the perception that the U.S. Patent and Trademark Office is allowing fairly narrow claims with respect to hybridoma technology, particularly with regard to MAbs themselves. If this turns out to be true, it may be easy to "invent around" the patented invention. Furthermore, because hybridoma cell lines are often unstable and may change over time, there may be a problem with regard to enablement. However, this problem may be solved by freezing the cell line so that it is available to the public when desired yet not continuously replicating and possibly changing.

*See *Chapter 9, The Technologies* for a discussion of hybridoma/MAb technology.

development and complexity of the field will make it difficult to determine as of a given point in time what is ordinary skill or what is obvious.

DISCLOSURE REQUIREMENTS

The requirement for adequate public disclosure of an invention is designed to ensure that the public receives the full benefit of the new knowledge in return for the granting a limited monopoly to the patent holder. Thus, a U.S. patent, which is a public document, must contain a sufficiently detailed description of the invention to enable others in that field of technology to build and use the invention without "undue experimentation." This is known as the enablement requirement. The patent also must disclose the best mode known to the inventor for carrying out the invention at the time the patent application is filed.

In the case of biological inventions, satisfying the enablement requirement is a major hurdle. Because of their complex and unknown nature, many biological inventions, especially organisms, cannot be sufficiently described in writing to allow their predictable reproducibility on the basis of that description alone. Even with fairly precise techniques such as rDNA, random events provide uncertainty as to predicting the exact nature of the final product. There is always the possibility during the manipulation of DNA fragments, plasmids, and transformed organisms that random changes have occurred. The final product may in fact be quite different from the description provided by the experimenter, even though the experimentation process itself may have been accurately described.

This problem has been dealt with for patent applications on new micro-organisms or processes involving them by permitting the micro-organisms to be placed in culture depositories, where they are available to the public (31). The depository and the culture catalog number are then referenced in the patent application, and if the patent issues, the public gains access to the culture.* There is some debate over whether such things as plasmids must be deposited, because there is some question as to the reproducibility of the plasmids on the basis of a written description alone.**

*The case law has left open the possibility of satisfying enablement in ways other than through a deposit (25,31).

**One of the questions raised by the patent examiner in the pending Cohen-Boyer patent application on the products of rDNA technique, e.g., plasmids, was whether the application disclosed a reproducible way to make a certain plasmid (5).

In any event, the enablement requirement will be one major hurdle to the patentability of higher organisms because of the logistical problems associated with depositing those organisms.

DEPOSIT REQUIREMENTS

Deposit requirements in the United States have developed by court decision and administrative action. The practice of the U.S. Patent and Trademark Office has been to require a deposit to be made at a recognized depository no later than the patent application filing date (50). The office further requires that deposits be maintained for the life of the patent (50).

Along with the other five countries being considered in this report, the United States is party to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure (14), which attempts to harmonize the deposit requirements of the signatory countries. Under the treaty, the signatory states recognize in their own patent procedures a micro-organism deposit made in another country if the deposit is made in a depository meeting the requirements of the treaty.* Thus, if the patent applicant is filing applications in several countries, only one deposit need be made. Deposits made under the treaty must be maintained for at least 30 years.

A potential problem that arises with respect to deposits should be noted. Although any valid patent must describe an invention with sufficient specificity so as to enable a person of ordinary skill in that technology to make the invention, there is a significant difference between describing an invention and actually turning it over to the other person. The know-how that is associated with the actual making and subsequent perfection of an invention clearly provides the inventor with an advantage over a competitor who must construct the invention from the description in the patent. Yet in the case of a micro-organism, the invention must actually be turned over to any competitor who desires it. In essence, therefore, the holder of a patent on a micro-organism that produces a commercially useful polypeptide such as insulin must turn his or her "factory" (i.e., the micro-organism) over to competitors. Given the current state of the technology, this situation is probably unavoidable. Possibly, however, consideration could be given to allowing various restrictions to be placed on access to the deposits.

*The American Type Culture Collection in Rockville, Md., and USDA's Northern Regional Research Laboratory in Peoria, Ill., together with five foreign institutions, currently meet the requirements (45).

CLAIMS

Claims are the precise language that define the boundaries of an invention protected by a patent. U.S. law permits a series of claims, ranging from broad to narrow, to be made with respect to an invention, so that if one or more of the claims are subsequently held invalid (e.g., for covering some of the prior art or being indefinite), the inventor may still be able to rely on a narrower invention. Of course, all of the claims could be held invalid.

The scope of permitted claims will be important for biotechnology. The scope is initially determined by what the U.S. Patent and Trademark Office will accept. In any new technology, the initial inventions tend to be broad and pioneering, so broad claims are usually permitted. As time passes, however, prior art develops and new extensions of the art become more obvious. Then, the claims permitted by the Patent and Trademark Office will be narrower. The Cohen-Boyer patent on the basic rDNA technique (U.S. Patent 4,237,224) is an excellent example of a broad, pioneering invention, although some commentators have questioned its validity (7). In the case of hybridomas and MAbs, however, there is some indication that the Patent and Trademark Office is being fairly conservative from the start. The data supporting this perception are largely anecdotal, because there have been few patents issued on hybridoma technology. If the claims being allowed are more narrow, however, the value of patents on this technology would be lessened.

A recent decision by the U.S. Patent and Trademark Office, *Ex parte Jackson* (24), has important implications for the scope of permitted claims on micro-organisms, cell lines, and processes for producing or using them (6). The case involved the isolation and purification of three strains of bacteria that made a new antibiotic. All three strains had been deposited and referenced in the patent application. Although the Board of Appeals

of the U.S. Patent and Trademark Office upheld a claim to producing the antibiotic by using a micro-organism selected from the deposited strains (or mutants thereof), it rejected a claim to producing the antibiotic by using any micro-organism of the same species on the grounds that the claim was not enabling. Thus, the scope of the patent on the applicant's process for producing the antibiotic will be limited, and others may be able to legally practice the invention by using other strains. This case, if broadly applied, may have a significant adverse impact on the incentive to patent many kinds of biotechnological inventions, because inventors may see the scope of patent protection as being too narrow.

Subsequent to patenting, the scope of the claims will be determined by Federal courts ruling in patent infringement suits. If the patent is upheld, the court has some discretion on how broadly to interpret the written claims. It will tend to interpret the scope more broadly for fundamental inventions. Sometimes the scope of the literal wording of the claims can be extended, if the infringing invention does substantially the same thing, by substantially the same means, and in substantially the same way, as does the patented invention, yet the literal wording of the claims in the patent for the invention does not cover the infringing invention (26). In such cases, the courts will interpret the claim as covering the infringing invention. This is known in patent law as the "doctrine of equivalents."

The fact that the claims define a new invention does not mean that the new invention does not infringe on a previously patented invention. For example, consider the Cohen-Boyer patent on the fundamental rDNA technique. Its existence will not prevent new applications of the rDNA technique from being patented (providing they also meet the other requirements of the patent law); however, the new inventions may infringe the Cohen-Boyer patent. Thus, for a holder of the new patent to make use of that invention, he or she may have to pay royalties to the owners of the Cohen-Boyer patent.

ENFORCEMENT

Patent infringement in the United States is defined as the unauthorized making, using, or selling of any patented invention within the United States (35 U.S.C. §271(a)). No liability for infringement exists prior to the date the patent is issued.

With respect to enforcing a patent, certain problems arise. One problem, generally not a problem for products but potentially a very serious problem for processes, is knowing whether or not an infringer is using the patent. If an unpatented product can be made by many different processes, the owner of a patent on one of those processes may have no way of knowing whether a product made by a competitor has been made by a different process or by the patent owner's process. This is a special problem for any process involving a micro-organism or cell line. To get a patent on such a process, a deposit must be made, making the micro-organism or cell line available to anybody who desires to use it. For this reason, processes using such organisms are likely to be held as trade secrets unless the process is truly a major advance.

Another problem with respect to enforcing process patents granted in the United States is the fact that the patented process may be used in other countries to make the same product, which can then be imported into the United States and compete with the product made by the owner of the U.S. process patent. Although many countries would define this action as infringement of that process patent, the United States does not. A remedy for the owner of the process patent is available through an action before the U.S. International Trade Commission. If the owner of the patent can prove that the foreign activity infringes the U.S. process patent and that importation of the product would injure an efficiently conducted U.S. industry (or prevent its establishment), the product can be excluded from the United States (19 U.S.C. §1337, §1337(a)). This remedy has been criticized as leaving much to be desired (39). However, one commentator has pointed out many substantial advantages of go-

ing this route as compared to an action in Federal district court (13). The requirement for proving injury to an industry is not as problematical as it might seem because the International Trade Commission has held that the domestic industry may consist of only one company, the U.S. patent owner (13). Thus, the issues of whether biotechnology is an industry or whether one imported product could injure that whole "industry" would not be relevant. In fact, an International Trade Commission action is one way the owners of the Cohen-Boyer patent might enforce it against foreign users of the rDNA process.

Another problem area relevant to biological inventions has been the general attitude of the courts in the United States toward patents. Despite a statutory presumption of validity, about one-half of all litigated patents are held invalid by the courts (48). There has been a certain judicial hostility toward patents because they are "monopolies," even though permitted by the U.S. Constitution and Title 35 of the U.S. Code (29). Certain language in U.S. Supreme Court decisions, for example, refers to such "monopolies" and states that patents must be construed very narrowly and must not be upheld on "mere gadgets" (27). In the 15 years before *Chakrabarty,* the Supreme Court had not ruled in favor of a single patent applicant or patentee (29).

On the other hand, this judicial hostility appears to be changing. In some recent U.S. Supreme Court decisions, including the *Chakrabarty* case, the Court has upheld the patents and has used broad language to do so (20,23).

PATENT V. TRADE SECRET PROTECTION*

Patents and trade secrets are alternative and not necessarily mutually exclusive ways to protect biotechnological inventions. Companies are likely to choose between them on a case-by-case basis. In choosing, they would evaluate the following factors:

- whether there is any significant doubt that the invention can meet the legal requirements for patenting,
- whether there is the likelihood of others discovering the invention independently or through reverse engineering,
- what the invention's projected commercial life is and how readily others could improve on it if it were disclosed in a patent,
- how easily the patent could be "policed,"
- whether it is a pioneer invention,
- the cost of the related R&D and regulatory approvals,
- whether there are any plans for scientific publication, and
- what the costs of patenting are versus reliance on trade secrecy.

The first factor speaks for itself. The next two factors require difficult decisions to be made on the basis of the characteristics of the invention and the competitive environment. If research to develop a particular product is widespread and intense (as is the case with interferon), the risk of a competitor developing the invention independently provides a significant incentive for patenting. On the other hand, reverse engineering by competitors is virtually impossible for most products of micro-organisms because of the variability and biochemical complexity of microbiological processes.

The fourth factor, how easily the patent could be policed, is especially relevant for processes. Greater protection may lie in keeping a process secret, even if the microbe and the process could be patented. This is especially true for a process that is only a minor improvement in the state of the art or that produces an unpatentable product already made by many competitors. The commercial life of the process might be limited if it were patented, beause infringement would be difficult to detect and not worth the time and money to prosecute. Reliance on trade secrecy might then extend its commercial life.

Most companies would patent truly pioneer inventions, which often provide the opportunity for developing large markets. Moreover, patents of this sort tend to have long commercial lives, since it is difficult to circumvent a pioneer invention and since any improvements are still subject to the pioneer patent. Furthermore, infringement is easy to detect because of the invention's trailblazing nature. This would be true for processes also.

*This section draws on the analogous section in OTA's report *Impact of Applied Genetics: Micro-Organisms, Plants, and Animals* (47).

High costs for research, development, and regulatory approval of products is a factor in favor of patenting because a company will want to protect its investment. The research-oriented pharmaceutical companies have traditionally relied on patents for this reason.

The last two factors involve considerations secondary to a product and its market. Obviously, any publication of the experiments leading to an invention forecloses the option of trade secrecy. Also, a company must evaluate the options of protection via either patenting or trade secrecy in terms of their respective cost effectiveness.

Plant breeders' rights statutes

Ownership rights in new varieties of plants are specifically granted by two Federal statutes: 1) the Plant Patent Act of 1930 (35 U.S.C. §§161-164) and 2) the Plant Variety Protection Act (PVPA) of 1970 (7 U.S.C. §2321 et seq.).

The Plant Patent Act, which covers new and distinct asexually reproduced varieties other than tuber-propagated plants or those found in nature, confers the right on the patent holder to exclude others from asexually reproducing the plant or from using or selling any plants so reproduced, for a period of 17 years. Because of the impossibility of describing plants with the same degree of specificity as machines and the inability to recreate a new plant solely from a written description, this law also liberalized the enablement requirement; the description need be only as complete as "reasonably possible."

PVPA provides for patent-like protection to new, distinct, uniform, and stable varieties of plants that are reproduced sexually, excluding fungi, bacteria, and first-generation hybrids. The breeder may exclude others from selling, offering for sale, reproducing (sexually or asexually), importing, or exporting the protected variety. In addition, others cannot use it to produce a hybrid or a different variety for sale. However, saving seed for crop production and for the use and reproduction of protected varieties for research is expressly permitted. The period of exclusion is 18 years for woody plants and 17 years for other varieties.

These acts are basically consistent with an international treaty designed to provide consistency in the international protection of plant breeders' rights—the International Union for the Protection of New Varieties and Plants—known as UPOV.* UPOV has been signed by 16 countries, including all those discussed in this chapter, but not all of those countries have yet conformed their laws to it.

Until the *Chakrabarty* decision, the Plant Patent Act and PVPA were generally viewed as the sole source of plant breeders' rights in the United States. The *Chakrabarty* decision raises the possibility of protecting plants under 35 U.S.C. §101, because the essential point of the decision is that a human-made organism is a "manufacture" or "composition of matter" as those terms are used in §101. Further, there is no indication in the decision that the Plant Patent Act and PVPA preempt protection for plants.

There would be certain advantages and disadvantages of securing protection of sexually and asexually reproduced plant varieties through §101. One advantage is that more than one claim could be presented, as opposed to the single claim permitted under the Rules of Practice relating to plant patent applications (37 C.F.R. §1.164) This would allow parts of the plant to be covered as well as the whole plant. Further, a patent grant under 35 U.S.C. §101 for a new variety would provide more comprehensive protection against infringement in certain situations.

The disadvantages of proceeding under 35 U.S.C. §101 are that other currently irrelevant sections of the patent law would come into play. For example, the Plant Patent Act (35 U.S.C. §162) significantly modifies the disclosure requirements of 35 U.S.C. §112, simply requiring that the description be as complete as reasonably possible. This would at least theoretically no longer be true. However, the use of depositories for plant material, as required for micro-organisms, could satisfy the enablement requirement. A further potential factor is the applicability of the nonobviousness

*The Plant Patent Act conforms, but PVPA does not. Since the United States is a party to UPOV, some changes in PVPA may be necessary. At this time, however, it is hoped that conformity can be achieved through administrative practices (45).

requirement of 35 U.S.C. §103. This test is inherently difficult for plant material.

On balance, the *Chakrabarty* decision is likely to provide yet another protection option which can, in certain circumstances, be very useful. For example, tuber-propagated plants such as potatoes, which are not patentable under the Plant Patent Act, would appear to be patentable under 35 U.S.C. §101.

Comparison of U.S. and foreign intellectual property law

Much of the analysis in this section is based on the more detailed description of intellectual property law of the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan found in *Appendix G: Intellectual Property Law*.

Patent law

The Federal Republic of Germany, the United Kingdom, France, and Switzerland, along with seven other Western European countries, are signatories to a treaty that creates a European patent system. That treaty, known as the European Patent Convention (EPC), went into force on October 7, 1977. The EPC establishes a legal system for granting European patents through a single supranational European Patent Office and a uniform procedural system with respect to patent applications. The single European patent application, if granted, become a bundle of individual European patents, one for each of the countries designated by the applicant.* The EPC system and the resulting patents exist in parallel with the patent systems of the member countries. Enforcement, however, is handled by the individual member countries. The ultimate goal is for each of the member countries to adopt in its national law the same substantive law of patents set forth in the EPC. The following discussion compares the patent law of the EPC countries and Japan with that of the United States.

*A proposed European Community Patent Convention would take the EPC one step further by providing for a single patent covering the entire European Economic Community.

PATENTABLE SUBJECT MATTER

One of the most difficult problems facing the owners of biological inventions is the inability of the law to respond rapidly enough to keep pace with the development of the technology. This is especially a problem in the case of the law's definition of patentable subject matter. Questions about what constitutes patentable subject matter create a significant degree of uncertainty for owners of inventions.

One of the basic decisions to be made by owners of inventions is whether to maintain their inventions as trade secrets or to attempt to protect them by patents. An intelligent decision is nearly impossible when one does not even know which basic subject matter is patentable under the laws of particular countries. In the United States, the trade secret route can still be selected in the event that no patent protection is ultimately secured. In most foreign countries, including the United Kingdom, France, the Federal Republic of Germany, and Japan, however, pending applications are published before it is known whether patenting will be possible, thereby providing complete and enabling disclosure to the public, including samples of any deposited micro-organisms necessary to carry out the invention. Such publication usually occurs 18 months after the application is filed. This situation effectively precludes reliance on trade secrecy once a patent application is filed. As a result, there exists in many foreign countries today considerable disincentive to seek patent protection for certain types of biological inventions, particularly those involving basic genetic procedures and the resulting products. However, with respect to the five

foreign countries under study here, much of the uncertainty surrounding subject matter patentability of biotechnological inventions has been resolved.

This uncertainty in many foreign countries may indirectly discourage U.S inventors from filing for patent protection in the United States, since there is no way available at present to confine within the United States the culture deposit samples which must be made available once a U.S. patent issues. While enabling disclosure theoretically is communicated upon issuance of a U.S. patent to all countries, regardless of whether corresponding protection is available or is actually sought in those countries, it is only in connection with many biological inventions that an applicant is required to provide also the physical means to carry out the invention, i.e., a self-replicating organism, which in many instances is a "factory" capable of carrying out the invention.

One important aspect of this problem of uncertainty in the definition of patentable subject matter is the uncertainty of classification of certain types of biological inventions. It is not clear in the case of certain lower organisms, for example, whether they are to be classified as plants, animals, or something else (e.g., protista) (see, e.g., 15,19). Fortunately, in the United States, it seems to be a matter of choosing between multiple options for protecting such subject matter by either utility patents or plant patents, but in most other countries, plants and animals are explicitly excluded from patentability. Thus, a definition may be determinative of patentability.

As a result of the 1980 U.S. Supreme Court's decision in the *Diamond v. Chakrabarty* case, the U.S. definition of patentable subject matter is very broad. It is broader than that under the EPC or any of the national laws of the five other countries being examined in this assessment. In contrast to the United States, the EPC, which has a very liberal definition of patentable subject matter, excludes methods for treatment of the human or animal body by surgery or therapy and diagnostic methods. Also, the EPC excludes plant and animal varieties and biological methods for producing them, which are apparently not excluded by *Chakrabarty*. In all other respects pertaining to biological inventions, the United States and EPC appear to permit patenting of the same general classes of subject matter. France, Switzerland, the United Kingdom, and the Federal Republic of Germany follow the EPC, except Switzerland does not allow patents on micro-organism themselves.

Japan's definition of patentable subject matter is essentially coextensive with the definition of the EPC, excluding processes in the fields of medicine, diagnosis, therapy, and pharmacology in which the human body is an indispensible element. However, certain microbiological inventions could be excluded from patentability in Japan if they are "likely to injure the public health." The situation with respect to plants and animals in Japan is unclear.

NOVELTY

U.S. law requires the patent application to be filed by the inventor. If two different applicants happen to have the same invention, the patent will issue to the one who invented it first. Hence, the U.S. system is called a "first-to-invent" system. The laws of the other five countries, in contrast to U.S. law, permit someone other than the inventor (e.g., the employer) to file the patent application. If there are two applications for the same invention, the patent will issue to the applicant who filed first. These countries thus have what is called a "first-to-file" system. The combination in the United States of a first-to-invent system with the provision of a 1-year grace period between the date of any publication relating to an invention and the filing of a patent application makes the U.S. system fundamentally different from nearly all foreign systems, which are generally first-to-file systems are characterized by absolute novelty (i.e., allow no grace periods).

This difference manifests itself in connection with prior disclosures by the applicant. Under U.S. law, the general rule is that a disclosure of an applicant's own invention cannot be used to prevent the applicant from obtaining a patent, unless the disclosure satisfies the requirements of one of the statutory bars under 35 U.S.C. §102 (18). For example, consider the following types of possible disclosure by an inventor of his or her own work:

1. Communicating with colleagues by telephone, letter or in person;

a. under expressed confidentiality;
b. with no indication as to confidentiality; or
c. under expressed nonconfidentiality.
2. Delivering a paper at a conference or seminar, orally only.
3. Delivering a paper at a conference or seminar, both orally and with a disseminated written text.
4. Submitting a paper for publication.
5. Submitting an abstract prior to a conference to the conference promoting organization.

Under U.S. law, items 1, 2, 4, and 5 would not bar patentability.* Item 3 will become a statutory bar 1 year after the paper is disseminated in some tangible form, assuming the disclosure was enabling.

Under the laws of the four Western European countries, items 2 and 3 would prevent the granting of a patent if they occurred before the earliest effective filing date (e.g., before a U.S. applicant filed a patent application in the United States which will later serve as a basis for claiming the right of priority in corresponding foreign applications).** Items 4 and 5 would normally not bar a patent, assuming that the paper and/or abstract were not disseminated to members of the public, (e.g., conference attendees) prior to the actual date the patent application was filed. This is based on the implied confidentiality under which submissions of this type are usually handled by publishers. Similarly, the concept of expressed or implied confidentiality prevents items 1(a) and 1(b) from constituting prior art under German law concepts, which commentators believe will apply to the EPC and other European countries (11). It appears that even item 1(c), in and of itself, does not necessarily constitute prior art under German principles, inasmuch as such a nonconfidential disclosure must be available to an *unlimited* number of persons (43). If the disclosure were limited to the colleagues contacted and not otherwise made freely available, it would not defeat novelty of a subsequently filed application. It is too early to tell how EPC law will develop on this issue. The same can be said for the United Kingdom, where introduction of the EPC novelty standards represents a significant change from prior law and practice.

The Japanese law provides a limited 6-month grace period for publications and papers presented before scientific organizations. Thus, items 1, 4, and 5 would not bar patentability, and items 2 and 3 would bar patentability after 6 months.

It must be noted that the above discussion regarding bars to patents because of lack of novelty is predicated on the assumption that the disclosure is enabling. If the disclosure is *not* enabling, even a published paper about the invention would not bar patentability.

Because of the different approaches with respect to novelty, the U.S. patent law provides a competitive advantage in that scientific information can be quickly disseminated in the United States without forgoing patent rights, if the application for a patent is filed within a year. This advantage is qualified by the fact that the inventor who also wishes to file abroad cannot publicly disclose the invention until the priority application is filed. The case of the Cohen-Boyer patent on the rDNA technique is a well-known example of a case in which the inventors were able to obtain a U.S. patent, even though they had published papers about the techniques, but were unable to file for foreign patents because of the absolute novelty requirement in other countries. The probable result will be a substantial loss of income from foreign royalties.

UTILITY

The U.S. patent law's requirement for practical utility differs slightly from the requirement of European and Japanese law for industrial applicability. The U.S. utility doctrine has been criticized by the American patent bar, but has not proved to be a major obstacle for industry (45). It has undoubtedly disadvantaged some researchers and simultaneously deprived the public of

*If a paper or proceedings of conference were published, however, then the inventor would be barred if he or she filed a patent application more than 1 year after the date the proceedings or paper were published. Also if the invention were sufficiently disseminated so that it was deemed to be "in public use," then the inventor would be barred by sec. 102(b) from patenting it after the expiration of the 1-year grace period.

**Under the Paris Union Convention, to which all six competitor countries subscribe, applications filed in any country within 12 months of the first filing in a member country have, as their *effective* filing date, the filing date of the first application. This is known as the "right of priority."

prompt disclosure of research on, for instance, new pharmacological compounds and processes that do not yet have an established utility (45). In some cases, effort has undoubtedly been wasted in establishing trivial or unimportant yet "practical" utilities for such inventions in order to satisfy the U.S. Supreme Court's definition (45). This problem will affect researchers in biotechnology to some extent, particularly those working with pharmaceuticals.

On the other hand, the foreign systems present a different problem of "utility." They exclude method inventions in the field of therapeutic or diagnostic treatment, at least those involving treatment of humans, as not being part of "industry." Thus, certain types of biological inventions (e.g., monoclonal antibody diagnostic assays) will not be patentable in EPC member countries or possibly in Japan, although patent protection can be obtained for them in the United States. This is, in most cases, not a serious obstacle, since patent protection is not precluded for the materials that are used in the excluded methods or the products of those methods.

DISCLOSURE REQUIREMENTS

U.S. disclosure requirements are stricter than those of the EPC and Japan. The U.S. law requires (35 U.S.C. §112):

- a written description of the invention,
- enablement both with respect to "how to make" the invention and also with respect to "how to use" the invention, and
- a disclosure of the best mode known to the inventor for carrying out the invention as of the time of filing.

As to the basic enablement standard, however, U.S. law does not differ substantially from the foreign laws. Under the U.S. law, the test of enablement is whether the invention can be carried out by a person of ordinary skill in the art without "undue experimentation" (30). This is another way of stating the requirement for "reproducibility" which is fundamental to European law.

As previously mentioned, compliance with the enablement requirement creates serious difficulties for many biological inventions, because such inventions may have been produced by random mutation and selection or another procedure that cannot be repeated with the certainty of obtaining the same results. The solution that has been adopted essentially worldwide is to permit a deposit of the appropriate biological material in a depository, from which samples will be made available to the public.

The Federal Republic of Germany's requirement for reproducibility raises additional obstacles to patenting a micro-organism itself. It requires that a patent application describe a repeatable procedure for reproducing with certainty the deposited organism apart from the deposit itself (i.e., "from scratch" so to speak) before a patent can be granted on the organism per se. This is not required if one claims only a method of using such a deposited organism. Thus, this requirement, in effect, could preclude patents on many micro-organisms.

Neither the EPC countries nor Japan specify a best mode requirement in their respective laws. In the United States, the best mode requirement arguably requires the best producing micro-organism strain to be deposited, but this issue is not resolved.

The written description of the invention requirement under U.S. law is not articulated as such in foreign laws, but a requirement similar in principle is applied in some situations under the laws of most countries.

DEPOSIT REQUIREMENTS

At present, uncertainty regarding the deposit requirements exists in many countries. The circumstances under which a deposit is necessary are not clearly spelled out. Moreover, before receiving a substantive examination on this question in the EPC, for example, the patent applicant must take action that has the effect of making the deposit, and also access thereto upon publication of the application, irreversible. In the United States, the same basic uncertainty exists, but the applicant need not make a commitment until after substantive examination is completed.*

*As a practical matter, however, if patent protection is sought in other countries, this irreversible effect will have taken place already, prior to conclusion of the examination in the United States because of the 18-month publication practice in other countries.

The United States does not have any explicit deposit requirements in the patent statute or rules thereunder. For deposits necessary in order to comply with the enablement requirement, however, certain requirements for the deposit have been developed by administrative action (50) and court decisions.

As far as timing and location of deposit, the U.S. practice is basically consistent with the practice most countries, i.e., the deposit is to be made no later than the patent application filing date and at a recognized depository (50). The United States does not have a specific list of recognized depositories and therefore maintains more flexibility than the EPC and certain national offices that do have such lists. Of course, the United States also recognizes deposits meeting the requirements of the Budapest Treaty.

The U.S. Patent and Trademark Office has required only that deposited cultures be maintained for the life of the U.S. patent (although any deposit made under the Budapest Treaty must be maintained for a minimum of 30 years). The EPC and many European countries have opted to apply the longer period of the Budapest Treaty to any deposit made in accordance with national law. This will require additional costs for the applicants in those countries.

Samples of deposited micro-organisms become available to the public under U.S. practice at the time the patent issues, after which time no restrictions on access are permitted. The situation in the United States is quite different than that in the EPC countries and Japan. In the EPC countries (except for Switzerland) and Japan, patent applications are published approximately 18 months after the effective filing date. Such publication, which also makes the deposit publicly available, may place foreign applicants at a disadvantage.

On the other hand, under many foreign systems, including the EPC, the patentee is entitled to maintain certain limited restrictions on those receiving samples of the deposited culture throughout the life of the patent. The restrictions also apply to cultures derived from the original one (EPC Rule 28(6)). The Federal Republic of Germany also allows territorial restrictions to be placed on deposited micro-organisms.

Potential problems exist in the present deposit system as a result of import/export restrictions imposed by countries. In one case, a German applicant was unable to perfect a deposit in a U.S. depository (one of two in the world which accepted his type of cell line) within the 12-month priority period because of health-oriented import restrictions imposed by the United States (9). It is also possible that a patentee could lose his or her rights entirely in a given country if that country imposed restrictions on the import of samples of a culture in a foreign depository that is otherwise recognized by its patent office. The same result could occur if the country in which the depository is located refuses to permit export of samples of the deposited culture. In the latter instance, however, the Budapest Treaty permits a second deposit to be made in another depository without loss of deposit date.

CLAIM PRACTICE

Claim practice in the United States is extremely liberal and is regulated primarily by the requirement for definiteness contained in the second paragraph of 35 U.S.C. §112. This fact, together with the fact that patentable subject matter in the United States is generally less restricted than in most other countries, results in an very broad freedom for an applicant to claim his or her invention in a U.S. patent application.

There is a dearth of experience with claims directed to the relatively new inventions of biotechnology, and the EPC itself is too new for any significant precedent. Existing precedent primarily involves processes for the use of micro-organisms.

Under U.S. practice, biological inventions can be claimed in many different ways. In addition to process claims directed to methods of genetic manipulation, the products thereof can be claimed with regard to their structure, or if their structure is not known, with regard to their chemical and/or physical characteristics or in terms of the process steps for preparing them. Despite this flexibility, however, the previously discussed *Jackson* case (24) indicates that the U.S. Patent and Trademark Office may impose significant limitations on the breadth of claims.

Some of the patent offices in foreign countries have taken positions similar to that taken in the *Jackson* case. Switzerland and Japan have refused to grant claims that are broader than the specific micro-organisms disclosed in the application and deposited (Swiss Patent Ordinance, Section 15.15.3, May 12, 1980; Japanese Examination Guidelines).

There is little reported precedent regarding judicial interpretation of claims pertaining to biological inventions in infringement cases. Nevertheless, one can extrapolate from general principles of claim interpretation in the various foreign patent systems. The law in most countries provides for application of the doctrine of equivalents in some form, although in some countries, including Japan, the scope of equivalents is apparently very limited. As a general rule, it can be said that the scope of equivalents must be determined on a case-by-case basis, depending on factors such as the degree of unpredictability of the technology (i.e., equivalents must be obvious to persons of ordinary skill) and the degree of advance which the claimed invention exhibits over the "prior art." The more unpredictable the subject matter, the smaller the scope of equivalents, whereas the more pioneering the invention, the broader the scope of equivalents. Biological inventions typically involve highly unpredictable phenomena; thus, claims are likely to be narrowly interpreted.

Even if it is assumed that a reasonable degree of equivalents will be given for biological inventions, the next problem is to determine what constitutes an equivalent. No precedent is available, and, of course, the determination will be made on a case-by-case basis. It would seem that good arguments can be made to the effect that closely related strains of the same species can be looked on as equivalents, that different species normally would not constitute equivalents, and that mutants of the basic strain would, in most instances, be expected to have equivalent properties to the basic strain (see 8).

ENFORCEMENT

The United States, the four European countries, and Japan define patent infringement in similar ways. The major difference is that, unlike the other countries, the United States does not grant extraterritorial effect to process patents by defining as infringement the importation of a product made by the patented process without the authorization of the patent owner.

The United States grants the basic remedies of injunction and monetary damages for infringement (35 U.S.C. §283, §284), as well as reasonable attorneys' fees to the prevailing party in exceptional cases (35 U.S.C. §285). The foreign countries provide for similar remedies. There are no criminal penalties provided under the U.S. patent statute, contrary to many foreign patent laws.

Enforcement of patents claiming biological inventions involves unique problems. The first is simply identification of infringing activity. Many of the products will be unpatentable for lack of novelty and will be manufactured in small quantities. Thus, it will be difficult to determine if a competing product infringes one's patented process. In addition, strains of micro-organisms can be altered through mutation and other modification techniques to produce different organisms that possess the same basic characteristics of the protected organism.

It may prove to be an essential, or at least important, element of the case for the patentee to establish that the alleged infringer actually derived his or her organism from a sample obtained directly or indirectly from the culture deposit of the patentee's organism. Without adequate controls on the access to samples of deposited strains, proof of this fact will be extremely difficult.

Proving the identity and equivalence of the patented micro-organism with an allegedly infringing micro-organism can also present difficult problems for the present state of this technology. The technology is still sufficiently undeveloped that much room exists for honest differences of opinion among experts. Most questions of infringement will probably turn out to be a battle between the respective parties' expert witnesses, until more objective criteria are established.

Trade secret law

Of the countries considered in this assessment, the Federal Republic of Germany seems to have

the strongest statutory system for the protection of proprietary information, and its courts are most consistent in enforcement of those statutes. Switzerland's system, which closely resembles West Germany's, has also been very effective in protecting such information. However, Swiss law does not recognize as trade secrets the secrets held by professors, scientists, and others not engaged in a business (45). This could affect the exploitation of commercial rights by educational institutions in Switzerland.

The United States and the United Kingdom appear to be slightly less effective than the countries just mentioned in protecting proprietary information. The British courts emphasize the "confidential" over the "secret" aspects of such information. Breaches of confidence are therefore not tolerated, regardless of whether the particular information misappropriated fits within a preestablished "trade secret" category. The U.S. courts often overlook the breach of obligation aspect of misappropriation and concentrate on determining whether or not the information qualifies as a "trade secret." As a result, misappropriators of confidential information are sometimes held not liable in the United States, whereas they would be held liable for the same activity in the United Kingdom (45). Nevertheless, U.S. courts have shown much greater flexibility than their British counterparts in fashioning remedies that prevent the use of misappropriated information. Furthermore, U.S. law provides for criminal penalties in addition to the usual civil remedies provided for under U.K. law. Finally, the sheer mass of successful trade secret cases, including favorable rulings from the U.S. Supreme Court in the *Kewanee* case (38) and in *Aronson* v. *Quick Point* (4), indicates that the United States is probably more effective than the United Kingdom in safeguarding such information (45).

France does not have as strong a system for protection of proprietary information as the United Kingdom or the United States. French courts have been rather restrictive in defining the types of information that may receive protection and more protective of the employee who leaves with the employer's confidential information than the courts in other industrialized countries (45).

The protection of proprietary information in Japan has been improving over the last two decades, but still is not on a level with the protection in the United States or the major European countries. As Japan continues its development from a technology-importing country to a technology-generating country, further progress in this area may be expected (45).

Plant breeders' rights

CHOICE OF TYPE OF PROTECTION

A breeder of asexually reproduced varieties of plants in the United States will normally proceed under the Plant Patent Act. However, 35 U.S.C. §101 may provide a viable option. Although additional disclosure requirements for asexually reproduced plant material will be required (e.g., the deposit of plant material in a satisfactory depository), this is not an onerous burden. Moreover, with the depository, there is the additional advantage that the patented plant material will be available during the life of the patent for comparison purposes with any alleged infringing varieties. The public would also be able to practice the invention when the patent expired.

For sexually reproduced plant varieties, the principal advantages of proceeding under 35 U.S.C. §101, as opposed to PVPA, are the substantially reduced costs of filing a patent application (as opposed to an application under PVPA)* and the possible increased protection afforded by the patent as opposed to the protection certificate issued pursuant to PVPA. Moreover, whereas numerous judicial decisions have been rendered under the patent statutes, judicial interpretation of PVPA is relatively limited.

In the United Kingdom, the Federal Republic of Germany, Switzerland, France, and Japan, a single statute covers both sexually and asexually reproduced plant varieties. As previously noted, protection is in the form of protection certificates rather than patents. Therefore, there is no choice of the type of protection obtained in these countries.

*The cost of filing an application under PVPA is $1,000, as compared with the cost of filing a utility patent application ($150 for small entities and $300 for others).

LIMITATION ON PROTECTABLE VARIETIES

In the United States, only tuber-propagated plants or plants found in an uncultivated state are excluded from protection under the U.S. Plant Patent Act. As a practical matter, this exclusion affects only the Irish potato and the Jerusalem artichoke. All other plant varieties that can be propagated true to type through asexual reproduction can be protected. Similarly, under PVPA, only first-generation hybrids are excluded, and all other varieties otherwise meeting the act's requirements can be protected.

In most countries other than the United States, by contrast, the number of specific genera or species that can be protected is restricted. The 1978 UPOV Text requires only a very limited number of designated genera or species for a country to comply with the provisions of the text. Thus, the protection provided in the European countries and Japan is relatively limited when compared with the all-encompassing protection provided by the U.S. Plant Patent Act and PVPA.

EFFECT ON COMPETITIVENESS

With respect to plant breeders' rights, U.S. law provides a competitive advantage over the other countries. The scope of protection is much broader in terms of the types of varieties than can be protected, and U.S. law provides the additional option of using §101 of the patent law (35 U.S.C. §101).

Evaluation of effectiveness of intellectual property law to promote the development of biotechnology

United States

U.S. patent law embodies a number of pro-innovation features: a "first-to-invent" system coupled with a 1-year grace period; secrecy of the invention subject matter until grant of the patent; and, as a result of the latter, no requirement for owners of biological inventions to grant access to deposited cultures until after protective rights have been established. These features provide incentive for owners of biological inventions to utilize the patent system, thereby making their inventions known to the public to aid further development. They also provide a sufficient period of time for the patentee to develop a leading position in the technology before being forced to hand over his or her enabling disclosure (including means for immediately practicing the invention, in the case of culture deposit samples) to competitors, both domestic and foreign. The "first-to-file" systems in the other competitor countries do not provide these advantages to applicants.

Another strength of the U.S. system is the choice of protection routes it now offers to inventors. Developers of new varieties of plants can now choose between the special plant protection provisions of the law and the possibility of obtaining a utility patent.

The 1980 *Chakrabarty* decision has far greater significance than merely holding that living organisms constitute patentable subject matter under U.S. law. It, together with other recent cases, represents the first truly positive pronouncement in many decades from the U.S. Supreme Court regarding the role and value of the patent system in promoting and maintaining technological competitiveness of U.S. industry (37,45).* This should have an effect on the way in which the lower courts will treat patents in the future. In addition, creation of the new Court of Appeals for the Federal Circuit should provide uniformity and consistency at the appellate level, as well as a body of law that is well informed and respected by those whom the patent laws serve. The important role of trade secret protection has been reaffirmed by the Supreme Court in its 1974

*Justice Jackson was prompted to state in his dissenting opinion in *Jungerson* v. *Ostby & Barton Co.* (35) that: "The only patent that is valid is one which this Court has not been able to get its hands on."

Kewanee decision (38). Finally, the United States has responded to the needs of plant breeders of asexually reproduced varieties by adhering to UPOV, and conformity between UPOV and the Plant Variety Protection Act of 1970 involves only a matter of the time to necessary reconcile minor language differences. With these positive developments, the intellectual property law of the United States may be viewed as entering a period of unprecedented strength and vitality (45). It should play an important, positive role in the development of biotechnology in the United States and thereby aid the international competitiveness of U.S. companies.

There are also several weaknesses in the U.S. system. One is that the patentee is not permitted to maintain sufficient control over samples of deposited cultures. A second is that the U.S. system provides less protection for process inventions than foreign systems, because the U.S. system allows competitors to practice a patented process invention outside the United States (e.g., in a jurisdiction where patent protection may not be available) and import the product into the United States, thereby lowering the value of the U.S. process patent. This may prove to be particularly relevant to the field of biological process inventions, especially those inventions in connection with which the patentee is obliged to provide to competitors with a culture sample. The U.S. process patent holder has a remedy in the form of a proceeding before the U.S. International Trade Commission, but its usefulness has been questioned.

Foreign countries

It would appear that the United Kingdom, the Federal Republic of Germany, Switzerland, France, and Japan have provided adequate incentives under their intellectual property laws for development of biotechnology. All provide reasonably broad definitions of patentable subject matter, and most protect plant varieties, even though these are generally excluded from patent protection. Animal husbandry does not enjoy such widespread possibilities for protection. Trade secrets are adequately protected.

Some disadvantages or disincentives for the development of biotechnology can be seen in the rigid manner in which many of these countries approach the subjects of disclosure requirements, reproducibility, and culture deposits. In Switzerland and, to a large extent in the Federal Republic of Germany, micro-organisms per se are not protectable. This may not be a serious problem, at least not at this stage of the technology, in view of the other ways in which an invention can be claimed (e.g., as a process using the micro-organism). The practice in Europe and Japan of requiring access to deposited cultures upon the publication of unexamined applications can be viewed as a disincentive, and it may foster a greater reliance on trade secret protection. This could restrict the flow of information and thereby retard the development of the technology.

Findings

Although there is a large degree of uncertainty in most countries over what kinds of biotechnological inventions can be patented, much of this uncertainty has been resolved in the United States, the United Kingdom, the Federal Republic of Germany, Switzerland, France, and Japan. Of the six countries, the United States has the broadest interpretation of patentable subject matter for biotechnology. The EPC has adopted a broad interpretation of patentable subject matter in the field of microbiology, even though plant and animal varieties are excluded from patentability. This broad interpretation will make it possible to patent under the EPC most of the technology dealing with the techniques of genetic manipulation. The EPC has affected or will ultimately affect the law of the Federal Republic of Germany, the United Kingdom, France, and Switzerland. Switzerland now diverges from EPC practice, however, by not permitting micro-

organisms per se to be patented. A major departure from U.S. law under the EPC and in Japan is the exclusion from patentability of therapeutic and diagnostic methods.

Japan appears to be moving in the direction of providing significant patent protection for biotechnology products and processes. One possible obstacle, however, is that Japan has strict health and safety guidelines regarding genetic research, which may bar patenting of genetically manipulated organisms viewed as hazardous.

The concept of utility in the patent laws of most foreign countries is based on industrial (including agriculture) applicability, which differs in interpretation from the utility standard in the United States. In countries with the former concept, including the five foreign countries discussed in this chapter, even products and processes of scientific research satisfy the utility requirement, as long as the basic endeavor falls into the broad category of industry; however, therapeutic and diagnostic methods do not. In the United States, certain chemical products and processes of research interest only are considered not to satisfy the utility requirement. The fact that utility under U.S. law includes utility in the therapeutic and diagnostic fields, however, helps U.S. competitiveness in biotechnology.

The four European countries studied here have an absolute novelty standard, with no grace period for either oral or written disclosures of an invention by the inventor before the date he or she files an initial patent application covering the invention. The United States has a 1-year grace period, and Japan has a limited 6-month grace period for presenting scientific papers before filing a patent application. In all of the countries, the novelty defeating disclosure must be enabling. Thus, the notion that *any* disclosure before filing a patent application will bar patentability is incorrect.

Most countries have a disclosure standard for inventions based on the concept of enablement. This standard typically includes an aspect of reproducibility, i.e., an invention must be repeatable with a fair degree of certainty and the results must not be merely randomly achievable. Particular problems in satisfying the disclosure standard have been encountered up until now in connection with many biological inventions. This situation has led to the practice of requiring a culture deposit of new micro-organisms used to carry out an invention or forming the subject matter of the invention. The Federal Republic of Germany has refused to grant patent protection on micro-organisms themselves in those cases where disclosure of a reproducible method for producing the micro-organism cannot be given apart from a culture of the micro-organism itself.

In those countries that publish unexamined patent applications (all but the United States and Switzerland of the six competitor countries), a serious problem for owners of biological inventions is the fact that deposited cultures can become publicly available before any patent rights are granted. Although the access to deposited cultures usually is granted with some safeguards in the form of assurances given by the recipient, these safeguards often do not adequately protect the valid interests of the technology owner (e.g., they usually are not geographically limited or do not restrict the activities of the recipient to only experimental use). In fact, it may be desirable to have some restrictions on access even after the patent grant, in view of the fact that the patentee must furnish a "working model" of the invention, which patentees in other fields are not required to do.

Because of the nature of biotechnology, special problems are faced by patentees in the enforcement of their rights. Apart from the general problems of policing for infringement, the possibilities for disguising the use of a biological invention by genetic manipulation will present difficult questions of law and fact. The law and practice of claim interpretation in this field are in their infancy. In the present state of the technology, it is likely that patent-granting authorities generally will limit claims to the specific organisms or parts thereof disclosed in patent applications.

All of the countries studied provide some element of legal protection for trade secrets. Most aspects of biotechnology lend themselves to protection via the trade secret route, and owners of such technology may rely on trade secrets when patent rights are uncertain or when they judge

trade secrecy to be more advantageous in a particular case.

With the major international and national efforts regarding plant variety protection, culminating in the 1978 UPOV treaty, there is a trend toward providing such protection without requiring satisfaction of any enablement standard. The nature of the protection for plant varieties is different from traditional patent protection in that it protects basically against derivation and copying.

The U.S. intellectual property law system appears to offer the best protection for biotechnology of any system in the world. In general, it appears that the United States offers protection for broadest scope of biological subject matter, especially because of the 1980 ruling by the U.S. Supreme Court in the *Diamond* v. *Chakrabarty* case (21) that the inventor of a micro-organism could not be denied a patent solely because the invention was alive. The United States also offers some of the best procedural safeguards for inventors, including the 1-year grace period and no publication of the patent application before patent grant. In addition, the United States offers a choice of protection to plant breeders. Finally, the trade secrecy protection offered in the United States is as good as that offered in most countries, with the exception of the Federal Republic of Germany and Switzerland.

Issue and options

ISSUE: How could Congress improve U.S. competitiveness in biotechnology by strengthening U.S. intellectual property law?

Option 1: Pass a statute specifically covering living organisms and related biological inventions.

The advent of the new biotechnology has raised questions in the United States regarding what inventions will be patentable, under what conditions, and what the scope of protection will be. Although the *Diamond* v. *Chakrabarty* case in 1980 answered in the affirmative the basic question of whether living organisms would be patentable, other questions remain.

A statute specifically covering living organisms and related materials could help resolve this uncertainty. Greater certainty would allow companies to plan their R&D and marketing strategies better and in some cases would lower the financial risks involved. The result should be increased innovation. The alternative is to rely on case-by-case developments in the U.S. Patent and Trademark Office and the courts. Patent litigation is extremely expensive and may be unaffordable for small, new biotechnology firms.

Another argument in favor of a special statute is that it could help patentees to secure better ownership rights in biological inventions. The existing U.S. patent law was developed primarily for inanimate objects and processes. Living organisms are fundamentally different. Unlike a machine, a living organism reproduces itself and occasionally mutates during its lifetime. Furthermore, a living organism is extraordinarily more complex than any machine. Although the inventor of the most complex machine knows all of its parts and understands completely how it functions, no one knows all of the components of the simplest micro-organism or understands completely how it functions. Finally, many biochemical pathways in an organism are not unique to that organism; because there are many different ways to produce a product, a patent on one of the ways may provide only limited protection. In the case of biological inventions, therefore, there may be problems in meeting the enablement and written description requirements, in securing an adequate scope of protection for inventions, and in policing for infringement.

The complexity of living inventions will make it difficult to fully describe them. Although depositing a micro-organism in a culture collection may circumvent these difficulties with regard to enablement, it may be of little help in establishing novelty and the bounds of patent protection. Mi-

crobial taxonomy is an imprecise art. Micro-organisms have different characteristics in different environments, and taxonomists often disagree on their classification and description. Thus, it may be impossible to distinguish sufficiently a micro-organism for patent law purposes from similar ones created by other inventors or from ones existing in nature.

The fact that organisms reproduce may require a change in the definition of infringement. The law currently defines infringement as the unauthorized making, using, or selling of the patented invention. If someone took a patented organism from a public depository, reproduced it, and gave it away to many users, would this be infringement? One could argue that the person did not "make" the invention.

The fact that organisms mutate may cause problems with respect to the scope of the claims and infringement. For example, if a patented organism subsequently mutated, it might no longer be within the scope of the claims. Also, if the deposited organism is the standard against which infringement is measured, a patent holder may have difficulty enforcing the patent if the organism mutated after it had been deposited. On the other hand, culture deposits generally are preserved by freezing, so mutations may not be much of a problem.

Finally, there is the problem of adequately protecting a product that can be made many different ways, only some of which may be known at the time the patent application is filed. For example, because of the degeneracy of the genetic code, a particular protein can be made by various base sequences. Claiming a particular sequence will provide insufficient protection, and claiming the protein will not help if the protein is not novel. Claiming the novel organism is one solution, but others can easily construct different organisms to produce the same product.

These problems have been addressed in PVPA (and to a lesser extent in the Plant Patent Act), which could be used as a model. For a plant variety to be protected under PVPA, for example, it must be distinct, uniform, and stable. The definitions of these terms embody the concept that it is necessary only to know the important characteristics of a new plant variety in order to distinguish it from others and that only these characteristics need to be stable through succeeding generations. In addition, PVPA defines infringement to include unauthorized reproduction. If this approach were taken, the plant acts could be subsumed in the new statute.

There are several arguments against this option. First, any new technology raises questions about the scope and nature of patent protection, and many of these will only be able to be resolved on a case-by-case basis rather than by statute. Second, most patent attorneys argue that the patent laws are flexible enough to accommodate any new technology, including biotechnology. Third, despite the possible limitations in applying the patent law to living organisms, utility patents actually may provide the patentee with the greatest degree of protection when compared to the protection provided by a statute like PVPA. One of the principal reasons is that a multiplicity of claims is permitted for utility patents, which could cover components of organisms, whereas just the plant itself (and its seeds) is covered by a plant variety protection certificate. Fourth, many experts would argue that since the *Chakrabarty* case resolved the fundamental issue—the patentability of living organisms—there is no need to undertake the major effort needed to pass legislation to solve more minor problems. In addition, since there is some degree of public sentiment against patenting living organisms, the fundamental issue also would be raised again. Finally, a new statute would create its own new issues and questions of interpretation.

Option 2: Allow patentees to place restrictions on micro-organism cultures supplied to third parties.

U.S. patent law requires complete and enabling disclosure of an invention in order to place it in the public domain. In the case of patented micro-organisms, the patentee is in effect required to turn over more than his or her invention—the micro-organism is virtually a complete "factory" ready to begin production. For this reason, inventors may be more inclined to rely on trade secrets than on patents, and the public will not gain the benefits of the new knowledge

embodied in their inventions. This problem is even greater for process patents involving micro-organisms, which are difficult to police. Reasonable restrictions on micro-organism cultures supplied to third parties, designed not to prevent public access to the culture deposits but to prevent patent infringement, would be consistent with the aims of the U.S. patent system. For example, restrictions might be placed on how the organism is used and subsequent transfers of the organism. The other countries surveyed, particularly the Federal Republic of Germany permit certain restrictions on culture deposits.

A drawback to the option might be that the restrictions could hinder the dissemination of information, one of the fundamental goals of the patent law. However, those who support such restrictions argue that they can be devised so as not to hinder the dissemination of information yet prevent infringement, another important goal of the law.

Option 3: Amend section 271 of Title 35 of the United States Code to define as infringement the importation of a product made outside the United States by a process patented in the United States without the authorization of the patent owner.

The four Western European countries and Japan grant extraterritorial effect to their process patents in the way that is envisioned by this option. Although U.S. law provides a different remedy to the situation—an action for unfair competition before the International Trade Commission—many attorneys believe this remedy leaves much to be desired. This option would strengthen the patent system by providing an additional way for patentees to protect their rights. Although the effect of this option would not be limited to biotechnology, it would be important to this technology because of the ease with which micro-organisms used in patented processes can be acquired and used by overseas competitors. Many companies using biotechnology and their patent attorneys see this option as a potentially important part of their program to protect the results of their R&D efforts.

A bill to implement this option (H.R. 3577) was introduced on July 14, 1983.

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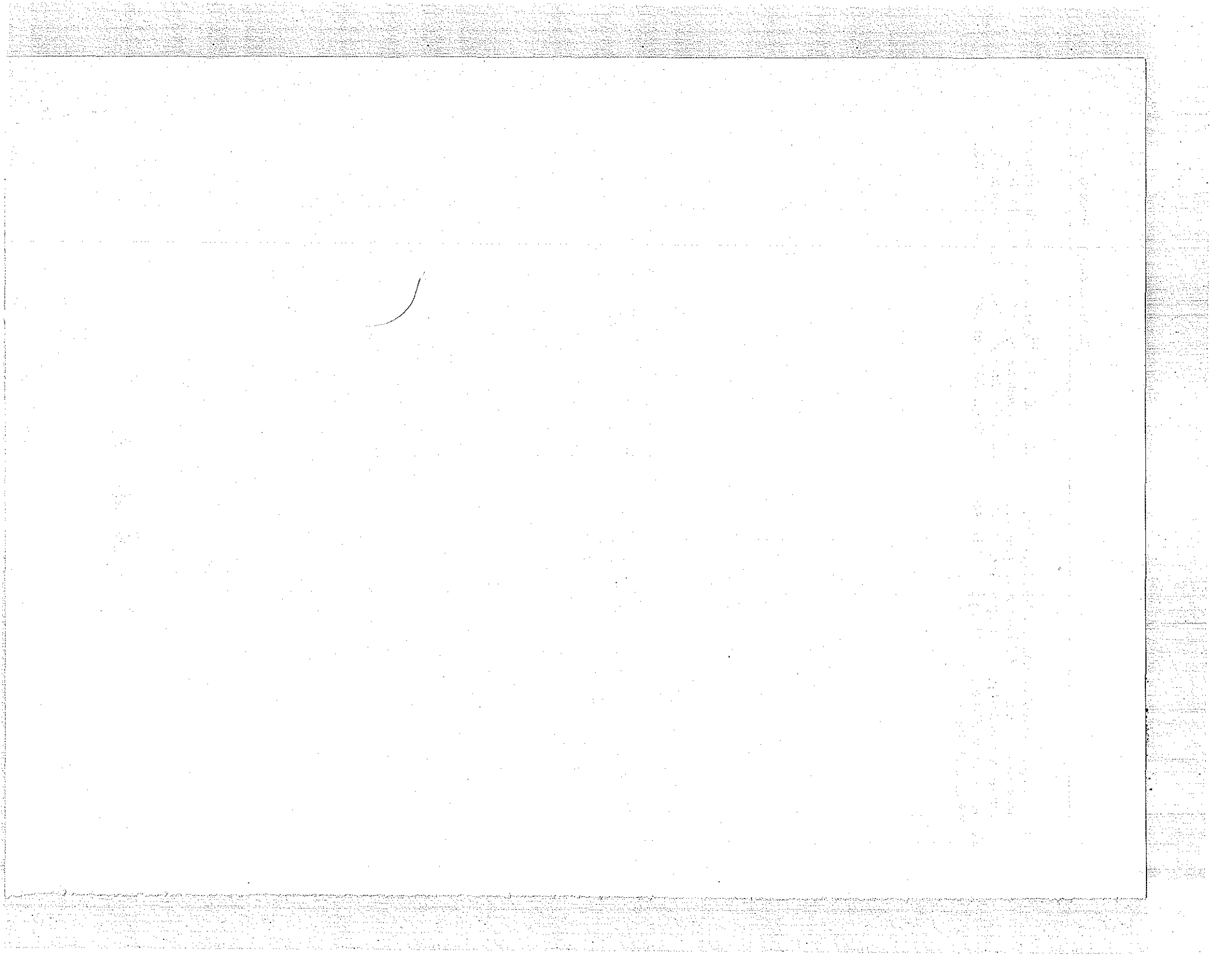

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Introduction

The recent spectacular advances in molecular biology in the United States have arisen from basic research, most of which is federally funded and carried out in university laboratories. Led by the promise of biotechnology's commercial potential and the need for technical expertise, U.S. and foreign companies have been developing closer ties with universities, thus intensifying the process of university/industry technology transfer. At least in the United States, concerns have been raised about industrial sponsorship of university research (1,4,8,13,25,26). Some of these concerns are actually not new. What is new is that biology, rather than chemistry or engineering, is suddenly commercially promising.

This chapter focuses on university/industry relationships as a factor influencing the competitive position of the United States vis-a-vis other countries in the commercialization of biotechnology. Issues in university/industry relationships are not confined to relationships in biotechnology, so the chapter also includes some discussion of broader university/industry issues that have implications for competitiveness in biotechnology. The resolution of issues in U.S. university/industry relationships in biotechnology is extremely important, because the manner in which these issues are resolved will help determine the pattern of basic and applied research in the field for the next decade or so. Furthermore, research is likely to be critical to the development of biotechnology for some time.

Closer ties between universities and industry can be advantageous to the institutions involved and are important for the national innovative process. Industrial research questions can enrich the university research process, and there are financial benefits from increased industrial funding of university research. Industrial support of university research and development (R&D) in the United States currently represents about 6 to 7 percent of the total research budget of universities, although the percentage of industrial funding in some departments of universities may be much higher or lower (19). It is unlikely that industrial support will ever equal Federal support of university research, but increases in industrial funding could have significant effects on the types of research performed, especially in high-technology areas such as biotechnology.

American universities can expect some financial benefit from royalties derived from the licensing of patents, although it is unlikely that royalty income will ever be a significant portion of support. The Wisconsin Alumni Research Foundation (WARF), for example, has been instrumental in generating royalty income for the University of Wisconsin. It should be noted, however, that 39 of the 58 income-producing inventions assigned to WARF since 1925 have earned less than $100,000, and only 7 have earned more than $1 million (3,9). As shown in table 66, royalty income as a proportion of total Federal support is far less at nine other leading research universities in the United States than at the University of Wisconsin. If Public Law 96-517, the 1980 law that allows universities and small businesses to retain patent rights for federally funded research, encourages the development and marketing of products, U.S. universities' royalty income may increase. Stanford University and the University of California at Berkeley have already benefited from royalties (approximately $2 million) for the Cohen-Boyer patent for the basic recombinant DNA (rDNA) process. However, university income from biotechnology may be more dependent on whether the firms developing and marketing biotechnological products or processes rely primarily on patents or on in-house research.* If the more usual operating mode becomes in-house industrial research, then royalty income to universities may not be significant.

*The advantages and disadvantages of relying on patents or trade secrets to protect intellectual property are discussed in *Chapter 16: Intellectual Property Law*.

Table 66.—License and Patent Activity at 10 Leading U.S. Research Institutions

Institution	Fiscal year 1980 Federal R&D support		Type of activity	Current annual number of disclosures	Current annual royalty income (thousands of dollars)
	Total ($000)	Life sciences ($000)			
1. Johns Hopkins	$239,869	$60,275	Licensing program	20	$ 90
2. MIT	141,011	24,200	Licensing program	164	1,500
3. Stanford University	104,011	43,712	Licensing program	140	2,500
4. University of Washington	100,567	54,968	Research foundation	28	120
5. University of California, San Diego	90,703	37,327	Licensing program[a]	320[a]	1,700[a]
6. University of California Los Angeles	87,073	52,606	Licensing program[a]		
7. Harvard University	83,997	53,962	Licensing program	60	50
8. Columbia University	81,361	49,383	—	20	Minimal
9. University of Wisconsin	80,460	43,342	Research foundation	75	6,000 (with investment income)[b]
10. Cornell University	74,761	37,900	Research foundation	50	1,300

[a]University of California system.
[b]Investment income is the substantial portion.

SOURCE: G. S. Omenn, "University-Corporate Relations in Science and Technology: An Analysis of Specific Models," *Partners in the Research Enterprise*, T. W. Langfitt, S. Hackney, A. P. Fishman, et al. (eds.) (Philadelphia: University of Pennsylvania Press, 1983).

There are potential disadvantages to closer university/industry relationships, but some problems can be avoided if participants are aware of potential difficulties and adequate safeguards are in place. One potential disadvantage of closer relationships might be a tendency to increased secrecy on the part of university faculty; it should be noted, however, that some secrecy has always existed when a particular faculty member is close to a new discovery. A second potential disadvantage is the danger that basic research in universities will be directed toward profitable lines of inquiry instead of toward interesting questions raised by past or recent findings. This might occur if there were a precipitous decline in Federal support for research in universities and universities had to turn increasingly to industry for financial support. A third potential problem is that some universities might be associated with products and processes linking them to lawsuits for damages, causing subsequent impairment of the universities' impartiality and credibility. Finally, there is the danger that universities that traditionally have competed for the best faculty might compete instead for the most lucrative industrial contracts.

In general, the purposes of universities in the United States are education, the conservation of knowledge, and the pursuit of unrestricted knowledge. The ends of a university and its faculty are pursued in a relatively open environment that allows the exchange of ideas and unrestricted publication of research findings. This does not mean that there is no competition among scholars, nor is it to deny that secrecy can accompany the desire to be first to announce a discovery (31). Similarly, it does not mean that the pursuit of knowledge for its own sake cannot be diverted by the funds currently available for particular kinds of endeavors (e.g., a "war on cancer" or secret government research). Generally, however, the pursuit by universities of the principles of openness, aided by generous Federal funding for basic research, has enabled the United States to build the greatest research capability in the world.

In contrast to the purposes of universities, the goal of industry is to make a profit, and the mode of achieving this goal is competition. Industry is output oriented, i.e., industry aspires to the efficient production of goods and services. When a company pays for research, it may expect ownership of the results long enough to justify the investment to bring the product to market. In an industrial setting, there is less willingness than there is in a university setting to share research materials; such materials are often kept as trade secrets. The reason for greater secrecy in industry is that development of a product is often risky, costly, and fraught with many obstacles along the route to success. Although the costs of develop-

ing and marketing a product vary among industries and products, the development of a pharmaceutical product in the United States can cost from $50 million to $75 million, with no guarantee of profit (27). Thus, in industry, achieving a competitive edge in a market necessitates guarding communication and intellectual property, an operating mode quite opposite from that of universities (6,13).

Industries and universities undertake partnerships in biotechnology for a variety of reasons, ranging from the desire by industry to gain access to new technology, to gain a lead time in basic knowledge, or to obtain trained personnel, to the need by universities to fill shortfalls in funding. Ultimately, it is hoped, the effect of the partnerships in the United States will be to facilitate and speed up the process of domestic technology transfer, since this is critical to the maintenance of a competitive position by the United States. Examining U.S. university/industry relationships in biotechnology is necessary in order to gain insight into the process of technology transfer and to determine if technology is being transferred in a spirit of cooperation and without compromising the goals of two very different institutions.

E. David has described the fundamental characteristic of optimal technology transfer between universities and industry as a two-way synergistic process between equal partners (6). Basic research, usually carried out in universities, is essential to the process. It is important to note, however, that basic science itself cannot progress without advances in technology, which often is developed by industry. Just as, for example, Galileo and Newton could not have made their contributions to astronomy without the invention of the telescope, the recent advances in molecular biology could not have been made without advances such as the electron microscope, X-ray crystallography, radioisotope labeling, and chromatography. Thus, universities and industry alike must accept the requirements of the other institution and enter into agreements that maximize the ability of each to maintain its standards and goals.

The effectiveness of university/industry relationships in biotechnology transfer

Since most of the university/industry relationships in biotechnology are new, it is difficult to ascertain how effective the relationships in the United States will be in transferring the technology between universities and industry. An estimate of their effectiveness can be made however, by considering the following questions:

- Why are university/industry relationships in biotechnology being formed?
- Are the relationships working smoothly?
- Has the way research is done in university laboratories or the quality of university research been affected by the relationships?
- Has collaboration among university researchers been affected?
- Has the quality of education been affected?
- Are there lessons to be learned from university/industry relationships in fields such as microelectronics?
- What forms are university/industry relationships in biotechnology taking and what are the associated issues?
- Are university policies with respect to university/industry relationships (e.g., patent and royalty agreements, handling of tangible research property, and conflicts of interest) being formulated?
- What is the likely future of university/industry relationships in biotechnology?
- And finally, how effective is university/industry technology transfer in countries likely to compete with the United States in biotechnology?

At the request of OTA, two contractors interviewed university administrators, faculty, and graduate students (principally in biotechnology) from the University of California, Berkeley, the University of California, San Francisco (UCSF),

Stanford University, Harvard University, Massachusetts Institute of Technology (MIT), and Johns Hopkins University, and representatives from 15 companies (a mix of new biotechnology firms and other companies moving into the biotechnology area) to obtain their opinions. Although this sample was not statistically representative, it included some of the major U.S. companies and research institutions working in biotechnology; thus, the opinions came from individuals active and knowledgeable in the field.

Why are university/industry relationships in biotechnology being formed?

OTA found an almost unanimous consensus among both university and industry representatives in the United States that universities are seeking money from their relationships with industry, motivated in part by a reduction or fear of reduction in Federal funding. Industry representatives believe that universities want to gain more real-world exposure for faculty and students and offer them a look at "economic reality" (18). In addition, some faculty stated that industrial funding requires less administrative work and is longer term than Government-funded renewable grants.

Are the relationships working smoothly?

The perception of most of the respondents in OTA's survey is that university/industry arrangements in the United States are working well. The initial administration of agreements between universities and industry in the area of biotechnology was inefficient, because new policies were being formulated and new players (biologists, in contrast to engineers or chemists) are now involved in interactions with industry. In addition, some research administrators have had to learn how to administer technology transfer agreements (18). Some individuals have speculated that agreements are working well because there are almost no biotechnology products yet. Disagreements may arise, especially in limited partnerships, when product sales revenues are generated (18).

Has the way university research is done or the quality of university research been affected by the relationships?

Respondents in OTA's survey were asked to consider two potential effects of university/industry relationships on U.S. university research: effects on the way research is done (its focus or methodology) and effects on the quality of the research. Nearly 85 percent of those responding believed that university/industry relationships in biotechnology have had no effect on the way research is done, and virtually all believed there has been no change in the quality of research.

Has collaboration among university researchers been affected by the relationships?

Almost 85 percent of the respondents in OTA's survey who had an opinion about this issue believed that university/industry relationships in biotechnology have had no substantial effect on the exchange of information or the collaboration that has existed among U.S. university researchers. Most respondents believed that there is only limited collaboration in rapidly evolving areas of science anyway and that levels of communication vary among faculty. Industry representatives commented that faculty having consulting arrangements should keep proprietary information confidential (18).

Has the quality of education students receive been adversely affected by the relationships?

Slightly more than half of those who responded to this question said there has been no change in the quality of education students receive. The others said that if there has been any effect, it has been to enhance the quality. Two forces will probably keep the quality of education at American universities unaffected by university/industry relationships in biotechnology. First, the goal of the faculty and university administrators to protect and maintain standards of academic excel-

lence will continue to influence the arrangements that universities make with industry. Second, students themselves can be expected to monitor the situation and act to prevent any deterioration in the quality of education they receive. Some students have encountered problems at the University of California, Davis and Stanford University campuses, for example, and seminars and meetings have been held to address them. Faculty and university administrators have been involved in efforts to address the problems and to ensure that students' education is not compromised.

Are there lessons to be learned from university/industry relationships in fields such as microelectronics?

The development of the U.S. semiconductor industry is often suggested as a comparison for the development of biotechnology (see *Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology*). Virtually all of the basic research in electronic engineering carried out by U.S. universities during the 1950's and 1960's was supported by the Federal Government. In addition, however, a specific program in electronics research was funded by the Joint Services of the U.S. Department of Defense (DOD). DOD's program had four specific aims:

- extending basic knowledge in electronics;
- strengthening the scientific qualifications of electrical engineering faculty;
- training students to enter research positions at industrial, government, and university laboratories; and
- developing new ideas that could be exploited in the development of new systems and devices in applied research and development labs.

Because of the infusion of capital from DOD's program, there developed at U.S. universities a research and training infrastructure that facilitated the growth of the U.S. semiconductor industry. From the mid-1950's on, this infrastructure generated increasingly open cooperative ties between university electrical engineering departments and private companies. By 1961, nearly half of the 400 graduate students in Stanford's electronics program were employees of local industry who attended Stanford on a part-time basis and whose education was paid for by private company contributions. Moreover, members of Stanford's electrical engineering faculty sat as directors on the boards of 13 corporations (including one board chairman and one half-time company president). Nearly all of the 30-odd electrical engineering faculty members spent one-half to 1 day per week consulting for private industry. Moreover, four or five faculty members were virtual millionaires as a result of equity participation in companies with which they were associated as either board members or consultants. During the intensifying Cold War atmosphere surrounding the launching of Sputnik in the late 1950's, most individuals in academia, government, or industry were not troubled by these overt cooperative ties between the semiconductor industry and university electrical engineering departments. Neither the quality of the education nor academic freedom appeared to suffer substantially; in fact, all were probably enhanced (2).

The impact of Federal research funding at universities during the 1950's and 1960's thus had intended and unintended effects. Federal moneys purposefully developed the research and training infrastructure at universities necessary to feed industrial growth, and, in turn, laid the basis for widespread but largely unintended collaborative ties between American universities and the U.S. semiconductor industry. Major universities seized on Federal funds to become the concentrated locational foci for the rapid growth of the dynamic, new U.S. semiconductor industry. However, few semiconductor innovations emerged directly from federally funded university research.

The potential industrial applications of biotechnology, by contrast, have emerged directly from publicly funded academic biomedical research. As biotechnology has been moving to the market, universities have been buffers in commercializing the fruits of public funding, because they are virtually the *sole source* of basic know-how. Many of the new firms in the field of biotechnology have sprung out of academia, whereas in the semiconductor field, ample DOD procurement helped to create *industrial* know-how and encouraged *industrial* spinoff. In the area of biotech-

nology, the traditionally distinct roles of the university as source of research and training and of industry as source of commercialization are blurred. Though the consulting arrangements, equity arrangements, and research contracts between U.S. universities and industry in the field of biotechnology resemble in form the cooperative ties that emerged between U.S. universities and industry in the field of semiconductors, their timing, substance, and scale are significantly different (2).

What forms are university/industry relationships in biotechnology taking and what are the associated issues?

The major issues in university/industry relationships, though derived in part from the differences between the two institutions, are also set in a context of broader social and economic issues. Thus, the discussion of types of university/industry arrangements below is set in this context of broader issues. First a caveat: industry and universities are not monolithic institutions. The variability within each of these two institutions is as least as great as, if not greater than, the variability between them. This diversity is essential to the health of both and must be borne in mind in any discussion of university/industry arrangements, because no two arrangements are identical.

In the following discussion, five broad types of university/industry arrangements in biotechnology are considered:

- consulting arrangements,
- industrial associates programs,
- research contracts,
- research partnerships, and
- private corporations.

Additional information about specific university/industry relationships in biotechnology is presented in *Appendix H: Selected Aspects of U.S. University/Industry Relationships in Biotechnology*.

By far the most common form of interaction is personal interaction among scientists. Personal interactions can include consulting arrangements, personnel and publication exchanges, seminars, and speaker programs. Issues arise most often with regard to consulting arrangements.

CONSULTING ARRANGEMENTS

Consulting is important for several reasons. It allows direct technology transfer between universities and industry that goes in both directions. Academicians agree that consulting keeps them apprised of new innovations in industrial R&D and that their knowledge can be applied to new kinds of problems related to, but outside of, their on-campus research. University faculty who consult publish more than faculty who do not consult (this may be a chicken and egg situation); they also do more research and participate as actively in their administrative duties as faculty who do not consult (17). Furthermore, consulting plays a significant role in faculty salary supplementation: 44 percent of calendar year faculty at doctoral granting institutions in the United States report that consulting is their first or second largest source of supplemental income (17). Consulting relationships have led to longer term industrial support of U.S. university research such as that provided by Monsanto to Washington University (see below) and Harvard and that provided by Exxon to MIT.

Industry views consulting arrangements with university faculty essentially as having an expert on retainer. Most U.S. universities have policies on consulting, but the policies vary. Some examples of university policies on consulting are presented in appendix H.

University consulting policies typically have provisions regarding conflict of interest, time regulation, disclosure, and policy enforcement. In most cases, policy enforcement is based on an honor system; each faculty member who consults is personally responsible for adhering to this. Although some faculty members may not always observe the rules, with incentives to carry on good research, train graduate students, and publish findings, most university faculty are not motivated to pursue consulting activities to the point where conflicts of interest occur on a regular basis. Disclosure policies are of interest for public access to objective scientific information. An argument could be made that because the public has sup-

ported research in universities, it has a right to know whether a particular university faculty member who is giving testimony, for example, has a consulting relationship with a company that manufactures a particular potentially harmful chemical. The negative side of disclosure policies is that "objective" information may be judged "subjective" because of guilt by association. If a faculty member's consulting arrangement with industry is declared openly, it is not necessarily the case that his or her testimony is biased. In fact, the expert may have a more objective view because he or she understands both the research and development aspects of the technology.

INDUSTRIAL ASSOCIATES PROGRAMS

Industrial associates programs usually involve entire university departments or groups of specialists within a department. Companies pay a set annual fee that allows them to participate in seminars, interact with graduate students and faculty, and preview publications.

Industrial associates programs allow university/industry contacts and at the same time avoid conflict of interest problems and patent agreements. These programs exist at several U.S. universities, and some ongoing programs now include biotechnology. At MIT, for example, the Industrial Liaison Program has begun to include biotechnology as a subject of its symposia and seminar series. One of Stanford's 19 industrial affiliates programs is a program in biochemistry. And Pennsylvania State University has just initiated a Cooperative Program in Recombinant DNA Technology.

Industrial associates programs facilitate technology transfer between universities and industry, open up opportunities for further consulting and contract arrangements, provide funding for graduate students and faculty research, and give industry access to graduate students for future employment. Industrialists generally view these programs as useful. However, some industrialists believe that a few university programs tend to give the impression that research results are being sold to members only. Exclusivity is not the purpose of these programs; rather, their purposes are support of research activities and continuing open lines of communication of research results.

RESEARCH CONTRACTS

University research contracts with industrial sponsors have been and continue to be an important type of university/industry relationship in biotechnology. Research contracts differ from consulting arrangements in that the industrial sponsor is usually paying for a specific piece of research or supporting general research activities. Contractual arrangements often grow out of consulting or industrial associates programs and are usually motivated by industry's need for research that complements research being done in-house or for some expertise in a new area.

Several of the university research contracts with industrial sponsors in biotechnology have been large and have elicited questions regarding issues such as commingling of funds, patent rights, and disclosure of equity or other financial arrangements between the industrial sponsor and the principal investigator. The larger agreements have received extensive press coverage.

Issues of conflict of interest, invention rights, commingling of funds, and university policies regarding the processing of contractual arrangements are all important. It is interesting to note that MIT, which traditionally has had a close relationship with industry and has a relatively larger (7 percent) share of industrial sponsorship than other American universities, has the most explicit guidelines for consulting, disclosure, and processing of industry-sponsored contracts. Other universities, notably, Johns Hopkins, Harvard, and the University of California, are moving toward more explicitly stated policies. See appendix H for descriptions of selected university policies on sponsored research and patents.

RESEARCH PARTNERSHIPS

Another type of university/industry arrangement taking place in biotechnology is the joint establishment of a research foundation, institute, or long-term collaborative arrangement by an industrial sponsor and a university. Three recent ones, further described in appendix H, are well known: the Hoechst/Massachussetts General Hospital agreement, the Monsanto/Washington Uni-

versity agreement, and the Whitehead Institute/MIT agreement. These arrangements raise several issues, some of which are pertinent to only one or two of them, others to all three.

The agreement between the West German company Hoechst and Massachusetts General Hospital, for example, raises the issue of foreign investment in and foreign benefit from U.S. Government-funded research. This agreement also raised the issue of commingling of funds (see below). For both the Hoechst and Whitehead Institute agreements, faculty selection is an issue because of the need for balance in subdisciplines in biology in Massachusetts General Hospital's medical school and MIT's biology department, respectively. Other issues raised by these agreements are external peer review of projects and controls on rights to publish. Another issue is the terms of termination of the agreements and whether adequate notification provisions have been made for the university to seek other support.

In the Hoechst/Massachusetts General Hospital agreement, the company will pay for all equipment and other expenses in order to ensure that there will be no Federal support of the research. Questions will arise if faculty cooperate with other researchers who are funded, for example, by the National Institutes of Health. Provisions have been made in both the Hoechst and Whitehead agreements to separate faculty selection and consulting. Choice of directions of research is the responsibility of the Whitehead Institute's directors and scientific board, all of whom have high academic reputations. Provisions for termination of the agreements vary, but they have been clearly stated.

Several States have established institutes for biotechnology development that encourage interactions between industry and universities. The North Carolina Biotechnology Center and the Molecular Biology Institute in Michigan have already been established; other States are in the process of establishing such centers.*

*For a list of State government initiatives for high-technology industrial development, see *Technology, Innovation, and Regional Economic Development: Census of State Government Initiatives for High-Technology Industrial Development—Background Paper (28).*

PRIVATE CORPORATIONS

Innovative approaches to connecting university research to commercial developments in biotechnology are being initiated. The establishment of Engenics (with Stanford and the University of California, Berkeley) and the establishment of Neogen (with Michigan State) are examples of two different approaches. For descriptions of these arrangements, see appendix H.

The Engenics arrangement is funded by six corporations, with money flowing through the simultaneously established nonprofit Center for Biotechnology at Stanford. The Center for Biotechnology funds contract research on the campuses of the University of California, Berkeley, and Stanford (and also funds one contract at MIT) and will funnel royalty income back into the university to fund more research. Neogen was established to utilize limited partnerships and tax benefits as a vehicle to allow Michigan State University faculty to remain on campus and simultaneously allow entreprenurial ideas to flourish. Neogen's royalties are funneled back to the university through the nonprofit Michigan State University Foundation.

It is too early to evaluate the Engenics and Neogen arrangements. It should be noted, however, that potential challenges could arise with respect to adequate mechanisms for peer review of projects, applied research being done on campus, conflicts of interest of professors, and a private company doing the same type of work as is being done on campus with the on campus principal investigator having ties (equity, consulting, board membership) to the company.

Are university policies with respect to university/industry relationships being formulated?

The control of intellectual property, commingling of funds, tangible research property, and conflicts of interest are issues that cut across all university/industry arrangements and ultimately affect technology transfer and the U.S. competitive position in biotechnology. University policies with respect to these issues are addressed in the discussion that follows, and additional in-

formation about university policies is presented in appendix H.

INTELLECTUAL PROPERTY

Different traditions have developed in the United States to deal with different kinds of property. Although some U.S. universities allow the faculty member who developed the invention to retain any patent rights, most require those rights to be transferred to the institution. Created works are subject to copyright laws. Most institutions assert that ownership, but universities do not assert rights to books written by faculty (14).

Patents.—Issues relating to patent agreements can be divided into two kinds: those dealing with retention of rights to an invention and those dealing with decisions regarding exclusive or nonexclusive licenses.

The rights of small businesses, universities, and other nonprofit organizations to inventions made under research sponsored by the U.S. Government are addressed in the 1980 U.S. patent law, Public Law 96-517. An Office of Management and Budget (OMB) circular, Circular A-124, "establishes a standard Patent Rights clause to be included in all Government grants and contracts with such organizations, which gives these inventing organizations the right to retain title to the inventions. The Circular also requires agencies to modify existing regulations to bring them into conformity with the Circular" (7). Public Law 96-517 was passed with the recognition that the public interest can in most instances be promoted by allowing exclusive licenses under those circumstances. In a competitive economy, private enterprise will not invest funds to develop ideas that can be duplicated with impunity. Without exclusive licenses, important investigations made at Government expense would remain undeveloped because development costs are high. Thus, these inventions would never be available to the public (10).

The consensus expressed in recently developed university guidelines for industrial sponsorship of academic research is that granting of exclusive or nonexclusive licenses will be on a case-by-case basis to the corporate sponsors of research. Summaries of State Agricultural Experiment Stations (SAES) and Pajaro Dunes Conference guidelines are presented in appendix H. In some cases, an exclusive license is given to allow time for development of the product. There is a division of opinion on whether exclusive licenses should be granted on all discoveries that result from university research funded by an industrial sponsor: some university representatives believe that an exclusive license should be granted, while others believe that the university should provide a nonexclusive royalty free license (see Pajaro Dunes Conference guidelines in appendix H). Most agree, however, that if a faculty member's research is being sponsored by a company in which the faculty member has substantial interest and/or equity, the university should grant only a nonexclusive license. In most of the major multimillion dollar university/industry agreements being struck in biotechnology, the corporate sponsor is receiving some exclusive rights to inventions developed as a result of the funding. In all arrangements between industry and universities, it is essential that the patent issues be carefully thought out in advance.*

COMMINGLING OF FUNDS

Since one of the purposes of the 1980 U.S. patent law (Public Law 96-517) is to foster cooperative research arrangements among Federal Government agencies, universities, and private industry, one question that immediately arises is the potential for commingling of funds. Currently, for agreements struck after 96-517 became law, no exemption for Government de minimus provisions has been made. Where the Government has funded a small percentage—even 1 or 2 percent of direct costs—then the provisions of Public Law 96-517 and OMB Circular A-124 apply.

The Comptroller General of the United States, in his reply to Congressman Albert Gore concerning the possibility for commingling of funds in the Hoechst/Massachusetts General Hospital agreement stated, "MGH must account separately for all expenses leading to an invention, including the cost of research itself as well as indirect or overhead costs, to be able to show that the

*For a discussion of patent issues in such agreements, see P. Hutt, "University/Corporate Research Agreements" (10).

expenses were paid with funds provided by Hoechst" (23). After reviewing the terms of the contract, the Comptroller General ruled that it is possible for Massachusetts General Hospital to separate the funds properly.

TANGIBLE RESEARCH PROPERTY

A basic principle among scientists is that research findings should be communicated promptly to the scientific community by written and oral means. Written and oral processes, however, are not sufficient to disseminate tangible products of research such as the antibody-producing cell lines and plasmids used in biotechnology.

Stanford University developed in March 1982 a specific policy on tangible research property (TRP), defined as "tangible (or corporeal) items produced in the course of research projects," including items such as "biological materials, computer software, computer data bases, circuit diagrams, engineering drawings, integrated circuit chips, prototype devices and equipment, etc." (16). Stanford's policy was promulgated to protect the university's ownership in such property consistent with the policy of promoting the prompt and open exchange of TRP and associated research data with scientific colleagues outside the investigator's immediate laboratory. Controlling the distribution of TRP, subject to provisions of applicable grants or contracts and university policy, is the responsibility of the principal investigator. Such control includes determining if and when distribution of the TRP is to be made beyond the laboratory for others' scientific use.

WARF has developed a confidential disclosure agreement in order to disseminate or license intellectual property, tangible or intangible property, and products arising from work conducted at the University of Wisconsin. In order for the receiver to obtain the materials, the following conditions must be met (3):

- The materials will be received and held in confidence by the receiver. Only persons within the receiver's organization and only those essential in the evaluation of the materials will be permitted access to the materials.
- If opinions or services of other persons outside the receiver's organization are needed, then the receiver will notify WARF and the confidential disclosure agreement will be executed with that person.
- The receiver will not commercially utilize the material or any part thereof without written consent of WARF or prior to entering into a licensing arrangement with WARF.

Recently, a dispute over the ownership of a cell line that produces interferon arose between the University of California and the Swiss company Hoffmann-La Roche. The University of California, as the institutional home of the scientists who created the cell line, claimed ownership of the cell line and the right to future royalties. Hoffmann-La Roche also claimed ownership on the grounds that it had funded the university research that increased interferon production by the cell line and filed a patent application covering this interferon production process. Lawyers from the university sued the company, arguing among other things that the firm had made unauthorized use of the material, taking commercial advantage of the open exchange of information and material among academic scientists. This suit was settled out of court, but the settlement has not been made public.

Another recent case has left unresolved the issue of ownership of a cell line (24). H. Hagiwara, a visting Japanese researcher at the University of California, San Diego, took, without permission, a hybridoma fused from cancer cells taken from his mother and used the resulting monoclonal antibodies to treat her for cancer. Although the usefulness of the treatment has not yet been evaluated, the cell line may have commercial potential, so the issue of ownership is important. The University of California sued Hagiwara, stating that, as the research institution, it owned the cell line. This case has been settled with the Hagiwara Institute of Health (Hagiwara's father is the director) obtaining exclusive license in Japan and other Asian countries and the patent rights assigned to the University of California. Some argue that a hybridoma is a newly created entity, so the donor has no rights of ownership; others contend that cell donors should automatically be given a share of any subsequent profits (24).

CONFLICT OF INTEREST

Conflict of interest situations have both financial and intellectual components. A potential con-

flict of interest could arise if a university held equity in a company in which a faculty member of the university also held equity interest as a line officer. This situation arose in a Harvard proposal to establish a firm to commercialize the research of one of its professors. The proposal was subsequently withdrawn, and Harvard President Derek Bok described the potential problems with the arrangement (1):

- The administration could be exposed to disagreements not only with the faculty partners but also with other nonpartner faculty who might also want support.
- Commercial ventures could impose responsibilities on the university it doesn't have when its endowment invests only in shares of many companies.
- Conflicts could arise if the university were associated with particular products and a public that expects high standards from the university were dissatisfied with the standards of marketing or the products.
- The arrangement could inevitably change and confuse the relationship of the university to its professors. A faculty member who joins with the administration in founding a new company is no longer valued merely as a teacher and scholar; he becomes a source of potential income to the institution.
- There could be more doubt concerning decisions made with respect to qualifications for tenure, extra leave, larger laboratory space, more graduate students, salaries, etc.
- Professors might become so involved with the challenges of seeing an enterprise grow and develop that their work commitment to university duties might be diminished. The university would be in a prejudiced position regarding assessment of that person's performance of work since that person's commercial success would be linked to that of the university.
- Participation would increase the risk of secrecy, and the university could have a stake in supporting that secrecy.

A potential conflict of interest and commitment arises when a professor holds equity within a company that engages in the same type of activities as the university. This issue has been raised in the activities of Calgene. The State Agricultural Experiment Station (SAES) at Davis helps develop new varieties of plants for California growers. University of California professors, including Ray Valentine, have part-time employment at the station. Calgene, a company Valentine founded, is undertaking for profit the same kinds of activities as the SAES undertakes for growers. Thus, there is a potential source for conflict and for taking the results of work off campus and marketing them through the company.

University conflict of interest policies and consulting policies vary, but university policies are becoming more explicit, in part because universities are responding to developments in biotechnology. It is interesting to note that MIT, which has traditionally had extensive contacts with industry, has explicit policies on industrially sponsored research. In addition, several organizations are setting guidelines for industrial sponsorship of academic research (see app. H).

At the request of Representative Albert Gore, the American Association of Universities (AAU) reviewed the ethical dilemmas posed by increases in industrial support for research. AAU suggested that it serve as a clearinghouse and monitor activities at the major American universities with regard to the formulation of policies. AAU decided not to develop policies, because "conditions exist [in the universities] for intelligent and thoughtful decisionmaking on these issues and policies that are informed by wide experience and that are tailored to individual circumstances are preferable to injunctions broadly enough cast to cover the multitude of local circumstances that exist among many universities" (15).

Also, representatives from universities, industry, and the legal community are now meeting to review issues and communicate more effectively. Recent meetings have been hosted by Columbia University, the Gulf Universities Research Consortium, the Industrial Biotechnology Association, Florida State University, Harvard, and the Bar of the City of New York, and a meeting in Philadelphia in December 1982 was hosted by eight major research universities (15).

It is clear that recent activities to formulate explicit policies are advantageous in helping to define the role of the university and ultimately facilitating effective technology transfer between universities and industry. Technology transfer will be most effective if both sides are strong, vibrant, creative, and have something to offer each other.

What is the likely future of university/industry relationships in biotechnology?

A comparison of the responses to OTA's survey of university and industry groups in the United States shows that both groups see the future of university/industry relationships in biotechnology as depending largely on the success of biotechnology companies in getting products into markets. There was divergence of opinion among the respondents, however, on what kind of research assistance—broad basic research or more specialized research—industry would seek from universities. In biotechnology as in other fields, an increase in the actual number of industry/university relationships and an increase in the total amount of funding made available by industry can be expected to develop over the short term (18).

U.S. university/industry relationships in biotechnology will most likely follow the same pattern that they have in other high-technology areas. First, scientific breakthroughs generate a period of hyperactivity in university/industry relationships. This hyperactivity phase is characterized by the promise of "big bucks," which leads to a short-term faculty and post-graduate drain. After the industry goes through its initial phases, an equilibrium state is reached and a fairly healthy symbiotic relationship emerges.

How effective is university/industry technology transfer in countries likely to compete with the United States in biotechnology?

The countries identified in this assessment as being the most likely major competitors of the United States in biotechnology are Japan, the Federal Republic of Germany, United Kingdom, Switzerland, and France.

JAPAN

Japan has a mixed situation with regard to university/industry relationships in biotechnology. First, a distinction should be made between institutions and individuals. At the national universities, which are at the top of the Japanese university hierarchy, institutional ties are very strictly regulated. At the level of individual professors, however, there is considerable opportunity for interaction. A second distinction is between the basic and applied sciences. The distinction and separation of basic and applied science departments at Japanese universities is strong. Japanese professors in disciplines such as biology, biochemistry, and medical science are proud of their independence from industry. Professors in applied disciplines such as bioprocess engineering, on the other hand, have ongoing contacts with industry. Japanese professors in applied science departments are considered to have a moral obligation to place their students as employees. Consequently, they tend to maintain good relationships with industry. Furthermore, because former students are members of industry, informal contacts continue.

Even though Japanese professors in applied sciences have contacts with industry, the level of exchange of information between universities and industry in Japan is not as high as that in the United States. Japanese professors at the national universities are forbidden to take other positions simultaneously with their university work, and all donations toward their research must be made through formal university channels. No fees for consulting can be accepted, and offers of stock options are unheard of. Japanese professors were not allowed to hold patents or collect royalties until 1981. Because of the restrictions on both professors and industry, Japanese professors often quit their posts to work in industry or private laboratories where facilities and salaries are better than in the universities. They do this in spite of the fact that there is a great deal of social prestige attached to being a professor.

There are only two mechanisms through which Japanese industry can channel funds to a university. One of these, the "itakuhi," is commissioned research on a particular topic. The company supplies a researcher and some funds, usually only $500 to $1,000 (¥ 125,000 to ¥ 250,000), to a university professor. This mechanism allows the company to have its researchers trained by the professor and the professor's staff; the professor, in turn, gets extra help in doing his research. The second mechanism, the "shogaku kifukin," is a scholarship grant donated to a specific university researcher but not for a specific topic. The

grant money must be used only for equipment and other direct costs, not personnel costs; no overhead is charged by the university, and there is no limit on the amount. Money for these grants must be channeled through the Ministry of Education. Within this framework, there are a number of administrative obstacles in terms of hierarchy of approvals necessary, different policies on patents among departments, etc. In spite of the tight control of channels of funds and lack of consulting opportunities for Japanese professors, about 10 percent of all university funding for research in Japan does come from industry. Most of this is probably channeled to applied research (22).

The Science and Technology Agency (STA) has established the New Technology Development Fund in order to subsidize Japanese companies that develop and commercialize university research findings. The fund will probably be used to transfer technology between applied science departments and industry, which already have good relations, rather than between basic science departments and industry.

Another STA program is designed to cross traditional barriers between university basic science departments and industry and between the Ministry of Education and the Ministry of International Trade and Industry (MITI). Research responsibilities in STA's program are allocated between university and corporate laboratories. The success of the program will depend in part on getting MITI, the Ministry of Education, and basic research departments to work together. Basic researchers have already asked the Ministry of Education to supervise the project, so there is some doubt as to whether the program will be successful. If supervision stays in Ministry of Education, the link with industry will be weakened.

Research in Government institutes makes up for the lack of technology transfer from the heavily regulated Japanese universities. In almost every major industrial sector in Japan, there are a number of governmental research institutes that do background research for MITI policymakers and where professors, industry representatives, and Government officials meet for discussion. Mitsui Information Development and Normura Research Institute have been used for background research in biotechnology.

In addition, the Japanese Government is building two biotechnology centers, each with a P4-level laboratory facility: one in Tsukuba (a new university research community) and one at Osaka University. The P4 facilities will be available to private sector corporations via contacts with university professors. Four other universities were designated by the Ministry of Education to have P3 level facilities and received $640,000 (¥ 160 million) in fiscal year 1981 to help build them: 1) Tokyo University Medical Research Institute; 2) Kyoto University Chemistry Research Institute; 3) Osaka University Microbial Disease Research Institutes; and 4) Kyushu University Medical Department. These large-scale biotechnology facilities administered by the Japanese Government will provide a place for university professors, Government researchers, and company researchers to work together.

The applied science departments of Japanese universities have been instrumental in Japan in providing training and information exchange in biotechnology. At present, university basic research in Japan is peripheral to Japanese industrial activities. If Japan intends to develop a greater basic research capacity that industry can draw on, funding for basic research will have to be increased and mechanisms to increase communication between researchers and industry will have to be implemented. Japanese companies look to other countries to make up for the weaknesses in the technology transfer from Japanese universities. Whether the Japanese will have a competitive edge in biotechnology will rest, in part, on the differences in industrial relationships in applied and basic research. If biotechnology develops such that most research moves into industry, then the present system will be adaptive. If strong basic research and effective domestic technology transfer by universities is important to the development of biotechnology and if international technology transfer proves ineffective, then the Japanese system will have to change (22).

FEDERAL REPUBLIC OF GERMANY

Biotechnology research in the Federal Republic of Germany is carried out at the federally sup-

ported, private Max Planck institutes as well as in German universities.* Critics have charged that the Max Planck institutes may be depriving the universities of talent by drawing away promising researchers and that they are "ivory towers" conducting research of little relevance to the nation's technological well-being. The Federal Ministry for Research and Technology (BMFT, Bundesministerium für Forschung und Technologie) would like to see closer connections between the Max Planck institutes and industry. One successful outcome of its strategy is the recent cooperative agreement between the Max Planck Institute for Plant Research and Bayer Leverkusen.

The university system is in flux. Beginning in the 1960's, West German universities were subjected to a series of reforms that left the system in turmoil. According to one recent analysis (11):

> The underlying trouble is that West Germany has sought to reconcile several irreconcilables—the principle of open access to any university in the country, the doctrine that all universities are equal, the practice that the universities are run by the ministries of culture in the Länder in which they happen to be sited, and the phenomenal increase in the demand for higher education in the past twenty years.

The result is a university system in which litigation about the rights and duties of students and faculty sometimes seems to take precedence over research and teaching.

A lack of money has recently added to the administrative and legal conflicts created by the West German university reforms. Biotechnology in the universities, both because of financial cutbacks and because it is a new discipline, depends on outside sources of funding. Probably the largest single source of funding is the German Research Society (DFG, Deutsche Forschungsgemeinshaft), a nonprofit institution that serves as a German National Academy of Sciences and as a conduit for Government funding of basic research. The approval by DFG of a "special collaborative project" on bioconversion in Munich will give a boost to academic work in this area.

Other sources of funding for biotechnology in universities include the Fraunhofer-Gesellschaft and the Volkswagen Foundation, as well as private industry. Relations with industry in the past have largely taken the form of contracts or consulting agreements between individual professors and interested firms. Hoechst's arrangement with Massachusetts General Hospital (see app. H), however, has prompted BMFT to seek more systematic university/industry collaborations within West Germany. One product of BMFT's initiatives in this area is an agreement between the German chemical company BASF and the University of Heidelberg whereby the chemical company will give the university $450,000 per year for research over a 5-year period. BASF's commitment is more modest than Hoechst's support for Massachusetts General Hospital. Nevertheless, it marks an important step in the German Government's effort to engage the private sector in building up fundamental research in biotechnology inside Germany.

Among the factors cited to explain West Germany's slow entry into commercial biotechnology is an educational system that prevents the kind of interdisciplinary cooperation that is viewed by most experts as essential to the development of this field. In particular, the traditional separation of technical faculties from their arts and sciences counterparts means that process technicians, usually located in the technical schools, rarely come into contact with colleagues holding university appointments in biochemistry or microbiology.

One of BMFT's professed aims since the adoption of its performance plan for biotechnology has been to bridge this institutional gap.** A significant contribution toward meeting this objective is made by the German Society for Chemical Engineering (DECHEMA, Deutsche Gesellschaft für chemisches Apparatewesen). DECHEMA played a crucial role in the original formulation of BMFT's biotechnology program. Its working group on "technical biochemistry" was charged in 1971 with preparing a study on biotechnology that established the framework for the BMFT program.

*For a description of Federal applied research carried out through the Society for Biotechnological Research, GBF, see *Chapter 13: Government Funding of Basic and Applied Research.*

**BMFT's performance plan, *Leistungsplan: Biotechnologie,* is discussed in *Chapter 20: Targeting Policies in Biotechnology.*

DECHEMA continues to further interdisciplinary exchanges through a variety of means. Its expert group on biotechnology is a standing body that brings academics and industrial scientists into regular contact at seminars on biotechnology for small groups of experts. Attendance at these is by invitation, and one of their functions is to further a fruitful dialog between industry and academia. The confidential character of these meetings permits research scientists to discuss their results at prepublication stages. At the same time, industry representatives can present their own problems with the hope of interesting academic groups in their resolution. Finally, DECHEMA also organizes continuing education courses in various aspects of biotechnology, such as the use of immobilized enzymes or measurement and control of bioreactors (11).

UNITED KINGDOM

A traditional weakness in the United Kingdom has been a gap between university research and industry. This gap in the area of strategic applied research has been termed the "pre-development gap." There is consensus that the National Enterprise Board set up to foster university/industry relationships failed. The National Enterprise Board is now called the British Technology Group (BTG), and measures have been taken to improve its efficiency. Also, new institutions for biotechnology have been developed. Furthermore, direct contacts between British universities and industry have recently increased, in part because of economic conditions.

To stimulate the transfer of university basic science research in health-related fields to industrial applications, the British Government and four industrial partners created a new company, Celltech, Ltd., in 1981. In the original agreement, Celltech received the right of first refusal* on all work in hybridoma technology conducted by the Medical Research Council. Celltech also plans to commercialize the results of basic research in rDNA technology. Currently, the British Government owns 28 percent of the company and private companies hold the other 72 percent. Celltech's initial capitalization was $20 million (£11.4) million). Celltech currently maintains a staff of 130 persons, two-thirds of whom are scientists. It is likely to increase this number to 180 persons in the near future.

In an arrangement similar to that of Celltech, the British Government, through BTG and two private concerns (Ultramar and Advent Eurofund), recently established the company Agricultural Genetics. The objective of this company is to commercialize basic research results in nonconventional plant breeding, microbial resistance factors, and biological control products originating from research in the Agricultural Research Council. Agricultural Genetics has the right of first refusal on all work in the Agricultural Research Council. Though only about $1.2 million (£685,000) has been invested to date, the total initial capital promised approaches $28 million (£ 16 million).

To encourage direct links between academia and manufacturers, the Cooperative Research Grant Scheme has been initiated under the Science and Economic Research Council (SERC). SERC will support the academic side provided that the company in a particular arrangement makes substantial contributions in effort, materials, and expertise. Patent rights, subject to a small royalty, will be assigned to BTG. The number of projects in biotechnology under this scheme increased from 3 to 14 in the last 6 months of 1982.

Industrialists are also beginning to invest in university centers. At the University of Leicester, four companies have put up $1.7 million (£1 million) to establish a new biotechnology center. SERC is granting $316,000 (£180,000) for capital equipment.

Another program has been started by industry to help academics in British universities develop their ideas into commercial realities. At the initiative of Monsanto (U.S.) and including the Universities of Oxford, Cambridge, and St. Andrew, the Imperial College in London, and the Nuffield Foundation, $17.5 million (£10 million) initial capital has been raised (Monsanto contributed half). The program will include most fields of high technology as well as biotechnology.

Imperial College in London, in order to transfer its technology to industry, has launched a private company to exploit the pilot plant built at Imperial

*This is the right to choose whether to produce any good or service without having to bid competitively.

College in the 1960's. The plant is in good condition, but has been underused because of lack of funds. Imperial College has reserved 20 percent of the time of the plant for its own use in lieu of shares. Thus, there will be a continuing contact between research workers, the associated Imperial Biotechnology Center, and industrialists. Imperial Biotechnology's first major contract is with the Swiss firm Biogen S.A. to scale-up the firm's interferon production to 3,000 liters.

Engineers in British universities have traditionally done consulting for industry; biologists in British universities are now adopting the same practice. The extent of this phenomenon is not known, but all the large British companies involved in biotechnology are using the services of consultants in the universities. No general rules apply to consultancies in British universities; arrangements are left to individual institutions and to the consciences of the individuals involved. There is some concern on the part of the British Government, however, that foreign companies are making more use than domestic companies of British biotechnology experts.

Most authorities agree that the United Kingdom has an excellent basic research base with well-trained researchers. Traditionally, however, the United Kingdom has had a problem translating this expertise to industry; the next 5 years will determine how effective the new British measures to effect domestic technology transfer are (30).

SWITZERLAND

The field of molecular biology is highly developed in Swiss universities, particularly in relation to the size of the population. Centers of excellence include the universities of Basel, Geneva, and Zurich. The quality of research in these institutions is all the more remarkable in view of the fact that they are under cantonal jurisdiction and thus derive support primarily from local revenues.

The channels for transfer of knowledge from the Swiss universities to industry appear well established in the area of biotechnology. The president of the Federal Institute of Technology (ETH, Eidgenössiche Technische Hochschule), which established a department of biotechnology in 1976, for example, has endorsed the practice of direct contracts between professors in the biotechnology department and industry. Joint funding by industry and the Commission for the Encouragement of Scientific Research provides another avenue for collaboration with the private sector, one that has been actively utilized by the ETH biotechnology group.

The Swiss firm Biogen S.A. is closely linked to the Swiss university research system and has built an important share of its competitive strength on the productivity of these ties. Two members of the company's scientific board, Drs. Weissmann and Mach, have done seminal work for the company in the Universities of Zurich and Geneva, respectively. Finally, the city of Basel, as the fountainhead of Swiss research in the chemical and biological areas, provides unique opportunities for communication and collaboration between the academic and industrial sectors, a potential that the Basel-based pharmaceutical corporations clearly recognize and are prepared to exploit (12).

FRANCE

Universities in France are generally regarded as teaching institutions and not looked to for their research capabilities. Highly regarded research in France is usually funded by the National Center for Scientific Research (CNRS, Centre National de la Recherche Scientifique) or the National Institute of Health and Medical Research (INSERM, Institut National de la Santé et de la Recherche Médicale). Both of these are Government research institutes (grands organismes). CNRS operates its own laboratories, which are usually associated with universities. INSERM is concerned with the applied aspects of medical research. French universities that are important in biotechnology are those at Toulouse, Strasbourg, Marseille, Lille, Montepellier, Paris-Orsay, Grenoble, and Nancy. A newer university, the Technical University at Compiegne (modeled after the American university structure), which is an important center for enzymology and bioprocess technology, has concentrated on some of the disciplines underlying biotechnology and has developed good relations with industry.

There is divided opinion in France as to whether relationships between academics and industrialists should be encouraged. The December

1980 Pelissolo report concluded that relations formerly were poor; this situation has changed, however, and the problem now is not whether university research results should be transferred to industry, but how best to accomplish the transfer (29).

There are no formal constraints in France on relationships between academics and industrialists. The National Agency for the Funding of Research (ANVAR, L'Agence Nationale de la Valorisation de la Recherche) is an independent organization that stimulates the transfer of public research results to industry and encourages applied research in industry. ANVAR does not have any rights of first refusal on the results of public research, which includes university research, and apparently encourages direct links between universities and industry by offering general advice on suitable contract terms and on patenting problems. Large French companies such as Elf Aquitaine and Rhone Poulenc have organizations to keep in touch with and seek out public sector university research of interest and appear to have no problems developing and maintaining these links (except for occasional conflicts between the firms' desire for secrecy and the researchers' legitimate desire to publish). In addition, some companies are locating their new biotechnology facilities near universities in order to benefit from proximity (e.g., Elf Aquitaine at Toulouse and Transgene at Strasbourg). The University of Compiègne is situated in an agricultural region and works closely with the local foodstuffs industry. Also, according to ANVAR, a phenomenon similar to the involvement of American professors in U.S. venture capital firms is developing in France, although along more traditional lines—top French scientists are either acting as consultants to private firms or leaving the public sector for industry (this kind of transfer is generally much more common in France than in, for example, the United Kingdom (29).

Despite the absence of formal constraints on relationships between academics and industrialists, there remains a problem in France in the exploitation of the results of public sector research by industry. Except for large companies, industry has an insufficient number of qualified personnel to seek out opportunities, and French research scientists as a whole have not been very active in the pursuit of commercial opportunities (29).

The French Government has recently taken steps to encourage cooperation between the grands organismes and French industry. The institutes participated through the Committee for the Organization of Strategic Industries (CODIS, Comité d'Orientation des Industries Stratégiques)* in the establishment of the French pharmaceutical firm, Immunotech. More generally, in the recent law reforming these institutes, there are provisions for them to form profitable liaisons with industry (up until now they have been limited to contract research). This change is very recent, so it is impossible to judge its practical effect. But CNRS, in a change of statutes published on November 25, 1982, has for the first time appointed a scientific director of "Funding and Application of Research."

Fields related to biotechnology have not attracted large numbers of French researchers in the past. Government policies and funding changes have been promulgated to change and to foster university/industry relationships. It is too early to determine the effectiveness of these policies.

*CODIS mobilizes State funds from multiple sources to produce packages for project development in strategic industries.

Findings

The United States has the most effective and dynamic university/industry technology transfer process of the six countries being examined in this assessment. The process in the United States is facilitated by the openness of the university system and the freedom of faculty to pursue research. It is also facilitated by the many mechanisms by which the process can occur. These include dissemination of publications, professional meetings, consulting arrangements, con-

tract research, cooperative research agreements, and institutes within universities funded by industry. All these mechanisms are being exploited in biotechnology. U.S. universities and industry are benefiting from the present arrangements, and diffusion of knowledge is occurring.

University and industry representatives in the United States agree that Federal support of basic research is essential. Even if industrial support of university R&D were to rise to 15 percent of universities' R&D budget, it could never replace Federal funding. Furthermore, since the goals and philosophy of industry are different from those of universities, the focus of research in industry is different from that of research in universities. Of necessity, industry is mission oriented; the emphasis in industry is on applied research leading to products. By contrast, the purpose of university basic research is to extend knowledge itself.

Universities in the United States are formulating and implementing policies that are more consistent across disciplines and more specific with regard to consulting, conflict of interest, and disclosure than policies formulated in the past. There have been some cases of potential conflict of interests with researchers who have consulting or contract arrangements with firms in which they hold equity. University administrators, faculty, and students appear to be taking measures to reduce the potential for conflicts of interest and ensure quality research and education.

Although funding of large agreements between U.S. universities and industry in biotechnology has occurred, the consensus is that, after the initial excitement has dissipated and companies have developed in-house capabilities, most of the university/industry arrangements in biotechnology will be consulting and contract research as in other fields with close university/industry ties.

Universities are looking for financial support, but the promise of patent royalties from biotechnology may be premature. Especially if biotechnology becomes a rapidly moving process field where research is carried out primarily in industry, research in biotechnology will have to move off campus and royalty income to universities may not be significant.

Biotechnology has spawned a new kind of arrangement in university/industry relationships: for-profit companies established with nonprofit buffers to funnel contract research money and royalty payments between the university and the company. One arrangement (Neogen) takes advantage of new U.S. tax laws that permit funding of R&D through limited partnerships. The other (Engenics) is built on the support of six major corporations that are funding the research and have invested in the company. It is too early to predict whether these approaches will be viable.

Biotechnology is being transferred between industry and universities in the United States; most of the arrangements are working well. Some individuals have noted potential problems and administrative bottlenecks; these should lessen as individuals on both sides gain more experience and policies are formulated to standardize administrative procedures within universities. Some individuals believe that problems may arise when sales revenues are generated as a result of some of the limited partnership agreements.

The early history of the U.S. microelectronics industry can serve as a comparison for the commercialization of biotechnology. The U.S. semiconductor industry was fueled by and developed in a milieu of DOD support for basic research and training at universities, DOD procurement of the industry's products, and DOD's need for increasingly more sophisticated products from that industry. In the history of the U.S. semiconductor industry, relationships between universities and industry were very close. Many professors had equity in companies located close to campuses, and consulting was extensive. It appears that education in this field did not suffer; in fact, it was probably enhanced, and students gained an understanding of industrial career paths. The current leveling of Federal support for biology combined with the lack of consensus that biotechnology is a strategic industry (as was microelectronics in the instance of the space race) leads to the perception of more "potential conflicts" in industry/university relations in biotechnology than actually exist.

In countries other than the United States, there are varying degrees of cooperation between uni-

versities and industry. In Japan, the ties between university applied science departments and industry have always been close. Most people acknowledge that Japan already leads the world in bioprocess engineering research, and the close relationships that already exist between Japanese industry and university applied research departments benefit the commercialization of biotechnology in that country. Currently, the Japanese Government is implementing new policies to encourage closer ties between university basic researchers and industry.

In the Federal Republic of Germany, BMFT is encouraging domestic university/industry contacts, especially in light of Hoescht's agreement with Massachusetts General Hospital. After that agreement was announced, some West Germans were concerned because they felt that research money was being funneled into American universities instead of into German universities.

The United Kingdom has an excellent basic research base. University ties with industry have been few in the past, but are now being encouraged by the Government. The British Government helped to establish two firms, Celltech and Agricultural Genetics, to capitalize on British university research in animal and plant molecular biology.

In Switzerland, the field of molecular biology is highly developed, and patterns of interaction between individuals in universities and industry are well established. ETH established a department of biotechnology in 1976 and endorses the practice of direct contracts between professors in the biotechnology department and industry.

In France, an ambitious program is underway to tie universities and industry closer together. One problem in France is that the country lacks a cadre of experts in molecular biology, because this field has not been considered an important one.

Issue

ISSUE 1: Should Congress set guidelines for university policies on industry-sponsored research?

At the request of Representative Albert Gore, the American Association of Universities (AAU) reviewed ethical dilemmas posed in the United States by increases in industrial support of university research. A select committee drawn from the AAU membership suggested that the AAU could serve as a clearinghouse and monitor of activities at major universities with regard to the formulation of university policies on industrially sponsored research. Because one policy formulated by the AAU or Congress would have to be broad enough to cover all circumstances, it might be too general to be useful. Furthermore, as the committee noted, informed decisionmakers within universities are formulating policies that fit each university's needs.

In addition, in a report of joint hearings on university/industry relationships in biotechnology, the Subcommittee on Investigations and Oversight and the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology of the U.S. House of Representatives made the following recommendations: 1) universities should prepare guidelines for industrially sponsored research that require open disclosure of all faculty consulting and contractual agreements; and 2) full-time faculty should be discouraged from holding equity or directing such firms. The subcommittees further recommended that there be continued review by universities, industry, and the Federal Government of the benefits and problems resulting from large-scale corporate support for and involvement in university research programs in biotechnology.

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Chapter 18

Antitrust Law

chapter will examine the current impact of these laws on biotechnology-related R&D and the licensing of the results of that R&D. Finally, the issue of whether congressional action on antitrust law is needed to promote U.S. competitiveness in biotechnology will be addressed.

Antitrust implications of research joint ventures

A joint venture is a form of association between separate business entities that falls short of a formal merger, but that unites certain agreed on resources of each entity for a limited purpose. The form of a joint venture may range from a purely contractual agreement to take joint action, to an agreement where any participant acquires certain assets of another, to the creation of a separate entity in which at least one participant acquires an equity interest. Joint venturers often agree that they will share the management and control of the joint activity's results.

Reasons for entering an R&D joint venture are as varied as the companies and individuals involved. The reasons must be strong enough to overcome the powerful disincentives among individual companies of sharing management and profits. Three reasons stand out in particular:

- *Small firm limitations.* Often small firms have the capability of inventing a process and obtaining a patent but are unable to develop or market the product without the assistance of a larger company.
- *Interdisciplinary technological areas.* Companies of any size may need to draw on expertise outside their own. It may be cheaper and faster to tie up with another company than to develop the new expertise themselves.
- *Economies of scale in R&D.* On certain large and complex technological problems, even large companies may not be able to achieve economies of scale in research if they undertake the R&D themselves.

From the perspective of antitrust policy, the last reason is the most important, since one goal of the antitrust laws is to enhance economic efficiency. In addition, joint ventures could allow certain high-risk, costly R&D to be undertaken that might not be undertaken otherwise by individual firms. Thus, research joint ventures can increase R&D and promote innovation. It is precisely because of these potential benefits to society that the antitrust authorities in both the United States and Europe have set forth official policy statements assuring companies that research joint ventures are viewed very favorably under the antitrust law and rarely raise significant questions.

Despite the general encouraging attitude that antitrust authorities have taken towards joint R&D activity, there are potentially anticompetitive effects of R&D joint ventures. Because R&D joint ventures may involve market-dominating technology, may be conducted by competitors or potential competitors, or may involve restrictive agreements concerning the use of the results, such ventures can give rise to antitrust concerns (36). In its *Antitrust Guide Concerning Research Joint Ventures,* the U.S. Department of Justice identified three kinds of effects on competition (36):

- when the association itself would lessen existing or potential competition between the participating firms,
- when the joint venture agreement or related agreements contain restrictions that restrain competition, and
- when limitations on participation or access to the results of research create or abuse market power.

The first concern is straightforward. When research ventures include most or all of the major competitors in an industry, they could reduce the competitors' separate efforts and thereby reduce innovation. The incentive to finance research and rapidly develop the results is diminished when the participants know that any invention is available for everyone to use. As Assistant Attorney General William Baxter stated, "Rivalry, in short, is important in research as it is in any other commercial activity" (4). There may be cases, however,

where an industrywide effort is clearly the most efficient means to perform the research successfully (36).

In practice, the second antitrust concern is more common. Joint ventures in R&D often contain restrictions on the use of the technology once it is developed. Such restrictions may have anticompetitive effects.

Finally, a joint venture may create an important or even revolutionary new technology that would allow the participants to dominate the market. Such domination could create significant anticompetitive effects. Market domination itself, however, is not necessarily illegal; what is important is how that market power is exercised. In any event, the antitrust law must balance these anticompetitive effects with the reasonable desire of the participants to be rewarded for the risks and costs incurred by entering the joint venture.

Antitrust aspects of technology licensing

An inventor's ability to protect his or her invention long enough to reap sufficient benefits to make the inventor's investment of time and capital worthwhile will have a major impact on the inventor's decision to undertake R&D in the first place. Both the patent laws and laws permitting an inventor to license* a product, process, or discovery serve the social goal of promoting R&D. By protecting the inventor from interlopers who would otherwise benefit at little or no cost from the inventor's labor, ingenuity, or financial investment, these "legal monopolies" help ensure that invention is both encouraged and sufficiently rewarded.

Although they may at times appear to conflict, the U.S. patent laws (see *Chapter 16: Intellectual Property Law*) and the U.S. antitrust laws have virtually identical goals—the fostering of competition and innovation. Competition and innovation improve the allocation of scarce resources so that the maximum type and quantity of goods are produced at the lowest cost. The patent "monopoly," which is expressly recognized by the U.S. Constitution, is essentially a property right—the right to exclude others from making, using, or selling an invention for a limited period of time. A patent may or may not provide an economic monopoly. But even the existence of an economic monopoly based on a lawfully acquired patent is not of concern under the antitrust laws, because a patent is granted to encourage inventions that might not occur if a patent were not available. Inventions benefit the public by creating new products or more efficient means of making old products. Thus, the creation and introduction of inventions is an important form of competition.

The exploitation of the patent right involves its use by the owner or its use by other parties via a licensing agreement whereby these parties pay royalties to the owner. The antitrust laws do limit the exploitation of the market power resulting from patents. The patent owner is naturally interested in obtaining the greatest possible economic return from that market power. In patent licensing agreements, therefore, the owner/licensor may attempt to place certain restrictions on the licensee that are designed to enhance that economic return. (For example, the licensor may want the licensee to use a patented process only with materials supplied by the licensor.) However, these restrictions are not always compatible with society's goal of maximum production of goods at the lowest cost. Thus, patent licensing agreements may violate the antitrust laws.*

*A license is a contractual right granted by the owner of the technology to another party to use the technology. It is one way the owner can exploit the invention.

*In addition to the antitrust laws, the doctrine of patent misuse also serves to limit the patent owner's exploitation of the patent. It is available as a defense in a patent infringement case, and, if established, it renders the patent unenforceable. It is established by facts that do not establish an antitrust violation and is available even to a defendant who is not affected by the misuse (27). The doctrine has been criticized as vague, subjective, and mostly detrimental to innovation (5). An extended discussion of the doctrine is beyond the scope of this chapter.

For similar reasons reflecting both the concept of proprietary interest and the concept of rewarding invention, trade secrets and other forms of know-how may receive protection against improper disclosure.* And, like patents, they may be exploited through licensing agreements. Under appropriate circumstances, then, know-how licensing is a legitimate procompetitive action that promotes research and product development. Know-how licensing, however, will be subject to antitrust scrutiny.

Whether a particular form of patent or know-how licensing is anticompetitive is a determination that is fact specific and requires a detailed analysis of the terms of the agreement and the markets involved. The courts have developed various principles to guide the analysis, which will be discussed in greater detail in the next section.

*Know-how may be defined as technological information relating to manufacturing processes not protected by a patent, not generally known or accessible, and of competitive advantage to its owner (20). Legal protection of know-how is based on a theory of breach of trust and misappropriation. To the extent know-how is known only by its owner, the owner holds a limited monopoly.

A review of relevant U.S. and foreign antitrust laws

Antitrust laws and policies relevant to biotechnology in the United States are described below. Also discussed are the laws and policies of the EEC, the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan.

United States

Four provisions of the U.S. antitrust laws are most relevant to this discussion. Section 1 of the Sherman Act (15 U.S.C. §1) prohibits "[e]very contract, combination . . . or conspiracy, in restraint of trade or commerce among the several States or with foreign nations . . ." Section 2 of the Sherman Act (15 U.S.C. §2) condemns monopolization, attempts to monopolize, or any combination or conspiracy to monopolize "any part of the trade or commerce among the several States, or with foreign nations . . ." Section 7 of the Clayton Act (15 U.S.C. §18), as amended in 1980, prohibits partial or entire corporate acquisitions " . . . by any person engaged in commerce or in any activity affecting commerce . . ." where "the effect of such acquisition may be to substantially lessen competition or to tend to create a monopoly." Section 5 of the Federal Trade Commission Act (15 U.S.C. §45 prohibits unfair methods of competition.

Taken together, these four statutory provisions prohibit any behavior that results in a substantial lessening of competition. The U.S. Department of Justice and the Federal Trade Commission have the power to investigate agreements or actions for anticompetitive effects. Violators of the antitrust laws face criminal penalties or injunctions. In addition, "injured" private parties can sue for violations of the law, which supplements Government enforcement. Under section 4 of the Clayton Act (15 U.S.C. §15), a private plaintiff* may sue for treble damages or seek injunctive relief. While in many instances private antitrust lawsuits follow successful Government litigation, private lawsuits can be the sole action challenging a given practice (32). The threat of private antitrust enforcement, coupled with the treble damages remedy, is a significant adjunct to U.S. Government enforcement and an important deterrent to anticompetitive behavior.

The U.S. antitrust laws are very different from most other statutes because they do not provide a checklist of specific, detailed statutory requirements, but instead set forth very broad principles. This approach requires private parties, Government prosecutors, and the courts to consider the

*Since enactment of the Clayton Act in 1914, Congress has twice amended §4 to qualify the rights of certain plaintiffs bringing actions under its provisions. New subsection (b) of 15 U.S.C. §15 limits monetary recovery in successful actions brought by foreign corporations to actual damages unless the plaintiff meets each of four specified tests. Other additions limit the time in which lawsuits may be filed to 4 years and establish rights and procedures governing parens patriae actions and instituted by Federal and State attorneys general. *See* 15 U.S.C.A. §§15, 15a-c,f,g (1983 Supp.).

overall purpose and effect of a business arrangement. Most arrangements are evaluated under a "rule of reason" test first enunciated by the U.S. Supreme Court in 1911 (28). Under this test, restraints on competition are evaluated by a full factual inquiry as to whether they will have a significant adverse effect on competition, what their justification is, and whether that justification could be achieved in a less anticompetitive way. Terms of an agreement may restrict some competition, yet be permitted, provided the restriction is clearly ancillary to some legitimate purpose and is appropriately limited in scope (35). The necessary vagueness of this test can create uncertainty about the legality of business arrangements, and this uncertainty may dissuade some types of arrangements.

Some types of agreements are not evaluated by the rule of reason test; instead they are considered illegal per se. Agreements between existing or potential competitors to fix prices or to allocate markets or customers, for example, are considered illegal per se. For such agreements, experience has established that their "pernicious effect on competition and lack of any redeeming virtue" makes an "elaborate inquiry as to the precise harm . . . or the business excuse" generally not worth the effort (22).

To assess the competitive impact of R&D joint ventures, the U.S. courts generally have used the rule of reason test. Under this test, a fact-intensive analysis is undertaken in which numerous factors are considered and their pro- and anticompetitive effects are balanced to assess the legality of certain behavior. The number of factors that must be assessed is often large. In *United States* v. *Penn-Olin Chemical Co.* (38), for example, the Supreme Court listed 15 factors to be considered in determining whether a joint venture violated section 7 of the Clayton Act.

In assessing the legitimacy of research joint ventures under the antitrust laws, the U.S. Department of Justice indicated in its *Guide to Research Joint Ventures* the most relevant considerations to be the following (36):

- *Whether the individual joint venturers would have undertaken the same or similar R&D on their own.* "If the cost and risk of the research in relation to its potential rewards are such that the participants could not or would not have undertaken the project individually, then the venture will have the effect of increasing rather than decreasing innovation."
- *The number and size of competitors in the relevant market, as well as the level of existing competition.* "The greater the number of actual and potential competitors in an industry, the more likely that a joint research project will not unreasonably restrain competition." The Justice Department has stated a preference for a series of several competing joint research projects, rather than industry-wide joint ventures, though the latter may be justified due to necessity.
- *The nature of the research.* "In general, the closer the joint activity is to the basic research end of the spectrum—i.e., the farther removed it is from substantial market effects and developmental issues—the more likely it is to be acceptable under the antitrust laws."
- *The scope of the research joint venture (how it is limited in time and subject matter).* "The narrower the field of joint activity and the more limited the collateral restraints involved, the greater the chances that the project will not offend the antitrust laws." Any ancillary restraining agreement is viewed more favorably if it is an important additional factor necessary to assure the venture's success.

The U.S. Department of Justice has procedures for reviewing and giving advice on the proposed business joint ventures before they are undertaken (28 C.F.R. §50.6). Though the grant of immunity is not guaranteed, approval through this procedure almost always is an effective grant of immunity from subsequent Government prosecution. From 1968 to 1978, the Department of Justice considered 29 specific requests for advice concerning proposed research joint ventures. Utilizing the procedure, the Department fully cleared 90 percent of the research joint ventures considered (14). Of all ventures granted clearance, none have been subsequently sued by private plaintiffs.

There have been few Justice Department enforcement actions with respect to R&D joint ventures. In fact, a pure research joint venture without ancillary restraints has never been challenged by the Antitrust Division (9). In the past 15 years, the Justice Department has formally challenged only one joint research arrangement, and only because it involved patent pooling and ancillary restraints that hindered the coventurers from undertaking the R&D themselves (8,24).*

Of the few private suits in the United States attacking R&D joint ventures, one recent case is the most significant. In *Berkey Photo, Inc.* v. *Eastman Kodak Co.* (7), the plaintiff, Berkey, contended that Kodak had extracted secrecy agreements from General Electric (GE) and Sylvania, its coventurers, that precluded other camera manufacturers from competing to produce cameras that could be used together with the certain new flash devices made by GE and Sylvania. The court noted that Kodak and GE were not direct competitors and that Kodak and Sylvania were potential competitors at best. However, because of Kodak's market power over cameras in general, the court found an exclusionary potential. The court recognized that if several substantial companies in an industry undertake joint research on a scale unattainable by the remaining companies and those remaining companies are not permitted to join the group, the coventurers might gain a decisive and unjustified advantage over the others. While the court had found market power to be a significant factor in assessing the joint venture's legality, it had been necessary for the plaintiff also to demonstrate that Kodak was gaining competitive advantages which were not the pure products of technological improvement (30).

Like joint ventures, technology licensing agreements are generally evaluated by the rule of reason when they contain terms that may restrict competition. Examples of license provisions that have raised antitrust concerns are limitations on how much the licensee can charge or sell, restrictions on the licensee's dealing in competing products, restrictions on the resale of the patented product, and tying arrangements.* Restraints may take several other forms, such as territorial restraints, field-of-use restrictions, and grantbacks.** Similar restraints also exist for know-how licensing. Factors relevant to assessing the legitimacy of such restraints are as follows: whether they are ancillary to a lawful main purpose of the agreement, have a scope and duration no greater than that reasonably required to achieve that purpose, and are not part of some larger pattern of anticompetitive restriction (36).

There is relatively little case law on the subject of know-how restrictions, but the existing cases state that the same type of ancillary-restraints analysis will be followed in this area as well. This is not to say that the outcome will be the same as for patents, since there are differences between patent and know-how licensing.*** Recognizing these differences, particularly the fact that know-how lacks the legislative status of the patent system, the U.S. Department of Justice at one time took the position that "know-how licenses will in general be subject to antitrust standards which, if anything, are stricter than those applied to patent licenses" (36). Further, the Justice Department took the position that restraints in know-how licenses should not last longer than the time necessary for the licensee to develop equivalent know-how for itself, "a reverse engineering

*The challenged R&D venture involved an alleged agreement between auto manufacturers to delay installation of existing emission control devices or stall the improvement of such devices. The case was ultimately settled and it enjoined the defendants from preventing or delaying the development or installation of these devices (37).

*A tying arrangement requires the licensee to purchase unpatented materials from the licensor.

**Territorial restraints are restraints that limit the licensee's use of the invention to specified geographical areas. Field-of-use restrictions limit the use of the invention to something less than all of its potential applications. For example, if Stanford licensed the Cohen-Boyer recombinant DNA process patent to a company only for making specialty chemicals but not for making pharmaceuticals, that would be a field-of-use restriction. A grantback is an agreement by the licensee to give back to the licensor (the owner of the basic patent) rights to any improvement patent.

***Some of these differences are the following: 1) all the patent claims must be definite in scope while know-how is usually of an amorphous character and cannot be described precisely; 2) patent protection is limited to the territory of the country granting the patent, while know-how could be protected, at least in theory, wherever the domestic law of the forum protects trade secrets; 3) patents are limited to the 17-year period of protection, while know-how is protected for as long as it does not become generally known; 4) a patent grant protects its owner from a duplicative independent invention, but the character of know-how can be destroyed by an independent invention; and 5) know-how content changes as new information is incorporated, and old information becomes publicly known (29).

period" (23). The rationale for the concept of the reverse engineering period appears to be that a restraint limited to the length of time necessary to invent around the licensed know-how "does not eliminate competition which would have taken place in the absence of the licensing agreement" (12). The current policy is to be more flexible on these restraints (2).

European Economic Community

The Federal Republic of Germany, United Kingdom, and France are members of the European Economic Community (EEC). The EEC, or Common Market, was created in 1958 by the Treaty of Rome. One of the goals of the treaty was the "establishment of a system ensuring that competition in the common market is not distorted." The result has been a two-tiered system of antitrust law in the Common Market. EEC law coexists with the national systems of antitrust law and is considered part of the national law of each member state. If there is any conflict between the national law and the law of the EEC, the latter prevails. Responsibility for enforcement of EEC law rests primarily with the Commission of European Communities ("Commission"). The Court of Justice, located in Luxembourg, reviews the formal decisions of the Commission.

Articles 85 and 86 of the Treaty of Rome govern anticompetitive practices. article 85(1) prohibits "all agreements . . . and concerted practices . . . which have as their object or effect the prevention, restriction or distortion of competition within the common market . . . ."* Article 86 prohibits abuses by one or more enterprises "of a dominant position within the common market," such as "limiting of production, markets, or technical development . . . ."

Article 85(3) of the Treaty of Rome provides for exemptions from article 85(1) for certain agreements or practices such as those that promote economic and technical progress and do not impose ancillary restrictions or afford the possibility of eliminating competition. A notification procedure has been created which allows the Commission to review agreements for which an article 85(3) exemption is claimed. The grant of an exemption by the Commission is binding on the national authorities and courts of the member states.* Thus, clearance by the enforcing agency is much more important in the EEC than in the United States.

The articles in the Treaty of Rome give the Commission of European Communities broad authority to prohibit: 1) R&D joint ventures that have the potential to eliminate competition between major companies, and 2) ancillary restrictions of R&D joint ventures that could restrain competition. The criteria that the Commission has shown to be important in judging whether a venture comes under the first category have generally been similar to those of the U.S. Department of Justice, i.e., the market share of the relevant companies, the ability of other enterprises to perform the research, and the extent to which the research is applied as opposed to basic. In the second category, restraints ruled illegal usually have been restrictions on the ability of the participants to compete with the joint venture itself and restrictions concerning distribution of the joint venture's end results.

Though 15 years ago the Commission published an official notice intended to reassure enterprises of the legality of most R&D agreements (in particular ventures with R&D as the "sole object"), later decisions of the Commission have showed some of its statements of leniency to be unreliable (6). For example, in 1972, two of the largest manufacturers in the oligopolistic European soap industry created a joint, equally owned subsidiary in Switzerland to conduct research into soap products.

*Article 85 will apply to an agreement only if it "may affect trade between Member States." Thus, if a contract only affects internal trade of one nation, trade between nonmember nations, or trade between a member and a nonmember nation, it is not covered by article 85 regardless of its impact on competition (40).

*In addition to the ability to petition for article 85(3) exemptions, an enterprise can request the Commission to rule that, based on the information supplied, it will not challenge the agreement under article 85(1). Such a ruling is provided for under article 2 of regulation 17 and is called a negative clearance. The grant of a negative clearance means that article 85(1) does not apply to the agreement at all. In practice, applications for negative clearance are often accompanied by requests for an exemption, so that if the commission finds a violation of article 85(1), it can consider whether to grant an exemption. Failure to disclose all pertinent facts or a subsequent change in the factual situation may result in cancellation of an exemption or a negative clearance.

The Commission found that the agreement eliminated competition in research and therefore violated article 85(1) (18).

Since the Commission may not grant an exemption in the absence of a notification of the agreement and its provisions, the EEC legal system has ensured that most major research ventures among European companies of different nationality are filed with the Commission.* The soap case mentioned above was in fact notified and granted an exemption because the commission ruled that the joint research would promote economic and technical progress. The exemption was subject to the condition that the companies inform the Commission of all license agreements emanating from the results of the joint research.

The Commission will also exempt anticompetitive collateral restraints on the basis of article 85(3). In one case, an agreement between two enterprises for joint R&D work on a new type of electrically powered bus was granted an exemption, even though its provisions prohibited cooperation with third parties within the field covered by the agreement (19).

The Commission's decisionmaking process differs substantially from the U.S. adjudicatory process in the sense that it is much less formal and less procedurally oriented. Before giving approval, the Commission is willing to negotiate and, wherever necessary, mandate conditions that will guarantee that the parties will remain competitive once the joint research venture has terminated.** It is rather frequent that harmful collateral restrictions are found, which usually can be eliminated or redrafted without prohibiting the joint venture itself. Although there have been no Commission decisions to prohibit research joint ventures, many recent decisions have in some way limited or controlled joint research agreements, in most cases with respect to their collateral restrictions. Since 1968, the Commission has modified at least eight cases involving joint research and subjected others to reporting obligations or otherwise limited the exemption granted in time or scope of coverage.*

Considering the list of cases that have been modified and the mandatory notification requirement, it appears that in practice the EEC is at least as tough as, and probably tougher than, the United States on joint research, particularly with respect to collateral restraints. The Commission has not hesitated to impose reporting obligations and to review periodically whether a joint venture may become anticompetitive in future years.

Patent and know-how licenses are agreements that may come within the scope of article 85. EEC law and the law of the member countries generally follow the traditional doctrine that restrictions on the licensee are valid if they do not expand the scope of the patent. A body of law has developed, based mainly on Commission decisions, with regard to what kinds of restrictions in licensing agreements are legal and what kinds are not.** The Commission has also issued a proposed exemption from article 85(1) for two-party patent licensing agreements (10). The proposed exemption is very narrow and has received substantial criticism (40).

Federal Republic of Germany

In the Federal Republic of Germany, the Act Against Restraints of Competition (GWB, Gesetz-gegen Wettbewerbsbeschrankungen) prohibits restrictive business practices and is concerned with maintaining competitive market structures.

*Article 4(2) of regulation 17 provides that certain classes of agreement need not be notified to the commission in order to obtain an exemption. This means merely that they are eligible to be considered for the grant of an exemption under article 85(3) even if notification has not been filed. Though agreements which have as their "sole object . . . joint research and development" do not have to be notified [(Article 4)(2)(iii)(b)], R&D agreements with any sort of ancillary restraints must be.

**An example of this was the *ICI/Montedison* case (17) where the Commission proposed to mandate an obligation that would insure that "on the termination of the agreement, Montedison should be in a position to continue as an independent producer of a line if it wished, thereby increasing competition in an oligopolistic market."

*See ACEL/Berliet, 1968 C.M.L.R. D35 (1968) (modification); Henkel/Colgate, J.O. 1972, L. 14/14 (1972) (reporting obligation, exemption limited to 5 years); SOPER:EM/Rank, 1975-1 C.M.L.R. D72, (1974) (modification, reporting obligation, exemption limited to 10 years); Vacuum Interrupters, 1977-1 C.M.L.R. D67 (1977) (reporting obligation, exemption limited to 8 years); General Electric/Weir, 1978-1 C.M.L.R. D42 (1977) (modification, reporting obligation, exemption limited to 12 years); SOPELEM/Vickers, 1978-2 C.M.L.R. 146 (1977) (reporting obligaton, exemption limited to 5 years) *modified*, 1982-3 C.M.L.R. 443 (1981) (exemption extended until 1991); Beecham/Parke Davis, 1979-2 C.M.L.R. 157 (1979) (modification, reporting obligation, exemption limited to 12 years).

**For information on particular kinds of clauses, see (40).

This law is intended expressly to promote "competition based on efficiency" and is regarded as the "constitution" of the German social market economy (31). Section 1 of the law establishes a general prohibition against agreements made for a common purpose by enterprises that restrain competition, production, or market conditions. Thus, this section can preclude a research joint venture having anticompetitive market effects.

Section 5b permits small- and medium-sized firms to form rationalization cartels,* assuming no substantially adverse effect on competition and assuming that the result promotes the firms' overall efficiency. Such cartels may include cooperative R&D ventures.

The application of German law by Government authorities appears to have been at least as tough as in the United States in regard to research joint ventures. Between 1979 and 1980, the German Cartel Office caused the abandonment of two agreements involving joint research. A proposed venture between Siemans AG and VDO Adolph Schindling to develop, produce, and market liquid crystal gages for use in automobile instrument panels was prohibited, because the arrangement already jointly held 80 percent of the market for automobile instruments (13). Another proposed joint venture between Takeda Chemical of Japan and Bayer AG of Germany to develop, test, and market pharmaceutical products in the Federal Republic of Germany was prohibited because it would have represented a combination of two of the world's eight largest pharmaceutical companies and eliminated Takeda as an independent potential competitive force in West Germany (13).

With respect to technology licensing agreements, GWB section 20(1) is relevant. It nullifies agreements covering the acquisition or use of patents or protected seed varieties to the extent they impose restrictions on the business conduct of the acquirer or licensee that go beyond the scope of the protected right. However, German cartel authorities may grant an exemption to this provision under GWB section 20(3) if the economic freedom of the licensee or other company is not unfairly hurt and market competition is not substantially impaired. Thus, the approach of West Germany is similar to that of the United States in terms of having a general prohibition against agreements that extend the scope of the patent, but German law gives the antitrust authorities discretion to exempt agreements on a case-by-case basis, which makes the German system more flexible.

*A rationalization cartel is one formed to improve efficiency of production through concerted action.

United Kingdom

The U.K. antitrust law is contained in several statutes. The ones most relevant for R&D joint ventures and technology licensing are the Fair Trading Act of 1973 and the Competition Act of 1980.

Under section 76 of the Fair Trading Act, the Director General of Fair Trading has the duty to be generally informed about all mergers and to decide whether to recommend to the Secretary of State referral to the Monopolies and Merger Commission. Not all joint ventures are affected by the legislation. The Fair Trading Act does not apply if the joint venture is merely the result of an investment of capital by the coventurers in a jointly owned company. In most instances, a research joint venture will not involve the type of agreement constituting a merger under the Fair Trading Act.

Should a "merged" R&D venture be referred to the Monopolies and Mergers Commission, its legality is assessed on the basis of whether it will operate in the public interest. The five factors considered are whether the merger will promote: 1) effective competition, 2) the interests of consumers, 3) reduced costs and the development of new techniques and products, 4) a balanced distribution of industry and employment, and 5) competitive activity in British markets. Even if a proposed research joint venture were subject to the Fair Trading Act's reporting provisions, it is likely to be characterized as activity helping to develop "new techniques and products" and therefore not violate the Fair Trading Act.

The Competition Act was designed to provide a comprehensive approach to anticompetitive practices not already covered by existing statutes. Generally, the act applies to all activities that prevent, restrict, or distort competition. Thus, it

would apply to R&D joint ventures and to technology licensing agreements.

Generally, the antitrust regime in the United Kingdom is relatively loose, and enforcement actions on joint R&D ventures and licensing agreements have been few. But U.K. companies formulating agreements with companies of other European countries must take into account the EEC laws.

France

The relevant statutes in France are Title II of Act No. 77-806 and Articles 50 and 51 of Price Ordinance No. 15-1483. Under title II, the Minister of Economic Affairs may act against a "concentration"* that is "of such a nature as to prevent adequate competition in the market." Articles 50 and 51 apply to concerted actions or agreements that prevent, restrain, or distort competition.

R&D joint ventures could be prohibited under title II if they involved major French companies. However, an anticompetitive concentration may be exempted under section 4 when the concentration is found to make "a sufficient contribution to economic and social progress" to compensate for its restraints on competition. A determination on this point considers the international competitiveness of the companies concerned. A biotechnology R&D joint venture among large companies would likely be exempted under this provision, and such a joint venture among small firms is unlikely to raise problems in the first place.

Ancillary restraints which accompany many joint R&D agreements would come under paragraph one of article 50, which prohibits concerted actions or agreements that may prevent, restrain, or distort competition and specifically mentions impeding technological advance. However, article 51 provides for an exception where the anticompetitive practices further contribute to economic progress, particularly through enhanced productivity.

There is no French antitrust law that applies specifically to technology licensing, but the Competition Commission has taken the position that articles 50 and 51 apply to intellectual property rights. However, there is very little case law in this area (25).

French antitrust law is of recent origin and is still developing. It is unlikely to be applied to a biotechnology R&D joint venture. How it will be applied to biotechnology licensing agreements is somewhat unclear at this point.

Switzerland

Joint ventures and licensing agreements in Switzerland are governed under the provisions of the Federal Cartels Act. The mere creation of a joint venture would not trigger liability under this act. If the venture dominated or exercised a determining influence on a product market, however, the act would apply. Unless major companies joined a biotechnology R&D joint venture, the act would not appear to apply.

Exemptions to the Federal Cartels Act are outlined in article 5. Activities that are otherwise prohibited by the act may be permitted on the "grounds of overriding legitimate interests" if competition is not prevented "to a degree that is excessive." "Overriding legitimate interests" include those aimed at: 1) establishing reasonable requirements as to training, skill, or technical knowledge for a particular occupation or industry; and 2) promoting an economic or occupational structure that is desirable in the general interest. Thus, even if a biotechnology research venture interfered with competition to a limited degree, it would appear to be exempt under article 5.

Swiss law appears to favor R&D joint ventures. There apparently have been no specific cases dealing with R&D joint ventures, and there has been no general treatment of the subject in Swiss legal periodicals (9).

The Federal Cartels Act would apply to licensing agreements in situations involving market

*A "concentration" is defined as, "the result of any legal act or transaction . . . having the object or effect of enabling one enterprise or a group of enterprises to exercise an influence, directly or indirectly, on one or more other enterprises which is of such a nature as to direct or even orientate the management or workings of the latter."

dominance. For example, a requirement that a licensee undertake no research in the same area as a patented invention would be objectionable under the act. Similar objections would be raised if a licensee were obligated to assign any improvements on the licensed technology to the licensor. However, cooperative agreements to exchange research results appear to be lawful.

Japan

Japan's antimonopoly law—the Act Concerning Prohibition of Private Monopoly and Maintenance of Fair Trade (Japanese Law 54 of 1947)—was first enacted in 1947 during the U.S. occupation and was revised three times subsequently, in 1949, 1952, and 1977. Enforcement procedures were established in the Japanese Fair Trade Commission (JFTC), an independent five-person regulatory body modeled after the U.S. Federal Trade Commission. Section 25 of the law allows private companies the right to sue for damages, but only after JFTC has found a violation.

The basic provisions of Japan's antimonopoly law are quite rigorous. Article 1 explains that the purpose of the law is to "eliminate unreasonable restraint of production, sale, price, technology, and the like . . . ." Revisions in 1977 reflected a concern for controlling large corporations so that the revitalized market structure could function more efficiently. Sections 3 and 6 of the 1977 revisions preclude entrepreneurs from engaging in any unreasonable restraints of trade or entering into international agreements with terms that might be unreasonable trade restraints. Research joint ventures could qualify, since section 2(6) defines "unreasonable restraints of trade" as: "business activities by which entrepreneurs . . . mutually restrict or conduct their business activities in such a manner as to fix, maintain, or enhance prices, or to limit production, technology, products, facilities, or customers or suppliers." The act also prohibits private monopolization.

Several provisions in articles 21 through 24 of the antimonopoly law specifically permit certain types of legal cartels, including research joint ventures. In total, there are 39 laws permitting businesses to form legal cartels exempt from the antimonopoly laws (26).

With the end of the occupation in 1951, Japan's antimonopoly law was ineffectively enforced by JFTC; its relatively severe antimonopoly restrictions and prohibitions against cartels drew considerable hostility from the Japanese Government, and JFTC virtually languished between 1952 and 1969 (15). In the meantime, Japan's Ministry of International Trade and Industry (MITI) often implemented a procedure known as "administrative guidance" in which persuasion would be used by MITI to influence businessmen within its oversight. In some instances, administrative guidance functioned to foster cartelization either by restricting production or investment, or otherwise influencing prices—all circumventing the antimonopoly law.

The last decade, however, has seen a marked increase in JFTC's enforcement activities. In 1980, for example, JFTC completed 62 cases, 24 of which involved price-fixing. It has also ordered 279 businesses to pay a total of $10 million in fines and has prosecuted a wide variety of unfair business practices (33).

Despite the increase in enforcement activity, the Japanese Government has to date not prosecuted any R&D joint ventures. The Research Association Law, passed in 1961 and amended in 1963, provides an important perspective on the Japanese Government's competition policy as opposed to its enforcement of its antimonopoly laws. This law allows several companies to undertake long-term R&D or to pool financial, personnel, and capital resources. In almost all such instances, the approved association involves R&D in which some Japanese Government ministry or agency participates. Rather than being anticompetitive, these research associations often serve to undermine collusive behavior by increasing entry into advanced industries and helping to diffuse new technology (26). Pursuant to the Research Association Law, the Ministry of Finance has specifically recognized the recently created Biotechnology Research Association.

There is one significant difference between the Japanese and U.S. antitrust perspective on research joint ventures. In Japan, there would be no objection in the case of a new technology if all the companies involved were to join in the same venture. In the United States, such a ven-

ture would raise serious antitrust problems. However, if the Japanese joint venture restricted entry into or subsequent use of the technology by competitors, then it would probably violate the antimonopoly law.

Japan's antimonopoly law creates a mechanism for Government oversight of international technology transfer. Section 6 of the law prohibits a firm or entity from "enter[ing] into an international agreement or contract which contains such matters as constitute unreasonable restraints of trade or unfair business practice." On July 23, 1982, section 6 was amended to require that international agreements that *may* constitute unreasonable restraints of trade or unfair business practices be filed with JFTC. Technology licensing and joint venture agreements are among those required to file. JFTC has promulgated a regulation covering patent licensing agreements (3). Thus, JFTC can monitor these agreements for restraints on competition.

Applicability of antitrust law to biotechnology research joint ventures

The use of joint ventures in biotechnology, as discussed in *Chapter 4: Firms Commercializing Biotechnology,* is prevalent. The capital markets have not funded all the long-term, high-risk R&D that NBFs wish to undertake. Joint ventures have been used as an important source of revenue by NBFs until they can develop the production and marketing capabilities to distribute their own products. Large, established companies have entered into several different kinds of joint ventures with NBFs, in most cases to obtain access to the new technology until their own in-house capabilities can be developed.

Joint research ventures in biotechnology currently run very little risk of violating either the U.S. or foreign antitrust laws. Two factors in particular support this assertion. One is the very high risk of biotechnology R&D. For example, total sales of biotechnology products reached $20 million in 1982 and are projected to range from $150 million to $3 billion in 1987 (16). This huge range reflects the considerable uncertainty and risk at this time over the size of future markets, a factor that depends on the number of commercially available products (16).

The track record of the first rDNA product, the human insulin product Humulin®, provides an instructive example of the risks involved in commercializing biotechnology. The micro-organisms used to produce Eli Lilly's (U.S.) product Humulin® were first provided by the NBF Genentech (U.S.) over 5 years ago. Lilly sponsored both the research and the marketing and agreed to pay Genentech royalties (see *Chapter 5: Pharmaceuticals*). The commercial success of this product, however, remains uncertain. In clinical trials, Humulin® has not shown any special advantages over naturally produced porcine insulin and has been found to cause immune reactions similar to the porcine product. Furthermore, production difficulties may have caused Eli Lilly to have run short of the drug during clinical trials. Finally, according to some critics, a newer and cheaper method of producing human insulin may already be available (11).

Eli Lilly's experience with Humulin® demonstrates that the commercial development of biotechnology products may take several years and may generate products that may become rapidly outdated. Combined, these factors indicate a very high level of risk. When the risks are as substantial as they currently are in biotechnology, enforcement authorities are far more tolerant of joint ventures.

The second reason joint research ventures in biotechnology do not currently raise antitrust concerns is the decentralization of biotechnology R&D. At the end of 1983, there were about 200 companies using biotechnology in the United States. The major thrust of all systems of antitrust

law is to prevent dangerous trends towards concentration and monopolization—conditions that could signal a downturn in innovation. Although the point where dangerous concentration in R&D occurs varies from case to case, the biotechnology field remains far from that point today.

Because of the deconcentration of biotechnology R&D, research joint ventures are essentially procompetitive, assuming the absence of ancillary restraints. Most established companies that have participated in joint ventures with NBFs are also undertaking in-house R&D. The revenue earned by joint ventures for NBFs is sustaining the viability of a larger number of competitors.

Thus, joint ventures in biotechnology R&D in the United States (and most likely foreign countries as well) currently face virtually no significant antitrust restraints. The absence of measurable product markets and the lack of R&D concentration means that research joint ventures are not reducing competition. Only when successful products and measurable market shares become apparent will joint research activities among major companies invite major antitrust challenge.

Antitrust law has come under much scrutiny recently, and the trend in the U.S. Department of Justice is toward a policy that an action is unlawful only if the injury to competition outweighs the benefits. For instance, the Department of Justice recently gave preliminary approval to the formation of one of the largest cooperative research arrangements in U.S. industrial history—an amalgam of 12 major computer firms called the Microelectronics Computer Corp. (MCC) (39). Although the Department of Justice press release gave little guidance on the antitrust aspects, the decision not to challenge MCC's formation at least demonstrates that a carefully structured R&D joint venture can include most of the U.S. competitors without being considered anticompetitive.

Application of antitrust law to biotechnology licensing agreements

The preceding survey of the antitrust laws of the competitor countries in biotechnology indicates that most restraints on competition in licensing agreements will be evaluated by a rule of reason test. The authorities of the various countries have applied this test to various types of provisions in licensing agreements, including grantbacks and field of use restrictions. Other provisions, such as tying arrangements, are generally treated under per se rules. It is not useful to examine these in detail, since virtually none of them raises any unique issues with respect to biotechnology.

One type of factor relating to restrictions may have unusual significance for biotechnology. As a general rule, restrictions extending beyond the life of the technology being licensed are considered suspect. For U.S. patents, the life of the technology is arguably no more than 17 years, i.e., the term of the patent. For know-how, however, the useful life is not so easily defined. At least two commentators have suggested that most know-how can be reverse-engineered in 3 to 5 years and that restrictions exceeding 5 years should therefore be considered in the United States per se unreasonable unless the licensor can provide a special justification (1). On one hand, this view may make sense for biotechnology know-how, given the pace of technological development. On the other hand, many, if not most, production processes for biological products, i.e., the organisms themselves, are not capable of being reverse-engineered because of their complexity. Thus, the rigid and unthinking application of a 5-year rule would unfairly and unnecessarily hinder licensors in their ability to exploit their technology.

Findings

U.S. companies using biotechnology face no major antitrust compliance problems. Nevertheless, there is some degree of uncertainty about the scope and applicability of the antitrust laws to R&D joint ventures and to licensing agreements. This uncertainty, plus the expense of litigation and the threat of treble damages, could discourage some activities that might lead to innovation in biotechnology and could limit the ability of U.S. companies to commercially exploit their technology. Furthermore, the rigid application of certain per se rules in the area of licensing may actually lead to anticompetitive results. Thus, the current antitrust laws in the United States may have some modest adverse effect on biotechnology.

The antitrust laws of the United States, the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan are generally similar in that they all prohibit restraints of trade and monopolization. Unlike the U.S. laws, however, the foreign laws generally provide for exemptions and vest much discretion with the enforcement authorities. Most of the kinds of arrangements that would be of interest to firms using biotechnology would be evaluated under a rule of reason test, but others are now per se illegal.

Under U.S. antitrust law, the legality of a research joint venture is judged on the basis of a balancing of its procompetitive v. anticompetitive effects. Factors considered important are whether the individual joint venturers would have undertaken the same or similar R&D on their own, the number and size of competitors in the relevant market, the scope of the research (basic v. applied), and the scope of the research joint venture (how it is limited in time and subject matter).

It is by no means clear that more favorable treatment is given to R&D joint ventures by the laws and enforcement authorities of European countries. Authorities in the EEC and the Federal Republic of Germany in particular have caused the abandonment or modification of a larger number of joint R&D ventures than their U.S. counterparts have. Though Switzerland, France, and the United Kingdom appear to have less stringent antitrust enforcement than the United States, European company activity across national boundaries of member states comes under EEC law.

Japan has probably been more tolerant than the United States toward anticompetitive aspects of R&D joint ventures. The highly publicized research associations sponsored by the Japanese Government best exemplify this attitude. However, this attitude may be changing, as indicated by the growing number of antitrust enforcement actions in general.

At the present time, companies applying biotechnology both in the United States and foreign countries face virtually no significant antitrust compliance problems with research joint ventures, excluding blatantly anticompetitive activities like price-fixing. In biotechnology, there is a lack of concentration of industry research and an absence of measurable markets. Only when biotechnology-related industries develop increasing concentration, successful products, and measurable market shares will R&D joint ventures be exposed to the antitrust statutes.

Technology licensing agreements are reviewed by the governmental authorities under the general principle that the agreements should not extend the scope of the patent or know-how in ways that are on balance anticompetitive. The only issue unique to biotechnology raised by the application of the antitrust laws to these agreements relates to the length of time of permissible restrictions on competition. The rule that such restrictions should not extend beyond an arbitrarily determined useful life of the licensed technology may not be especially relevant to biotechnology, and its application may hinder the exploitation of inventions through licensing.

Despite the fact that U.S. antitrust law is not likely to be a major concern with respect to biotechnology R&D joint ventures or licensing, there will be some degree of uncertainty regarding the antitrust implications of any corporate activity in this area. The degree of uncertainty is less in for-

eign countries than in the United States because these countries have more well-defined procedures for prior review of transactions by government authorities and less onerous penalties for violations. Lessening the uncertainties under U.S. law could be expected to have a positive effect on the development of biotechnology in the United States.

Issue

ISSUE: Should Congress change U.S. antitrust laws to encourage more joint research in biotechnology or to facilitate biotechnology licensing?

U.S. companies using biotechnology face no major antitrust compliance problems. For the reasons discussed in the findings of this chapter, however, current U.S. antitrust laws could have some modest adverse effect on U.S. competitiveness in biotechnology. The impact of these laws is not particularly unique to biotechnology, as distinguished from other areas of technology. In fact, the impact will probably be less for biotechnology than for more mature technologies, given the current lack of concentration in commercial R&D in biotechnology and the absence of measurable markets for products. Therefore, despite the many proposals to change the law and enforcement procedures now being discussed, no policy options are discussed here, because their broad applicability to technology in general is beyond the scope of this report.

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*Note: C. D. Cal. = Central District of California.
F. Supp. = Federal Supplement.
U.S. = U.S. Supreme Court Reports.
F.2d = Federal Reporter, Second Series.

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Chapter 19

International Technology Transfer, Investment, and Trade

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Chapter 19

International Technology Transfer, Investment, and Trade

Introduction

Intense international research and development (R&D) activities in biotechnology have stimulated equally intense efforts to diffuse the resulting knowledge and to sell the products of the research, both in the United States and abroad. Academic scientists are racing to publish their research results or to share them with colleagues at international conferences. Established companies and new biotechnology firms (NBFs)* are funding university research programs to gain access to potentially valuable new developments. U.S. and foreign patents arising from the increase in biotechnology R&D and international licensing agreements formulated to exploit the patents are diffusing the technology and promoting worldwide commercialization. Finally, NBFs in the United States and large U.S. and foreign companies have undertaken many R&D joint ventures to develop and market new products.

Several other chapters of this report have examined factors basic to the commercialization of biotechnology research (e.g., venture finance and patent rights). This chapter focuses on the legal environment surrounding the international exploitation of biotechnology and access to foreign markets through international technology transfer, investment, and product trade.

Although most companies are not yet marketing biotechnology products, the legal environment surrounding licensing, investment, and trade is already influencing the strategic decisionmaking of companies commercializing biotechnology—strategic decisions, such as negotiations on licensing, locational decisions for R&D, production, and clinical trials.

This chapter considers laws that can be employed directly by governments to control or influence access to foreign or domestic markets: export controls, patent laws, compulsory licensing provisions, investment and exchange controls, and trade laws. *Export controls* on technology and on products have a direct effect on potential demand and may affect the price that technology will fetch. Controls also bring delay and red tape into export transactions. *Patent laws* may contain secrecy provisions that restrict outward technology transfer for security, economic, or foreign policy reasons. They are similar in purpose and effect to export control laws. *Compulsory licensing* can be used to force inward technology transfer and can diminish return on R&D; where aggressively used, it may simply deter foreign and domestic investment in local R&D. *Investment and exchange controls* as well as *technology transfer controls* can be used to reserve national markets for locally owned firms and to force inward technology transfer. *Nontariff barriers* to trade such as product certification systems that discriminate against imported products, may block access to important markets abroad. However, trade remedy statutes such as *section 301* of the Trade Act of 1974 offer a means of negotiation for opening markets.

Any company generally has three means of exploiting its technology in a worldwide market:

- it may license the technology directly to a foreign company,
- it may invest in a foreign manufacturing subsidiary or joint venture, or
- it may make the product in its home market and export it.

Companies may also combine these alternatives, for instance, by licensing technology tied to sales of raw materials, or licensing to a joint venture abroad.

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are firms that have been started specifically to commercialize new biotechnology. Most NBFs are U.S. firms.

At present, most NBFs in the United States have licensed at least some of their technology to established U.S. or foreign companies, the reason being that these NBFs lack the capital and expertise for full-scale manufacturing and marketing, much less manufacturing or marketing abroad. Typically, NBFs that license technology to established U.S. companies surrender their rights to the U.S. market in exchange for future royalties from sales. But a number of NBFs have preferred to reserve the U.S. market for themselves and have made licensing agreements with foreign companies, especially Japanese companies, whose production and marketing expertise resides in foreign markets. These NBFs and the licensors of their technology are interested in export controls on technology and other laws that can be employed directly by governments to control or influence biotechnology transfer.

For some NBFs and most established U.S. companies, domestic or foreign manufacturing are viable options and are particularly desirable to the extent that the alternative, licensing of technology, confers long-term benefits on foreign competitors that are not recouped by the royalties and other provisions of the licensing contract. However, in a situation in which, for instance, a foreign government makes it difficult or impossible to import biotechnology products into that country or to manufacture them there through a wholly owned subsidiary, a U.S. firm seeking to work a patent in that foreign market may find it necessary to license its technology to a local company or to enter a joint venture with a local company on terms that reflect the U.S. firm's lack of market access and therefore favor the local licensee. One NBF has expressed concerns about this issue concerning its licensing negotiations with a Japanese company (14). The short-term consequence of forced technology transfer is that part of the potential return from the technology is transferred from the U.S. licensor to the foreign licensee. The foreign licensee may also receive a valuable technological boost in the short and long term.

Even though there is already substantial diffusion of biotechnology itself, via licensing, joint ventures, and scientific journals, it is difficult to quantify and assess the present amount of biotechnology transfer,* investment, and trade and their potential impact on U.S. competitiveness in biotechnology. Studies of more mature technologies only emphasize the difficulties associated with estimating the level or direction of technology flow (13). Most observers would agree that the net flow of biotechnology is outward from the United States, but such judgments are impressionistic at this time. Also, the net flow of technology outward from the United States is likely to diminish as foreign companies enter the U.S. market (via subsidiaries or foreign manufacturing operations) bringing with them foreign technology. It is not possible to provide reliable estimates of the size of the net outflow, nor is it possible to compare biotechnology with other more advanced technologies in this respect.

In examining the effects of international technology transfer, investment, and product trade, on competitiveness in biotechnology, the first question to be asked is whether biotechnology raises any new issues at all in these areas. For instance, will the growing application of biotechnology in many industries create any new problems in these areas, problems that the existing U.S. or international legal framework does not adequately cover? The answer to this question depends largely on whether there will be relevant significant differences between:

- transfer of biotechnology and transfer of existing chemical or biological technology;
- biotechnology investment and other technology investment; or
- trade in biotechnologically-produced products and trade in the chemical or biological products they supplement or replace.

OTA concludes that biotechnology will raise no such significant novel issues for the regulation of international biotechnology transfer, product trade, or investment. Even without truly novel issues, however, the existing legal framework bears examining, because it will affect access to foreign markets and ultimately competition in industries applying biotechnology. Furthermore, the laws embodying government practices can be changed.

*Ways technology is transferred include: 1) scientific and technical literature, 2) construction of industrial plants, 3) joint ventures, 4) licensing, 5) training, 6) technical exchanges, 7) sale of processing equipment, 8) engineering documents, 9) consulting, 10) documented proposals, and 11) trade exhibits.

Export controls and biotechnology

Export control laws restrict international technology transfer, as well as trade in products, for reasons of national security, foreign policy, or economic policy. From a biotechnology standpoint, the relevant questions are:

- What technologies or products are under what types of controls?
- What is the framework for controls and how are decisions made on controls?
- What is the potential impact of export controls on U.S. competitiveness?

Like the United States, Japan, and the four European countries being considered in this assessment all have some export controls. All but Switzerland belong to the Coordinating Committee for Multilateral Export Controls (CoCom)* and are subject to its multilateral export controls. Although current CoCom control lists do not include biotechnology products as such, CoCom lists on toxicological products and commercial chemicals could become relevant to biotechnology. However, there is no indication that companies would find CoCom requirements restrictive.

United States

In the United States, biotechnology products and data are subject to a number of export controls. The most significant are under the Export Administration Act (EAA) of 1979 (50 U.S.C. App. Sec. 2401, et seq.).** Under the EAA, export restrictions depend on the type of commodity or data and its destination. Exporters of any item on the Commodity Control List of the EAA regulations must have a "general license" or a "validated license" for all exports except most shipments to Canada. A general license is essentially an exemption because no application is required. A validated license, on the other hand, requires an application. The Office of Export Administration in the U.S. Department of Commerce, which administers the EAA, may deny permission to export or take a long time to issue the validated license.

With regard to biotechnology products, two groups on the Commodity Control List are especially relevant: Group 7 and Group 9. Group 7 includes chemicals, metalloids, petroleum products, and related materials, including industrial chemicals obtainable by bioprocessing, such as citric and lactic acids. The compounds in Group 7 require a validated license for export to communist countries with the exception of those compounds in a subgroup of Group 7 called "Interpretation No. 24 compounds" (CCL Category 6799G). These latter compounds include DNA, many enzymes, nucleosides, nucleotides, "protein substances," "prepared culture media," and pharmaceutical products for humans and animals. These can be exported to most countries without a validated license.

Group 9 ("Miscellaneous") of the Commodity Control List includes four pertinent categories: 1) "viruses or viroids for human, veterinary, plant, or laboratory use, except hog cholera and attenuated or inactivated systems" (CCL Category 4997B); 2) bacteria, fungi, and protozoa (except those listed in supplement No. 1 to sec. 399.2, Interpretation No. 28) (CCL Category 4998B); 3) bacteria and protozoa listed in Interpretation No. 28 (which basically covers inactivated, attenuated, or relatively harmless organisms); and 4) a catch-all category (CCL Category 6999G), which includes some medicines. Exports in the first category require a validated license for virtually every country except Canada. This category would include viral cloning vectors such as cauliflower mosaic virus, SV40, and bacteriophage lambda. Similarly, the second category requires, with certain exceptions, a validated license for export to any country other than Canada. The third and fourth categories have few restrictions unless the export is being made to certain countries like North Korea, Cuba, Vietnam, or Libya.

Certain bacteria of major industrial importance, such as those of the family Streptomycetaceae and of the genus *Lactobacillus*, fall into Interpretation No. 28 and are therefore exempted from validated

*CoCom is composed of the NATO nations, minus Iceland and Spain, plus Japan, and was formed to deny the Communist countries access to military technology and strategic materials.

**The following discussion is based on the EAA that expired on Sept. 30, 1983, but continues in effect indefinitely under the authority of the International Emergency Economic Powers Act.

license requirements. However, several other types of bacteria commonly used in industry and research, such as the genera *Escherichia, Bacillus,* and *Pseudomonas*, do not come within Interpretation No. 28 and therefore require a validated license for export to all countries except Canada (3). For a summary of the controls on biotechnology products under the EAA of 1979, see table 67.

One commentator has criticized the way in which Interpretation 28 (which will provide major exemptions for biotechnology products) was developed (6). First, the Office of Export Administration did not seek comments from the scientific community before issuing it. Second, the Office has not clarified the basis on which it decides if an organism should be placed on the list. Finally, the Office must formally amend Interpretation 28 by rulemaking before it can place new, nonpathogenic species of commercially important microorganisms on the list.

Data exports* or reexports** to certain countries are also subject to licensing under the ex-

*Export of data occurs whenever data are transmitted out of the United States, released in the United States with the knowledge that they will be transmitted abroad, or released abroad (15 C.F.R. §379.1(b)(1)).

**Reexport of data is the release of data of U.S. origin in a foreign country with the knowledge that the data will be transmitted to another foreign country (15 C.F.R. §370.2). The recipient of technical data must provide written assurances that the data will not be reexported.

Table 67.—Controls on Biotechnology Products Under the Export Administration Act of 1979

Commodity	Commodity Control List (CCL) category	Countries for which a validated license is required[a]
Organisms:		
Viruses	CCL 4997B	All except Canada
Bacteria	CCL 4998B	All except Canada
Human and animal bacterial vaccines	Interpretation No. 24 (CCL 6799G) or Interpretation No. 28	S, Z
Human and animal viral vaccines	CCL 4997B or CCL 6999G	All except Canada S, Z
Human and animal peptides and proteins (pharmaceuticals)	Interpretation No. 24 (CCL 6799G)	S, Z
Human and animal peptides and proteins (miscellaneous)	Interpretation No. 24 or CCL 6999G or CCL 5799D	S, Z P, Q, S, W, Y, Z
Recombinant DNA and related compounds (DNA nucleosides, nucleotides)	Interpretation No. 24	S, Z
Human and animal antibiotics	Interpretation No. 24	S, Z
Human and animal diagnostic agents	Interpretation No. 24	S, Z
Amino acids	Interpretation No. 24 or CCL 6999G or CCL 5799D	S, Z P, Q, S, W, Y, Z
Vitamins	Interpretation No. 24	S, Z
Enzymes	Interpretation No. 24 or CCL 57919D	S, Z P, Q, S, W, Y, A
Pesticides and herbicides (excluding microbial agents)	Interpretation No. 24 or CCL 4707B or CCL 5799D	S, Z All except Canada P,Q,S,W,Y,Z
Seeds	CCL6999G	S, Z

[a]The countries are grouped as follows: P - People's Republic of China; Q - Romania; T - essentially the Western Hemisphere, except Cuba and Canada; V - Southern Rhodesia and countries not in any other group (except Canada); W - Hungary and Poland; Y - Albania, Bulgaria, Czechoslovakia, Estonia, G.D.R., Laos, Latvia, Lithuania, Outer Mongolia, and the U.S.S.R.; Z - North Korea, Vietnam, Cambodia, Cuba; S - Libya.

Under a recent amendment to the Commodity Control List, the export of "medicine and medical products" to Libya does not require a validated license.

SOURCE: Office of Technology Assessment, 1983.

port control regulations. There are three categories of technical data that may be exported to any country under a general license (i.e., an exemption): 1) data already generally available without restriction and at nominal cost, such as in publications or through conferences; 2) scientific or educational data not directly and significantly related to industrial applications; and 3) data contained in foreign patent applications (15 C.F.R. § 379). However, if companies using biotechnology choose to protect information as trade secrets or if information has commercial value, these exceptions will not apply.

The U.S. export control regulations do provide another limited exemption of greater practical use for biotechnology data exports, depending on the destination and the nature of the exported data. Broadly speaking, exports of technical data to virtually all non-Communist countries and, under more restricted circumstances, to the eastern bloc or the Peoples Republic of China, may take place under a general license rather than a validated license.* However, a validated license is required for technical data related to Group 9 commodities, if the data is exported to Communist countries.

Controls on the export of "dual-use" technical data (data with both military and civilian uses) may become more important to the international commercialization of biotechnology in the future. In 1976, the Defense Science Board Task Force on Export of U.S. Technology issued a report (the Bucy report) which concluded that U.S. export controls should focus on design and manufacturing know-how for critical technologies rather than on products (7). In the EAA, Congress directed the U.S. Secretary of Defense to develop a "Militarily Critical Technologies List" (MCTL) and to incorporate it into the export control system after review by the U.S. Department of Commerce. The U.S. Department of Defense has developed a broad MCTL, most of which is classified (19). This list covers many technologies, including ones with primarily nonmilitary applications and has been criticized as covering virtually all of modern technology (19). The MCTL is being revised and has not yet been incorporated into the export control regulations.

Section 16.8 of the Defense Department's MCTL is most pertinent to biotechnology because it covers "technology for manufacture and dissemination of biological and toxic materials." It would cover know-how for: 1) design and production of bacterial, viral, and fungal products, including vaccines, specialized high containment facilities, and special instrumentation; and 2) design, production, and use of dissemination equipment. It would also cover related equipment, materials, and goods accompanied by sophisticated know-how. Although the MCTL has not yet been implemented, it appears that such a concept will be incorporated into the EAA renewal.

In addition, "biological agents adapted for use in war" are subject to controls under the Arms Export Control Act, as are technical data related to biological warfare agents, including "any technology which advances the state-of-the-art or establishes a new art in an area of significant military applicability in the United States" (22 C.F.R. § 125.01). Many pathogenic organisms could be viewed as biological warfare agents, yet their export could be for peaceful purposes such as for research to develop a vaccine. Ultimately, the decision on what products are "adapted for use in war" is left to the discretion of the U.S. Department of State. In addition, the broad definition of technical data could include even information indirectly related to military applications, such as information relating to cloning of genes for human neurotransmitters, because many chemical and some biological warfare agents act by affecting these neurotransmitters (4). On the other hand, a fairly recent case indicates that the courts will interpret the definition of technical data much more narrowly (17).

To sum up, the current impact of U.S. export control requirements is minimal except in the case of micro-organisms where the Commerce Department sees the need for broad controls on national security grounds. Exports of most products and technical information to non-Communist countries should be possible without need for a validated license under the EAA regulations. However, the export of most micro-organisms to all

*In many instances, the availability of this general license for exports to non-Communist countries is conditioned on assurances against unauthorized reexport to a controlled destination.

countries except Canada will require a validated license unless the micro-organisms are inactivated, attenuated, or fall within Interpretation No. 28 *E. coli* and some other micro-organisms of interest to biotechnologists do not fall within Interpretation 28 and therefore require a validated license for export (unless inactivated or attenuated). Controls over micro-organism shipments and data transfers will have most impact on those companies that do research abroad.

Although the impact of the current U.S. export controls on biotechnology companies appears to be fairly modest, the future impact is unclear. The EAA expired on September 30, 1983. Although U.S. export controls continue in effect under the International Emergency Economic Powers Act, it is not clear what form the EAA's successor will take.* Many different bills are pending. Some would strengthen U.S. export controls in general, while others would liberalize them. Furthermore, even if the broad framework of export controls does not change significantly, it is possible that controls could be tightened at the administrative level. The Undersecretary of Defense for Policy testified before Congress in 1982 that "microbiology" is one of the technologies that "pose the greatest risk to U.S. security" (11). Similarly, the April 1982 Central Intelligence Agency publication, *Soviet Acquisition of Western Technology,* identified microbiology, and especially "genetic engineering," as one of the major fields of interest to Soviet and Eastern European visitors to the United States (11). A recent interagency discussion paper for the White House Office of Science and Technology Policy (OSTP), on the other hand, concluded that more restrictive measures to control the transfer of biotechnology are not warranted and may be counterproductive (8). It also noted that existing export control regulations could be clarified and better administered. How much impact this latter report will have in the administration is unknown. OSTP has taken the position that the report is a draft only and will be part of a larger review of technology transfer and national security (4).

*For a complete discussion of the major bills and the various congressional options on export control, see the May 1983 OTA report *Technology and East-West Trade: An Update* (19).

Japan

Japanese export controls combine trade concerns with defense and foreign policy objectives. In addition, Japan cooperates with CoCom controls (18). Under the Foreign Exchange and Foreign Trade Control Law of 1949 (most recently revised in 1979) and the implementing Export Trade Control Order, Japan's Ministry of International Trade and Industry (MITI) may require export licenses on the basis of domestic short supply, export restraints for orderly marketing reasons, defense, and harm to public order or morals. The list of controlled items in the Export Trade Control Order includes blood derivatives, fertilizers, and bacterial agents for military use. (The policy of the Japanese Government is to ban all arms exports.) An export license from MITI is required to export these commodities to any foreign destination. The licensing process, in practice, involves extensive preliminary consultations resulting in informal advance clearances (18).

Federal Republic of Germany

Export controls in the Federal Republic of Germany are limited to commodities and information directly related to "implements of war," are limited in nature and scope, and must interfere as little as possible with freedom of economic activity (1). Except for data and documents concerning goods controlled multilaterally by CoCom, technical data are unrestricted. Certain biological and chemical warfare materials, including some micro-organisms, are controlled. Thus, export controls in the Federal Republic of Germany are much less restrictive than the controls in the United States. West Germany's export controls should have little or no impact on data or product exports by companies using biotechnology in the Federal Republic of Germany that wish to trade internationally.

United Kingdom

The United Kingdom controls the export of goods but not technical information under the Import, Export, and Customs Powers (Defense) Act. Export licensing decisions are national-security-based. No biotechnology products are on the Board of Trade's list of controlled commodities.

Switzerland

Swiss law formerly provided for export controls in the "national interest" on two categories of biotechnology products: serums and vaccines, and pharmaceuticals (16). Currently, however, there are no Swiss controls on biotechnology products or data.

France

The French export controls appear to be quite informal and a product of administrative action rather than statutory decree. The French Ministry of Economics and Finance's list of products requiring export licenses includes biotechnology materials usable in biological warfare and their related technical data. The controlled list does not include antibiotics, other medicinal products, or cultures of nonpathogenic organisms.

Comparative analysis

U.S. export controls in general are more restrictive than those of Japan or the four European competitor countries, and they are more restrictive with regard to biotechnology. The United States is the only country that controls exports of pharmaceuticals for foreign policy reasons and is the only nation that has perceived a national security interest in controlling the export of microbial cultures generally. The other nations only embargo shipments of biological warfare agents.

U.S. export controls could cause problems for U.S. firms using biotechnology due to delays in the export licensing process or uncertainties in the application of controls. These problems will occur primarily in the export of micro-organisms, many of which will require a validated U.S. export license. In contrast, exports of most biotechnology products and data will not require a validated license. If export controls are a significant handicap to U.S. firms' competitiveness in biotechnology, these controls may lead U.S. firms using biotechnology to source their exports from affiliates abroad, to first introduce new products abroad, or to site their R&D abroad.

Patent law provisions affecting international technology transfer

Patent laws of many countries, including the United States, contain secrecy provisions that restrict outward technology transfer for security or foreign policy reasons. On the other hand, compulsory licensing provisions can be used to force inward technology transfer. This section discusses these two types of provisions in the patent laws of the competitor countries.

National security restrictions on patent applications

The U.S. patent law provides a waiting period after filing for a patent in the United States during which the U.S. Patent and Trademark Office and the U.S. defense agencies may screen the invention on national security grounds and withhold the grant of a patent. In addition, procedures exist for the review of applications in foreign countries by U.S. parties, and secrecy orders can be issued in certain instances. The review period results in an effective prohibition against foreign filings within 3 months of the U.S. filing. French, United Kingdom, and West German patent laws have similar provisions. However, the Federal Republic of Germany will issue a secret patent instead of a secrecy order. Swiss patent law provides for expropriation with compensation; Japanese patent law does not place any national security restrictions on the application process.

National security provisions create delay in filing foreign patents for all patent applicants. It is too early to tell whether military uses of biotechnology will make patent secrecy orders a significant problem for biotechnology.

Compulsory licensing of patents

In most countries, patent owners who fail to put their inventions into practice in the country within a prescribed period may have their patent rights reduced or revoked. Failure to exploit a patented invention in the country is regarded as an abuse of the patent monopoly rights and may subject the patent to compulsory licensing, revocation, or automatic lapse (2). Compulsory licensing is the normal remedy employed in these situations. Proponents of compulsory licensing argue that it ensures early applications of a technology and diffuses control over technology. Its opponents argue that it discourages public disclosure of new technology through the patent system, expropriates property rights, and decreases incentives to innovate. In the United States, compulsory licensing is generally viewed as inconsistent with the patent owner's right to exclude others from making, using, or selling the patented invention, and U.S. law provides for compulsory licensing only in limited instances.

Countries with compulsory licensing recognize that it may be very difficult for a licensee to practice a patent without the benefit of the patent owner's continued technical assistance and that this assistance is unlikely to be forthcoming when unfavorable terms are imposed on the patent owner. Thus, compulsory licensing can discourage the transfer of know-how in conjunction with the license. This may be less of a problem in cases where an organism has been deposited in support of a patent. Since the organism is publicly available and is in esence a "factory" for the product, a licensee that obtained a compulsory license may not need the know-how. In this situation, compulsory licensing could be a threat to U.S. biotechnology companies because sufficient technology transfer could occur for the compulsory licensee to use the invention competitively without any assistance from the patent owner.

An international patent treaty known as the Paris Convention permits any of its member countries to require compulsory licensing of its patents after 3 years from the date of issuance, if the patent is not sufficiently worked. However, the Convention provides exceptions for reasons such as compliance with national safety requirements (15). All of the competitor countries are signatories to the Convention, and all but the United States have general compulsory licensing statutes consistent with the Convention.

In some cases, in the interests of free trade and regional cooperation, the requirement that an invention be worked in the country is waived when the demand for the patented product in the country is being met by manufacturing in a cooperating country. This is the case for the member states of the EEC. Bilateral agreements also exist between Switzerland and the United States and between the Federal Republic of Germany and the United States whereby the working of a patent in the territory of one of the parties is considered equivalent to its working in the territory of the other party.

Specialized compulsory licensing provisions of interest include United Kingdom and French provisions for compulsory licensing of pharmaceuticals in certain circumstances.

Although the U.S. system generally allows the patentee to use or not use the patented technology at will, certain statutes and judicially created legal doctrines provide for compulsory licensing in limited cases. For example, statutory compulsory licensing exists under the Plant Variety Protection Act* and the recent statute on ownership of federally funded inventions (Public Law 96-517). Compulsory licensing also exists de facto where courts do not enjoin patent infringement on grounds of patent misuse, antitrust violation, or public policy.

Assessing the impact of compulsory licensing laws on U.S. competitiveness in biotechnology is necessarily speculative at this time. Compulsory licensing of patents could result in transfer of biotechnology and could adversely affect U.S. competitiveness in biotechnology. Although compulsory licenses apply in theory equally to any company, foreign or domestic, in practice they could be used discriminatorily against U.S. companies; standards that provide for licenses "in the public interest" grant wide discretion to the governmental body that decides such cases.

*The act permits the Secretary of Agriculture to declare a protected variety open for use for up to 2 years at a reasonable royalty in order to ensure an adequate supply of food, fiber, or feed in this country when the owner is unwilling or unable to meet the need at a fair price (47 U.S.C. §2404).

Regulation of technology imports and foreign investment

Foreign exchange and investment control laws are sometimes applied to technology licensing or technical assistance agreements or to foreign investment, with the effect of restricting the importation of foreign technology or foreign capital and helping locally controlled firms retain control of the local market.* Such restrictions have two rationales. First, a nation in a precarious balance of payments position may look askance at what it views as the payment of exorbitant sums for foreign technology. Second, a nation might act to prevent or modify a transaction for political reasons in instances where imported technology or foreign investment might result in increased control of a local firm by a foreign firm.

The United States, the United Kingdom, the Federal Republic of Germany, and Switzerland currently have no significant formal exchange or investment control laws. Although these countries lack statutory and administrative mechanisms for direct control over private international technology transfer agreements, de facto means exist in the United Kingdom, the Federal Republic of Germany, and Switzerland under which these governments could block foreign investments in those exceptional cases in which it might be deemed necessary to do so for screening important investments* (14). France and Japan have investment or exchange control mechanisms that do affect technology transfers and foreign investment.

France moved in 1970 from a system requiring prior review of technology transfer agreements to a system requiring notification after the fact. Currently, the French party to an international "industrial property" or "scientific and technical assistance" agreement must notify and submit a copy to the Industrial Property Service of the Ministry of Industrial and Scientific Development within 1 month after the agreement is concluded (9). The French party must also submit yearly reports of payments made and reciprocal transfers of technology. The submissions are confidential, and compliance is a prerequisite to being able to transfer royalty payments (10).

This mechanism appears to be one primarily designed to gain statistical information, but one source indicates that it may have further ramifications (5). The French Ministry of Economy may express reservations if it considers the royalty payments to be too high. Such an action could result in the excess amount of royalties being prohibited from being deducted for tax purposes. Most of the reservations expressed by ministry officials have involved contracts in the chemical, pharmaceutical, and petroleum sectors (5). Thus, the ministry officials may be inclined to express reservations for biotechnology licensing agreements, if those agreements are viewed as not being sufficiently favorable to the French party.

France's investment control laws are relevant both to biotechnology transfer and to the ability to invest in the French market. Nonresidents of the European Economic Community (EEC) that plan to invest in France must submit a declaration to the Ministry of Economics and Finance. The declaration includes information on the identity of the investor, the business to be invested in, the forms, conditions, rationale, and consequences of the investment, and financial information on the companies involved. Within 2 months following the receipt of the declaration, the Ministry may order the suspension of the proposed action.

Direct foreign investment in certain industries is not encouraged in France. And in France as in

*Trade and investment restrictions, together with compulsory licensing provisions can act like pincers to extract a foreign technology owner's industrial property rights. The foreign technology owner may patent the product in an important market, be blocked from using the patent himself, and have to license the patent on pain of losing its benefits.

*For example, in the Federal Republic of Germany, any enterprise whether domestic or foreign that acquires 25 percent or more of the shares of stock in a German corporation must notify the provincial banking authorities and the target company when it buys the shares. Section 23 of the Foreign Trade Law authorizes the German Federal Government to ban the sale of a company to nonresidents on national security grounds. While the Federal Government has never had to use this power, its existence makes possible an informal but well-known agreement between the Federal Government and the major banks (which often are major shareholders of companies) that no company nor block of stock be sold without prior consultation with the Government.

all countries other than the United States, takeovers of local companies are not favored, particularly takeovers resisted by the local management (14). On the other hand, investments that provide for capital transfer or technology transfer into France are favored. Given the French Government's concerted efforts to stimulate biotechnology, investments by foreign companies in French companies using biotechnology are likely to be carefully scrutinized.

Of the countries under study, Japan has been most restrictive regarding technical assistance and licensing agreements between foreign parties and Japanese companies and direct foreign investment. In the period 1949-68, all licensing agreements and all foreign investments in Japan had to be reviewed in advance by the Japanese Government. Over the years, an increasing range of agreements and investments were given "automatic approval." Finally, the revised Foreign Exchange and Foreign Trade Control Law (effective Dec. 1, 1980) provided that foreign trade and investment is to be free in principle and restrictions are to be exceptional.

Under Japan's revised Foreign Exchange and Foreign Trade Control Law, the Japanese Government has the power to screen investments. Before a foreign investor can conduct a transaction characterized as "direct foreign investment," the investor must give notice to the Japanese Government. The foreign investor must then wait 30 days before proceeding with the transaction.* The Minister of Finance and the minister in charge of the industry concerned also have the power to designate specific companies for special controls on foreign ownership. Eleven companies have been so designated, including Sankyo Pharmaceuticals (25-percent ceiling on foreign ownership).

Articles 29 and 30 of Japan's Foreign Exchange and Foreign Trade Control Law deal specifically with "agreements for importation of technology." The parties to such an agreement must first notify the Minister of Finance and the minister in charge of the industry involved of the terms of the agreement whenever they intend to enter into, renew, or amend such an agreement. The agreement cannot be concluded until a 30-day waiting period has elapsed. (Normally, the ministries exercise their power to shorten this period for transactions not deemed "harmful.") The ministries review the agreement with respect to a number of criteria, ranging from national security to competition with other Japanese business. The Japanese Government has a fair degree of control over technology transfer agreements, although it is not clear whether the control is used to secure better contractual terms for Japanese companies, particularly terms that encourage biotechnology transfer to Japan.

The greatest significance of Japanese investment controls for biotechnology products is the lingering effect of past controls. In strategic industries where foreign companies' technology position was strong, liberalization of investment controls came late. In pharmaceuticals, for instance, 100-percent foreign ownership was not permitted in Japan until 1975, so non-Japanese drug companies either had to enter a joint venture with a Japanese firm (or license to a Japanese firm) or had to forgo the world's second largest drug market (22). Late liberalization of investment controls retarded foreign firms' establishment of their own marketing and distribution networks in Japan. Nevertheless, the international pharmaceutical companies have a strong and increasing presence in Japan, and some foreign pharmaceutical companies have even acquired smaller Japanese pharmaceutical firms. Merck's recent acquisition of Banyu Pharmaceutical, the number three firm in the Japanese industry, puts Merck in an extremely strong position in the Japanese market. Still, the waiting period for investments and for licensing contracts is at the least a nuisance to the inward investment or licensing transaction, although other factors such as interlocking directorships, cross-holding of stock, and labor resistance to foreign management may be very significant in discouraging investment entry into the Japanese market through a hostile takeover.

*If certain circumstances are found to exist, then within an extended waiting period, the Government may recommend that the agreement be altered; this power has seldom been used in recent years. If this recommendation is not accepted, the Government may suspend the transaction indefinitely by Cabinet Order.

Trade barriers affecting biotechnology products

While firms using biotechnology now trade mostly in technology through licensing and have in a few cases invested abroad, trade in the products of biotechnology is just beginning. The tariffs on biotechnology products are generally low in the competitor countries and are getting lower (as Tokyo Round tariff cuts are phased in).* Thus, it is nontariff barriers that are most likely to be important to trade in biotechnologically produced products.

Nontariff barriers to trade include any government intervention affecting competition between imported and domestic goods. The barriers most significant for biotechnology products will be those that affect technology development and technology transfer:

- health and safety standards and certification systems;
- subsidies;
- price regulation;
- to a minor degree, government procurement; and
- least significant, customs classification of new products.

Rather than addressing health and safety regulation per se, the discussion here addresses how such regulation applies specifically to imports. Similarly, rather than considering the specific production and R&D subsidies, it considers how these programs fit in with U.S. rights under trade agreements. For instance, Japan maintained until very recently a dual safety certification system that discriminated against imports, including imported drugs, medical devices (e.g., monoclonal antibodies), chemicals, and animal drugs (20).

Standards and certification systems

Product standard systems are a particularly thorny problem for exporters of health care products, because such products are extensively regulated and subject to the regulator's discretionary determination of whether imported products meet applicable standards. Product standards can affect the activities of both exporting and importing companies. Biologically produced pharmaceuticals, vaccines, foods, chemicals, and veterinary products will all be subject in some degree to inspection, approval, and/or certification of whether they meet local standards of safety and efficacy.

For a foreign manufacturer, registration and approval of a product in a certification process involves inevitable leakage of technology. Any manufacturer must explain its technology to local regulators to the extent necessary to get its products approved. In those countries where marketing approval for an imported product can only be given to a locally resident importer, as has been the case in Japan, the technology (including trade secrets and nonpatentable know-how) that is required for an application for approval must be transmitted to the regulating authority by the importer, whose possession of this information could provide the resident importer with leverage over the foreign manufacturer. This generalization applies equally to foreign manufacturers in the United States and to U.S. manufacturers abroad. Leakage of technology may also occur where a registration scheme involves disclosure of trade secrets, as in the case of disclosure of chemical identities for registration in the European Inventory of Existing Chemical Substances under the EEC's Sixth Amendment regulation scheme for toxic chemicals.

The Agreement on Technical Barriers to Trade ("Standards Code") addresses these problems. The Standards Code, negotiated in the Tokyo Round of multilateral trade negotiations, came into effect January 1, 1980 and covers all six countries discussed in this report. This code requires the following: 1) national or regional certification systems must treat products of code signatories no less favorably than domestic products, 2) imported products must be treated in a nondiscriminatory manner with regard to product testing and certification, and 3) signatories must use the same test methods and administrative procedures

*All of the competitor countries belong to the General Agreement on Tariffs and Trade (GATT). GATT is a multilateral agreement signed by 87 governments accounting for over 80 percent of world trade. GATT serves as a code of rules for international trade and as an international trade organization. A primary goal of GATT is to discourage the use of nontariff barriers to trade and then to reduce tariff levels through a series of multilateral trade negotiating rounds of which the most recent was the Tokyo Round (1973-78).

for imports and domestic products and charge comparable fees. Test results must be made available to the exporter, importer, or their agents, and confidentiality of information must be respected equally for foreign and domestic suppliers. The Standards Code does not implement a transnational standards system. It merely provides international rules for how individual national systems treat products of other code signatories, provides a forum for negotiations, and provides redress against foreign violations of the code (20).

JAPAN

Until recently, one of the most wide-ranging barriers to foreign market access in Japan was discriminatory certification systems (20). While various product standards were administered under different laws, the framework was remarkably uniform. Each law would provide two tracks: 1) an approval adapted to high-volume production and sales, requiring factory inspection and product-type approval; and 2) a low-volume approval, involving lot-by-lot inspection. The first track was legally foreclosed to foreign manufacturers. Because the person holding the product approval had to be subject to potential sanctions under Japanese law, that person had to be present in Japan. Furthermore, the product approval (and all data to obtain it) was the property of the approval holder, who under the second track had to be the Japanese importer. Transfer of the approval to another importer (even transfer of the approval from a joint venture to a wholly owned subsidiary) meant regenerating the data.

In response to foreign complaints, the Japanese Diet, on May 18, 1983, passed legislation amending 16 Japanese standards and certification laws, including the Pharmaceutical Affairs Law (drugs, medical devices), the Agricultural Chemicals Law, and the Toxic Chemicals Law. The amendments, together with their implementing regulations issued soon thereafter, are designed to give foreign producers direct access to certification systems, including direct ownership of approvals. Foreign regulated products—such as drugs or monoclonal antibody kits—still (as of fall 1983) must be unpacked, sampled, and tested, lot by lot, as they pass Japanese customs. Foreign manufacturers may now apply for, and be granted, factory inspection and U.S. product type approval. U.S. trade negotiators are now working for Japanese acceptance of factory inspections carried out by U.S. testing firms for this purpose.

The Japanese Ministry of Health and Welfare, which previously refused to accept entirely foreign clinical test data because of racial and dietary differences, agreed in January 1983 to work toward acceptance of foreign clinical data and to undertake objective studies of racial and dietary differences. However, as of December 1983 no such studies had been undertaken. In addition, the Ministry promised to clarify the line between (regulated) pharmaceuticals and (unregulated) foodstuffs and to shorten the approval period for in vitro diagnostics used as medical devices. The Ministry has also promised to allow approvals to be transferred between importers of drugs and importers of medical devices.

EUROPE

U.S. chemical exporters have been concerned about inadequate protection of proprietary data in the European registration process, in particular, the requirements for disclosure of chemical identities of substances. Another long-term concern of U.S. pesticide exporters has been pesticide registration procedures abroad, which may diminish the proprietary value of registration data by allowing national authorities to use data submitted by pioneer registrants in determining the safety of "me-too"* pesticides (20).

Subsidies

Subsidies (e.g., loans, grants, tax preferences) are a form of government intervention which, in some cases, can provide competitive advantages to domestic producers. There is basic disagreement between the United States and its trading partners both on how to define a subsidy and on how to measure its effect. The position of the United States is that a measure of a subsidy is the benefit conferred on the recipient; the position of the EEC is that the measure should be the cost to the government or the benefit to the recipient,

*"Me-too" products are generic products equivalent to an already existing product.

whichever is lower. In any case, subsidies used by governments may be important in international competition to commercialize biotechnology.

One of the most controversial agreements of the Tokyo Round was the Subsidies Code, which attempts to expand international discipline over subsidies. Three aspects of the Subsidies Code are important to firms using biotechnology. First, the code prohibits any export subsidies on industrial products. This means that neither the United States nor its competitor countries can grant export subsidies on biotechnology products without violating the code. Second, the code recognizes that domestic subsidies, which include all existing subsidies that affect biotechnology, can be used except in situations where the subsidies: 1) cause or threaten injury to another signatory's industry, 2) cause or threaten "serious prejudice,"* or 3) nullify or impair GATT benefits of another signatory. Third, the code provides for remedies. Two methods of obtaining remedies are available: countervailing duties (described under the discussion of U.S. trade law below) and multilateral dispute settlement.

The Subsidies Code sets limits on both the export subsidy behavior of our trading partners and on what the United States (and other signatories) can do to promote industry. The code also authorizes national governments to unilaterally impose countervailing duties** on subsidized imports to offset subsidies, where the importing country's government has found that there are subsidies and that injury to domestic industries is caused or threatened by reason of the subsidized imports.

All presently known government promotion measures affecting the commercialization of biotechnology are either domestic subsidies or other promotional measures that legally do not qualify as subsidies at all. Under U.S. subsidy and countervailing duty practice, R&D grants and preferential loans awarded by a government to finance research that has broad application and yields results that are made publicly available are not legally subsidies. The test of a subsidy in this case is whether the result of a government-funded research project in biotechnology is published and made available. Loans are deemed subsidized to the extent that the borrower obtains a better interest rate for the loan than that which would otherwise be available to him for a loan of similar size and terms. As for government equity ownership, the U.S. position is that government ownership implies a subsidy only when it is inconsistent with commercial considerations. If the government buys shares either directly from the company or the stock market, a subsidy arises to the extent the government pays more than the market price. Given the favorable market for most biotechnology stocks, even for those issues that have shown no operating profits to date, it seems unlikely that government investment in biotechnology companies such as Celltech would be classified as a subsidy under U.S. practice.

Price regulation and government procurement

Price regulation is central in importance to the world market in pharmaceuticals and may be an important means of discouraging foreign suppliers to enter particular domestic pharmaceutical markets. Thus, price regulation, particularly of new drugs, will be important to the marketing and profitability of biotechnology pharmaceuticals. The basis for price regulation is the local or national social insurance scheme, which pays for all or part of the beneficiaries' drug cost. Although the basic motivation for price regulation is health care cost containment, price regulation can be used to reward manufacturers for local production, local R&D, and other desired behavior. Thus, in countries where drug costs are paid or reimbursed by the government, in a real sense the government creates the market. Furthermore, inclusion on the government list of approved drugs, at a profitable price, is essential to market access for foreign drugs.

GATT Article III requires that products of GATT signatories be given treatment equal to that given local products with regard to price regulation, internal taxes, and other regulations. If there is a

*Serious prejudice relates to effects of subsidies in third-country markets but is not defined in the Code or GATT.

**Countervailing duties are imposed by governments to offset subsidies found to benefit imports into countries where the subsidized imports cause or threaten material injury to a domestic manufacturer producing a like product.

clear factual case of discrimination, enforcement of this requirement is straightforward.

In the United States, Federal and State funds pay for only 8 percent of out-of-hospital drug costs. The Maximum Allowable Cost program instituted in 1979 by the Department of Health, Education, and Welfare sets price ceilings on drugs paid for by federally financed health-care programs such as Medicaid. In addition, a growing number of States are instituting open or closed formulary systems (recommended or mandatory drug lists) for prescriptions paid for by State funds (22).

In the Federal Republic of Germany, all drugs are dispensed through the pharmacies or hospitals, which are reimbursed by the insurance plan to which the patient belongs. An official price list is set by the pharmaceutical manufacturers association, and the Government regulates the wholesalers' and pharmacies' markup.

In the United Kingdom, the Government pays for approximately 90 percent of drugs consumed (22). Dispensing of drugs is through the pharmacies, which are reimbursed on the basis of ingredient cost, profit, professional fee, and container allowance. The Department of Health allows a larger profit margin for companies that manufacture or perform R&D locally, a provision which may be inconsistent with GATT Article III and the Treaty of Rome (21).

In France, drugs are distributed primarily through pharmacies, and patients are reimbursed by the social insurance system at a set percentage (40, 70, or 100 percent) of the official list price. The Government sets not only the retail price for each drug on the official price list, but also the markups in the distribution chain. One report states that health care cost containment concerns have led to drug prices too low to finance R&D by the local pharmaceutical industry (21).

In Switzerland, dispensing of drugs is through pharmacies and doctors. Price regulation is the responsibility of the Federal Social Insurance Office which maintains two lists of drugs for reimbursement: 1) generic drugs, for which reimbursement is required; and 2) the "SL List," a list of specialty drugs for which reimbursement is not required but usually happens anyway. For imported drugs, sales prices abroad are carefully monitored; the Federal Social Insurance Office will allow a 25-percent margin over the selling price in the country of origin (excluding tax) (22).

The Japanese drug distribution system is unique. Almost all drugs in Japan are dispensed by physicians whose drug lists and markup are regulated by the national health insurance system. The doctor buys drugs from the wholesaler at a price that varies depending on the size of order, size of clinic, and other commercial factors. The doctor then resells the drug to his patients at the regulated price. The difference is the doctor's profit, which averages between 20 to 50 percent of the regulated price (12). Japan's price regulation system is used to encourage R&D. The recently revised (April 1983) method of drug price reimbursement allows a larger profit margin depending on desirability and efficacy of the drug; this, in combination with the more generous official prices set for new drugs, may be used to reward R&D and favor new drug (including biotechnology drug) development (14).

Government procurement

Under GATT, governments may buy products as they wish for their own consumption and target their procurement to favor local suppliers. However, the GATT Procurement Code, negotiated in the Tokyo Round reciprocally, opens bidding opportunities on certain procurement and provides fair procurement procedures. For biotechnology products, government procurement would have substantial impact only where consumption by the government is large relative to the total market or has a significant demonstration effect. It is unlikely that government procurement will play a role in biotechnology development comparable to the role of the U.S. Defense Department or the Japanese Government in the semiconductor industry. While governments do buy pharmaceuticals, many drug companies avoid bidding on government tenders for commercial reasons, and in developed countries, procurement markets are not significant relative to total pharmaceutical demand.

Customs classification

Customs classification might be a problem only for those biotechnology products for which classification is an open issue—i.e., either those products that are genuinely new or existing products assigned to a different classification due to their biotechnologically based production. Over the next several years, most biotechnology products with the exception of some vaccines will probably be replacement products for existing products. If the trading partners of the United States reclassify biotechnology products and raise tariffs, such strategic protectionism could raise new barriers around foreign markets. Since only a few products developed through biotechnology are traded at present, it is not clear whether the competitor countries will reclassify the biotechnology products under different (higher tariff) categories. There is, however, no reason to believe that they will be reassigned.

Trade laws

Trade laws may offer a means to improve the competitive position of U.S. firms using biotechnology. This section reviews the array of trade law actions relevant to U.S. firms using biotechnology and assesses whether biotechnology raises particular issues as to the adequacy of present trade laws.

While trade in biotechnology products is in its infancy, some factors will influence the likely interaction between biotechnology and trade law. First, to the extent that trade in a product is wholly under a licensing agreement or is an intracompany transfer of a patented substance (or organism), there are likely to be few problems with import competition. Second, there is no reason to believe that biotechnology products will trade differently or be classified differently from other products; human insulin will have the same distribution channels as animal-derived insulin, for instance. Third, since the efficacy of any type of import relief is tied to the pace of product obsolescence, which differs by industry, the import relief concerns of other industries such as the semiconductor industry will be of limited importance to industries using biotechnology.

Section 337 of the Tariff Act of 1930

The U.S. import trade statute most immediately relevant to firms using biotechnology is section 337 of the Tariff Act of 1930 (19 U.S.C. §1337), which provides for relief against unfair competition in import trade, including imports found to be infringing intellectual property rights, where such practices injure an efficiently operated industry in the United States, prevent the establishment of such an industry, or restrain trade. If the U.S. International Trade Commission (ITC) finds a violation, it may issue either an exclusion order prohibiting the import of the goods in question or a cease and desist order to proscribe specific conduct by parties over which ITC has jurisdiction. Investigations under section 337 are conducted by ITC. The President may disapprove such a determination for policy reasons within 60 days.

There are several points to note about section 337. If an import is found to violate section 337, it can be completely excluded from importation; ITC need not get jurisdiction over the foreign manufacturer. Second, section 337 investigations are faster (18 months maximum) and generally less expensive than other types of litigation (e.g., patent or trade secret infringement litigation). Third, where there is multiple-source infringement, ITC can issue a general exclusion order, excluding all infringing products made by any firm. Section 337a (19 U.S.C. §1337a) provides that section 337 can be used to enforce process patents; ITC in past process patent cases has been willing to issue broad exclusion orders, particularly where infringing and noninfringing goods are physically indistinguishable.

Section 337's greatest relevance for biotechnology is that at present, section 337 is the most effective means of enforcing process patents

against foreign producers. It could, for instance, be used to enforce the Cohen-Boyer process patent against imports from firms that have not taken a license from Stanford (although Stanford would run the risk that its patent might be found invalid by ITC). Furthermore, a firm need not have patented the intellectual property in question; section 337 applies as well to misappropriations of trade secrets. A firm that has elected to take the trade secret route instead of patenting its research results could use section 337 against goods incorporating stolen trade secrets.

A section 337 investigation concerning allegations of patent infringement and trade secret misappropriations with respect to "certain limited charge cell culture microcarriers" is now in progress.*

Section 301 of the Trade Act of 1974

The other important trade remedy for firms using biotechnology is section 301 of the Trade Act of 1974 (19 U.S.C. 2411 ff). Under section 301, firms can petition the U.S. Government to enforce U.S. rights under trade agreements or to negotiate to eliminate foreign government actions that unreasonably limit market access abroad. Section 301 also provides authority for the President to retaliate against any foreign government action that is "unjustifiable, unreasonable, or discriminatory" and burdens or restricts U.S. commerce (14).

*Certain Limited Charge Cell Culture Microcarriers, Investigation No. 337-TA-129, instituted Aug. 17, 1982, concerning allegations of: misappropriation of trade secrets; refusal to sell sieved beads; false and deceptive advertising; false and disparaging comments about complainants; direct, contributory, and induced patent infringement; and unauthorized manufacture abroad in violation of process claims of a U.S. patent. Complainants are Flow General Inc. and Massachusetts Institute of Technology; respondents are AB Fortia, Pharmacia AB, Pharmacia Fine Chemical of Sweden, and Pharmacia Inc. of New Jersey.

An investigation under section 301 of the Trade Act of 1974 is conducted by the U.S. Trade Representative and is normally initiated in response to a petition by any interested person.* The Trade Representative, with the advice of other U.S. Government agencies, recommends what action should be taken by the President. Firms using biotechology can use section 301 to gain U.S. Government action against foreign government actions that restrict market access or violate GATT, the Standards Code, or bilateral or multilateral agreements. For such problems, section 301 is often the best or only formal remedy. However, section 301 would not apply if there were no foreign government involvement (e.g., dumping or illegal private cartels). Also, even without formal section 301 action, the assistance of the U.S. Government is available for resolving market access problems abroad.

Countervailing and antidumping duty laws

Countervailing duties (19 U.S.C. 1671 ff) are imposed to offset subsidies found to benefit imports into the United States where the subsidized imports cause or threaten material injury to U.S. industry producing a like product. Similarly, antidumping duties (19 U.S.C. 1673 ff) are imposed to offset injurious dumping of foreign merchandise in the United States.** The U.S. Department of Commerce makes preliminary and final findings concerning subsidization or dumping, and ITC makes preliminary and final findings concerning material injury to the U.S. industry. Biotechnology products are unlikely to raise novel issues for these laws.

*Interested persons include any person representing a significant economic interest affected by the complained policy or actions.

**"Dumping" exists when goods are sold for export below their cost of production or more cheaply than for the home market.

Findings

Export control laws restrict outward technology transfer for national security, economic, or foreign policy reasons. Of the six countries studied, the United States is the only country that controls the export of medicines for foreign policy reasons. The United States also has imposed more far

reaching controls on the export of micro-organisms than have the European nations and Japan, which appear to limit their concern to biological warfare agents. With these broader commodity controls come commensurately broader controls over the export of technical data. These controls may have a slightly adverse effect on the competitiveness of U.S. companies commercializing biotechnology because they could cause delays that result in sales being lost to foreign competitors.

All of the countries studied, except the United States, have compulsory licensing provisions of general applicability for patents. The United States has special compulsory licensing provisions in some statutes, notably the Plant Variety Protection Act. In addition, compulsory licensing has been imposed in patent misuse cases. It should have little effect on U.S. competitiveness in biotechnology.

Exchange controls may delay or limit the remittance of royalties. Investment controls may obstruct inward foreign investment or licensing and technical assistance activities. The United States, the United Kingdom, the Federal Republic of Germany, and Switzerland do not have significant controls. France formerly required prior review of investments and licensing agreements but now requires only notification after the fact. However, non-EEC residents who plan to invest in France must submit a declaration of their proposed activity to the Ministry of Economics and Finance, which may order the suspension of the proposed action. Japan has had a prior notification system since 1980. However, both the French and Japanese systems give the Government the ability to object or order alteration of the transaction. This system may increase the leverage of French and Japanese prospective licensees of biotechnology transfers. It might also provide protection for domestic firms against foreign competition in the local market.

For biotechnology products such as pharmaceuticals, tariffs are relatively insignificant as a barrier to trade. The significant trade barriers are nontariff trade barriers, such as standards and certification systems, subsidies, and the use of price regulation to discriminate against imports.

Multilateral trade agreements such as GATT provide rules aimed at eliminating nontariff barriers to trade. Similarly, the Standards Code prohibits its parties from discriminating against imports in their standards and certification systems. The Subsidies Code prohibits certain forms of subsidies. All of the competitor countries belong to all three of these agreements. U.S. rights under these agreements can be enforced through dispute settlement proceedings before an impartial panel of arbitrators.

Biotechnology products may face significant nontariff barriers to trade because of the desirability of the technology and because of health and safety regulation likely to surround the product. For instance, certification of safety requirements may be difficult to gain, especially for imported biotechnology products. Additionally, price regulation in important overseas markets such as France and Japan may on occasion significantly impair return on R&D investment for biotechnology pharmaceuticals.

The U.S. trade remedy of greatest interest to U.S. firms engaging in biotechnology is section 337 of the Tariff Act of 1930, which provides a remedy against imports that create unfair competition, including those that infringe intellectual property rights. A firm using biotechnology producing a product in the United States can use section 337 to gain exclusion of infringing imports, even in the case of those made by a process patented only in the United States or where the firm has chosen the trade secret route rather than patenting. Section 337 proceedings are administrative (before the U.S. International Trade Commission) and can be much speedier than other types of litigation.

The other significant trade remedy for U.S. firms using biotechnology is section 301 of the Trade Act of 1974. This statute provides a window for U.S. parties to get the Government to negotiate to enforce U.S. rights abroad. Antidumping and countervailing duty laws may be of significance in the future as well.

Since trade in biotechnology products has barely begun, it is too soon to assess definitively whether the present trade laws are adequate to address the trade problems of this industry. However, since there are no trade issues peculiar to biotechnology and biotechnology products are likely to trade similarly to other products, biotechnology is not likely to raise new issues for trade law.

Issue

ISSUE: How could Congress respond to the international transfer of biotechnology?

Biotechnical knowledge is being rapidly transferred both domestically and internationally, but there is no empirical evidence showing the amount and net direction of the transfer. Much of the new knowledge is being generated in the United States, primarily in research universities and NBFs, and because of the openness of the university scientific establishment and the many joint R&D ventures between NBFs and larger manufacturing companies, particularly foreign ones, this knowledge is being disseminated worldwide. At the same time, however, high-quality research in molecular biology, immunology, and bioprocess engineering is done in many foreign countries, and the published results are available to U.S. scientists. The technique for making hybridomas, for example, was developed in the United Kingdom. Furthermore, patents granted in the United States and abroad to foreign inventors and companies make technology available to all. Finally, R&D joint ventures between NBFs and large companies presumably have resulted in the transfer of some technology to NBFs in the United States, although this is not certain because of the proprietary nature of these agreements. Despite the lack of empirical evidence showing the amount and net direction of biotechnology transfer, most observers would agree that currently the net flow of biotechnology transfer is outward from the United States. However, the net flow outward may change as foreign companies enter the U.S. market (via subsidies or foreign manufacturing operations) bringing with them foreign technology. The long-term effect of what appears to be an outward flow of technology on the international competitiveness of U.S. companies applying biotechnology is unknown.

Although certain laws affect the international technology transfer and will therefore affect the transfer of biotechnology, biotechnology raises few, if any, unique issues in this context. Similarly, since there are no trade issues peculiar to biotechnology, and biotechnology products are likely to trade similarly to the products they replace, biotechnology is not likely to raise new issues for trade law. The laws most relevant to biotechnology now are the export control laws, which could have a modest effect on U.S. competitiveness.

As this study went to press, the debate over replacement of the Export Administration Act of 1979 was still in progress. Although the delay and commercial uncertainty created by current U.S. export controls may adversely affect the development of biotechnology in the United States, these problems are general ones that are now under consideration in Congress, and as such, are beyond the scope of this report. The reader is referred to the OTA report *Technology and East-West Trade: An Update* (19) for a full discussion of the export control issue.

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Chapter 20

Targeting Policies in Biotechnology

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Chapter 20

Targeting Policies in Biotechnology

Introduction

During the past few years, some governments in countries other than the United States have designated the commercial development of biotechnology as essential to their nations' continued economic well-being. Unlike the U.S. Government, which has relied on a policy of funding basic research in the life sciences and encouraging research and development (R&D) in all industries with tax credits,* these governments have instituted targeting policies in biotechnology designed to promote the commercial development of biotechnology. In the context of this report, a targeting policy for biotechnology is defined as any policy that singles out the indigenous development of biotechnology for special attention from the central government. Foreign targeting policies in biotechnology may have the potential both to enhance the international competitiveness of foreign firms and to weaken that of U.S. firms.

This chapter examines the targeting policies in biotechnology of Japan, the Federal Republic of Germany, the United Kingdom, and France.* The targeting policies of most foreign governments are directed toward both "old" and "new" biotechnology. This chapter focuses on the aspects of these policies applicable to new biotechnology, as defined at the outset of this report. Although it does not address the issue of whether the U.S. Government should adopt a targeting policy for biotechnology, it does identify which targeting mechanisms could most readily be adopted in the United States if the U.S. Government chose to target biotechnology.

*See *Chapter 12: Financing and Tax Incentives for Firms* and *Chapter 13: Government Funding of Basic and Applied Research.*

*Switzerland is not considered in this chapter, because the Swiss Federal Government has no central policy for the industrial development of biotechnology.

Timing and coordination of policies

The biotechnology targeting policies of Japan and the Federal Republic of Germany have evolved out of at least a decade of interest in the commercialization of life-science-related technologies; these policies have more recently emphasized the incorporation of the new recombinant DNA (rDNA) and hybridoma/monoclonal antibody (MAb) technologies, as well as advances in bioprocess engineering. The biotechnology targeting policies of the United Kingdom and France, in contrast, have developed since about 1980, largely in response to the recent developments that have occurred in the field of molecular biology. The extent and degree of coordination of targeting policies differ among countries.

Japan

As early as April 1971, the Council for Science and Technology, Japan's highest science and technology policymaking body, including government, business, and academic leaders, stressed the importance of promoting life science on a nationwide basis because of its commercial potential (16). Since then, three governmental departments in Japan—the Science and Technology Agency

(STA), the Ministry of International Trade and Industry (MITI), and the Ministry of Agriculture, Forestry, and Fisheries (MAFF)—have specifically targeted the development of biotechnology.

STA responded in 1973 by establishing the Office for Life Science Promotion to plan and coordinate STA's R&D programs in life sciences. Until MITI's entry into major biotechnology programming in 1980, STA's R&D programs in fields related to biotechnology were the largest and the best funded in Japan. Even today, STA's programs are comparable in scale to those of MITI (25).

STA, in addition to being responsible for carrying out its own R&D program in the fields related to biotechnology, is responsible for interministerial coordination. It should be pointed out, however, that STA's influence on the formulation and implementation of Japanese biotechnology policy is not as pervasive as it might appear on paper. Interministerial rivalries and competition are common in Japan, and as described below, MAFF and MITI, each with substantially larger in-house staffs and laboratories than STA, have independently formulated their own biotechnology targeting policies. Nevertheless, STA's foresight with respect to the development of biotechnology has accorded the agency a more authoritative position for biotechnology than for other high-technology fields.*

MITI did not enter the biotechnology area until 1981. In that year, MITI reorganized itself to deal comprehensively with the challenges of new developments in technology and established its "System for Promotion of Research on Next-Generation Industrial Technologies," an overall plan to promote "next-generation" industrial technologies (25). Three "next-generation" projects in biotechnology were established within MITI's Basic Industries Division, and an Office of Biotechnology Promotion was established within this division to provide policy oversight for MITI's biotechnology effort and to serve as liaison between MITI's Biotechnology Long-Term Vision Advisory Group and possible MITI efforts to obtain from the Japanese Diet special legislation governing the promotion of biotechnology in Japan (25).*

MAFF has more recently established the Committee on Biological Resources Development and Utilization, which compiled a report recommending actions MAFF could take to promote biotechnology's development (21).

In addition to STA, MITI, and MAFF, three other Japanese Government agencies are funding R&D in biotechnology: the Ministry of Health and Welfare, the Ministry of Education, and the Environment Agency (26).

Federal Republic of Germany

The West German Government's interest in the development of old biotechnology, like that of the Japanese Government, is more than 10 years old. In 1968, the old Federal Ministry for Scientific Research explicitly recognized the potential commercial importance of old biotechnology by including it in a program to promote new technologies (15). In 1972, the newly reorganized Ministry for Research and Technology (BMFT, Bundesministerium für Forschung und Technologie), along with the Ministry of Education, commissioned a report on old biotechnology from the German Society for Chemical Engineering (DECHEMA, Deutsche Gesellschaft für Chemisches Apparatewesen) (7). The DECHEMA study, completed in 1974, laid the groundwork for a comprehensive Federal policy for the development of old biotechnology (15). In 1980, in light of increasing evidence suggesting potential commercial applications of advances in both scientific and engineering aspects of biotechnology, BMFT presented its *Leistungsplan: Biotechnologie,* a performance plan for biotechnology (5). This plan identified and targeted for support specific areas in which West German industry could commercially exploit both old and new biotechnology (15).

BMFT makes policy and coordinates German governmental activity for all biotechnology. BMFT funds basic and generic applied research in biotechnology through a number of public and non-

*STA was involved from the beginning with its own program and had the central role in the setting of rDNA regulations. The agency has a policy of reviewing on a case-by-case basis scaled-up production of genetically manipulated micro-organisms beyond 20 liters and has been reluctant to relinquish this authority (4).

*Several factors, including visible American concern with Japanese Government aid to high-technology industries, have made the passage of such programs unlikely (25).

profit research centers (15). Its most important function, however, is to oversee the development efforts of various industries in biotechnology, and it aids such efforts with a strong funding program (15).

United Kingdom

The formulation of official Government interest in the commercialization of biotechnology in the United Kingdom dates from March 1980, with the publication of the Spinks' report (1). This report identified major weaknesses in the country's biotechnology commercialization efforts and suggested ways of correcting them. The document elicited almost immediate Government action on its recommendations and sparked a spirited dialog among the various sectors with an interest in developing and incorporating the latest advances in this set of technologies into British industries.*

The Department of Industry is the United Kingdom's lead department for biotechnology. Other Government departments involved in health, energy, the environment, agriculture, and food, however, contribute to the advancement of biotechnology within their respective sectors, primarily by funding basic research (8). In April 1982, the Department of Industry established the Interdepartmental Committee on Biotechnology to strengthen the existing coordinating arrangements by focusing the Government's effort on the commercial development of biotechnology. This committee coordinates the activities of other related bodies, such as the Research Councils, the British Technology Group (BTG), and the Public Health Laboratory Service, and serves as a point of contact for those outside Government.

Biotechnology and Education: Report of a Working Group, The Royal Society, 1981; *Biotechnology*, Cmnd 8177 (London: H. M. Stationery Office, March 1981); *The Strategy for Biotechnology in Britain*, BCCB Seminar, London, October 1981, series of unpublished papers, widely circulated at the time; *Biotechnology: Interim Report on the Protection of the Research Base in Biotechnology*, Sixth Report from the Education, Science and Arts Committee, Session 1981-82, House of Commons Paper 289 (London: H. M. Stationery Office, July 29, 1982).

France

Official interest in the commercialization of biotechnology in France was marked by the appearance of the Pelissolo report (23) in December 1980. Since the election of the socialists in 1980, the French Government has resolved to push the development of several new technologies in French industries and has accorded a privileged position to biotechnology within this scheme.

In July 1982, the old Ministry of Research and Technology in France was reorganized into a new, more powerful Ministry of Research and Industry (Ministère de la Recherche et de l'Industrie) based on the model of Japan's MITI (29). Furthermore, a wide-ranging research law adopted by the French National Assembly in July 1982 stipulated a real increase in the civilian R&D budget of 17.8 percent per year for 5 years, economic conditions permitting, and set up seven technological "programmes," on which the majority of all civilian research funds are now to be focused (30).

Biotechnology was one of the seven "programmes," and a Biotechnology Mission (Mission des Biotechnologies), established in August 1981, produced a planning document for biotechnology in France in July 1982. This document, the "Programme Mobilisateur: l'Essor des Biotechnologies," called for the restructuring of biotechnology policymaking into three separate coordinating bodies: 1) a national committee, presided over by the Minister of Research and Industry; 2) an interministerial coordinating committee; and 3) a program team to work in daily liaison with other Government organizations most closely involved in distributing research funds (18).

Since the publication of the "Programme Mobilisateur," the Ministry of Research and Industry has undergone a further restructuring. The new name of this ministry, Ministry of Industry and Research (Ministère de l'Industrie et de la Recherche), further reflects the efforts of French policymakers to focus on the commercialization of research results, including those in biotechnology (9).

Industrialists' role in policy formulation

Formulating a policy with the assistance of the parties whose activities it is intended to affect usually makes its implementation far more effective. Foreign nations competing with the United States in the commercialization of biotechnology have various mechanisms which incorporate industrialists into the formulation of a government targeting policy.

Japan

In Japan, technological strategy is usually formed by a "bottom-up" process, and the formulation of the strategy for biotechnology was no exception. After the announcement of the Cohen-Boyer patent for the basic rDNA process in 1980, five major Japanese chemical companies organized a joint study group called the Biotechnology Forum. The Biotechnology Forum was instrumental in lobbying for the establishment of MITI's three major "next-generation" biotechnology R&D projects: rDNA technology, bioreactors, and mass cell culture (25).* Furthermore, discussions with industrialists helped narrow MITI's focus. A planned "next-generation" R&D project in cell fusion was dropped, because the chemical companies working with the Basic Industries Division of MITI were already rather advanced in this area and because MAFF and the Ministry of Health and Welfare were developing their own programs in the field (25).

Federal Republic of Germany

The biotechnology policy of the Federal Republic of Germany was formulated with industry consultation. As noted above, a report on old biotechnology from DECHEMA, the private sector research association of the German chemical industry (7), laid the groundwork for a comprehensive Federal policy. Much of BMFT's funding goes to nonprofit research centers such as the Society for Biotechnology Research (GBF, Gesellschaft für Biotechnologische Forschung) that conduct generic applied research useful to industry (13). The research institutes of these organizations have boards of directors with strong industrial representation, so their research strategy is thus usually formed by a "bottom-up" process.*

United Kingdom

The Department of Industry launched in November 1982 a new 3-year, $30 million program of support for biotechnology in industry (2). To promote and monitor its funding initiatives, the Laboratory of the Government Chemist, part of the Department of Industry, set up a Biotechnology Unit. The unit is headed by one official from the Laboratory of the Government Chemist and three full-time biotechnologists on loan from industry. The purpose of this group is to provide industrial biotechnology expertise previously unavailable in the Department of Industry (12). The establishment of the Biotechnology Unit in 1982 marks the first time the British Government has incorporated the industrial sector on a regular basis into the policymaking process for biotechnology. Previously, the direction of the United Kingdom's informal involvement in biotechnology was determined largely by Government officials and scientists acting through already existing committees, with only occasional input from the private sector.

France

The presentation of the "Programme Mobilisateur" in July 1982 followed an intensive period of analysis and discussion between French Government officials, research scientists, and industrialists. A product of the plan was a National Biotechnology Committee, presided over by the

*In fact, following the award of the Cohen-Boyer patent, the Committee on Life Sciences of the Japan Federation of Economic Organizations met in alarm to discuss a Japanese response. Included at this meeting were representatives of 30 major Japanese companies with an interest in biotechnology. The Cohen-Boyer patent was seen as a matter of concern because, according to their company sources, the patent would affect almost any product application of rDNA technology. Ironically, it was suggested that the United States was designating biotechnology as a strategic national industry and was weaving about it a network of protective patents (27).

*OTA's report *U.S. Industrial Competitiveness: A Comparison of Steel, Electronics, and Automobiles* (28) presents a general description of structural integration of business into West Germany's policymaking apparatus, pp. 196-200.

Minister of Research and Industry, with 30 to 40 members from the Government, academia, and industry responsible for providing general guidance in implementing the Government's policy. In the past, the industrial policy of France has been more autocratic than that of West Germany or Japan (31). For biotechnology, enthusiastic French Government officials advocated generalized support of R&D projects regardless of the prospects for successful exploitation, to the dismay of industrialists who doubted the viability of some of the projects designated to receive Government support (29).

Policy goals

An examination of the goals of foreign biotechnology policies indicates that the domestic development of biotechnology, rather than the advancement of knowledge per se, is their foremost objective.

Japan

Japanese Government programs for biotechnology R&D are concerned specifically with the development of Japanese industry.

MITI's interest in biotechnology has been almost exclusively related to a more general program of structural adjustment for Japan's extremely depressed basic chemicals industry (24,25). MITI's three "next-generation" biotechnology R&D projects are part of a 10-year program that is specifically designed to develop and diffuse biotechnology among Japanese companies. According to a recent MITI policy statement, it is not feasible to rely on the private sector for biotechnology-related research that involves huge economic risks, so "the Government itself must take the initiative in such R&D, while at the same time offering assistance to private corporations in various forms to expedite this R&D" (19).

STA also is directly concerned with providing the technological underpinning for industrial advancement in Japan. The essential distinction between the STA and the MITI biotechnology projects is that the former concentrate on medical applications and longer term development of advanced bioreactors, whereas the latter are mainly concerned with fine chemicals, biological routes to production, fertilizers, and enzyme technology (25).

Federal Republic of Germany

According to a September 1979 BMFT statement, a primary goal of Germany's Federal biotechnology policy is "to establish the preconditions for industrial innovation in this key area of technology" (15). Another goal is "to strengthen the performance and competitive capacity of the German economy in long-range growth-oriented areas, in the process, correcting weaknesses revealed through international comparison and preventing distortions in Germany's competitive position" (15).

United Kingdom

While the British Government recognizes the potential of biotechnology, it is fairly guarded about the objectives of its biotechnology policy. The Minister of Industry has stated that "many developments are only now beginning to emerge from the research phase, and the direction of development for commercial exploitation remains uncertain. In addition, new biotechnological techniques and processes may well emerge over the next 20 years with benefits as yet unforeseen" (8). Clearly, however, the British Government intends to assist the country's industries in realizing the commercial potential of biotechnological developments as such developments appear (8).

France

The French Government's "Programme Mobilisateur" plans to remedy the present deficiencies in qualified personnel and spending levels for

R&D in biotechnology in French industry and the lack of public sector applied research in 5 years. According to the document, French companies should account for 10 percent of the world market in the "bioindustries" (not defined) in 1990, compared with an estimated 7.5 percent now (18).

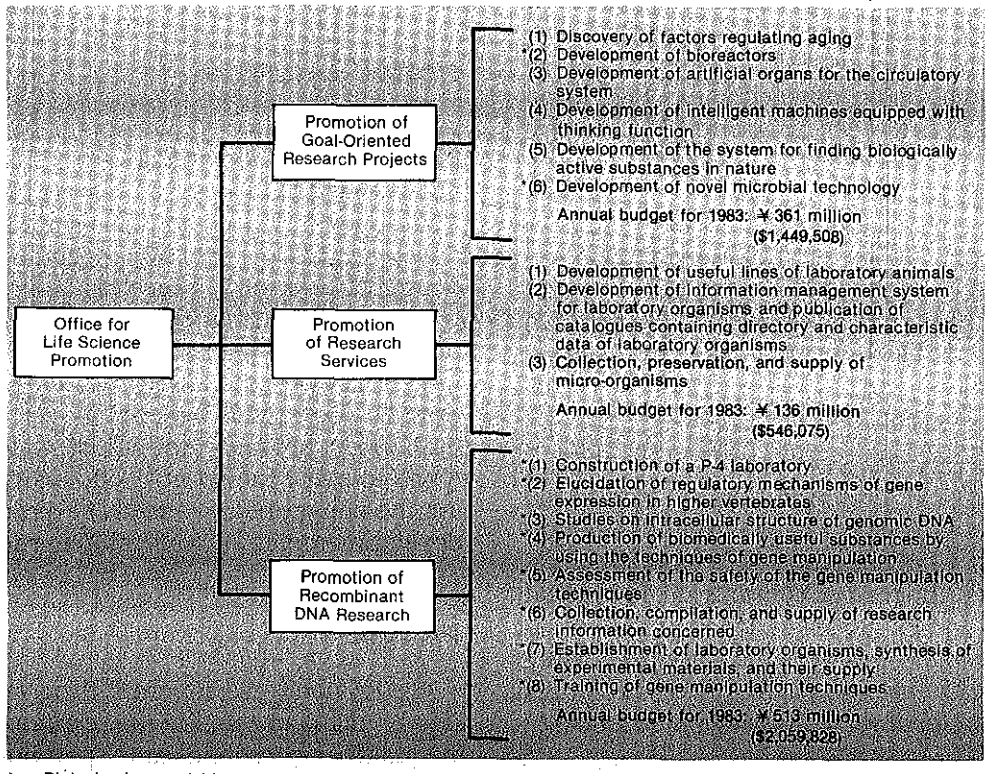
Policy implementation

Examples of the mechanisms used to implement biotechnology targeting policies in Japan and other countries illustrate the variety of forms which biotechnology targeting policies can take. Several examples are cited below. For more information on government funding, see *Chapter 12: Financing and Tax Incentives for Firms* and *Chapter 13: Government Funding of Basic and Applied Research*.

Japan

The activities of STA's Office for Life Science Promotion are shown in figure 32. As shown in the figure, the Office is funding two goal-oriented research projects in biotechnology. These projects are to be carried out in 10 years by research groups whose members are affiliated with Japanese universities and research institutes (26). One of the projects, the project on the development of bioreactors, aims to develop what the Japanese call "second generation" bioreactors and includes computer control, biochemistry, and systems design. STA has encouraged an interdisciplinary approach to the project by inviting a variety of Japanese companies skilled in various aspects of biotechnology to participate. This approach has been very productive (24). As shown in figure 32, the Office for Life Science Promotion is providing sup-

Figure 32.—Activities of STA's Office for Life Science Promotion



* = Biotechnology activities.
SOURCE: Office of Technology Assessment, adapted from *Science and Technology in Japan*, April/June 1983.

port for rDNA research. This support includes funding for the construciton of facilities. In 1982, construction was begun on a P-4 (highest physical containment level) facility in which experiments in genetic manipulation can be performed in Tsukuba Science City (26). In 1980, as one of the Office for Life Science Promotion's projects for the promotion of research services, the Japan Collection of Micro-Organisms was constructed to collect, preserve, and supply micro-organisms (26).

STA is implementing its policy in part through the general New Technology Development Fund. This fund has already commenced funding a number of biotechnology-related projects. A $4 million grant to the pharmaceutical company Green Cross in March 1980, for example, launched Green Cross into the international arena of competition in pharmaceuticals by enabling it to conduct research on rDNA methods for the production of alpha interferon (25).

MITI's three next-generation biotechnology projects, which are targeted to establish and diffuse scale-up techniques among companies, are even more illustrative of Japanese Government cooperation with industry. MITI has invited 14 companies to participate in the projects on a long-term (10-year) basis* and will provide allocations over 10 years of $43 million each to both the rDNA and bioreactor projects and $17 million to $22 million for the mass cell culture project (10). Although some 10 percent of the R&D work (by expenditure) for MITI's biotechnology projects is being conducted in the national laboratories** of the Agency for Industrial Science and Technology, the bulk of the work (90 percent) is conducted in industry laboratories. To facilitate coordination by the Office of Biotechnology Promotion and the Next-Generation Research Coordination Bureau of MITI's Agency for Industrial Science and Technology, the 14 companies receiving grants under the next-generation biotechnology projects have been organized into the Biotechnology Development Research Association. This association has its own central office through which the various companies communicate with MITI, but otherwise there are no intercompany institutions (e.g., there are no common laboratories being maintained by the companies). MITI subsidies to these companies cover 100 percent of all direct expenses (salaries and laboratory expenses) for biotechnology R&D, but no overhead is allowed and any capital equipment purchased is nominally the property of the Japanese Government. Furthermore, all patents resulting from the work belong to the Japanese Government, which, MITI has assured other companies, both domestic and foreign, will be freely available (14).

MAFF also is actively promoting cooperative research with private industry at its laboratories and is currently funding work with both Nippon Shokuhin Kako and Oriental Yeast at the National Food Research Institute and with Kao Soap at the National Institutes of Agricultural Sciences. Further joint research is planned in the areas of plant breeding and species improvement with private seed companies. Achievements from the research are used jointly by Government and industry, but those companies that participate in the research projects receive exclusive licensing rights to the patents resulting from these projects for 3 years (22).

Federal Republic of Germany

BMFT implements its biotechnology targeting policy in the Federal Republic of Germany through three categories of support. One category is funding for already existing schemes for industrial development. Another category is funding for third-party organizations to which BMFT contributes as part of more generalized funding programs for all areas of public research. GBF is the foremost example of such an organization. Originally founded to conduct generic bioprocessing research to meet the needs of industries (17), GBF employs 365 people and has a budget (1982) of $13 million (DM31 million), of which 89 percent came from BMFT (13). GBF's current activities include general development of bioprocess technology, scale-up of laboratory processes, screening

*The bioreactor project has been divided into two subprojects with Mitsubishi Chemicals as the overall leader. Sumitomo Chemicals is the leader of the rDNA project, and Kyowa Hakko is the leader of the mass cell culture project (25).

**These include the Fermentation Research Institute, National Chemical Laboratory for Industry, Research Institute for Polymers and Textiles, Government Industrial Research Institute, and Institute of Physical and Chemical Research (25).

of micro-organisms and plant and animal cell cultures, support of other research groups in biotechnology, participation in joint biotechnology projects with industry, and advanced interdisciplinary training for scientists, engineers, and technicians.

A third category of support is funding for biotechnology programs specifically designated by BMFT. For these programs, BMFT has funded a wide spectrum of projects with about $35 million (DM55 million) in 1982 (15): food requirements, biological pesticides, plant and animal cell culture techniques, biomass, metal refining, bioprocesses for commodity chemicals, bioreactors, and principles of biotechnological procedures (5).

The list of BMFT's grant recipients for these biotechnology programs includes every major German chemical and pharmaceutical company (5). BMFT's support for research on the development of interferon is particularly noteworthy. Between 1975 and 1977, BMFT gave Merck, Ltd., $300,000 (DM0.6 million) for the study of interferon induction. Rentschler, Inc., has been supported since 1976 with about $9 million (DM18.54 million) for its R&D effort on fibroblast interferon (6).

United Kingdom

In the United Kingdom, the Department of Industry has launched a new, 3-year $30 million "Biotechnology in Industry" program. The British Government also funds BTG, which encourages cooperative projects between industry and public sector laboratories. Government laboratories, such as the Centre for Applied Microbiology Research, carry out both applied research of potential interest to industry and specific industrial contracts.

In 1981, the British Government, through BTG and in association with four private investors, established Celltech, Ltd., to develop and market products made by some of the new technologies. In an arrangement similar to that of Immunotech in France, Celltech has a total initial capital of $20 million and the right of first refusal* on all work done in the Medical Research Council (20). In 1983, BTG, Advent Eurofund (a venture capital group), and Ultramar (a petroleum and financial group) established the firm Agricultural Genetics with a total initial capitalization of $28 million. This firm has the right of first refusal on all work done in the Agricultural Research Council (3).

France

The French Government is supporting R&D in various governmental agencies, including the National Institute of Health and Medical Research (INSERM, Institut National de la Santé et de la Recherche Medicale), the National Center for Scientific Research (Centre National de la Recherche Scientifique), and the Institut Pasteur. Government funding in applied areas is intended to benefit the pharmaceutical, food, and agricultural industries.

In 1982, the French Government supplemented its applied research program by creating a company, Immunotech, to facilitate the commercialization of biotechnology and transfer the results of immunology research, a traditional French strength, to French industry. Immunotech does applied research on bioprocessing and hybridoma technology for the production of immunoassay and immunopurification systems. The Ministry of Research and Industry contributed $3.2 million to its formation. Immunotech has the right of first refusal on all work financed by INSERM.

*This is the right to choose whether or not to produce and market any good or service without having to bid competitively with other firms.

Findings

The governments of four leading industrialized competitors of the United States—Japan, the Federal Republic of Germany, the United Kingdom, and France—have instituted programs to target the development of certain areas of biotechnology. The targeting policies are intended to reduce

economic risk and lessen corporate duplication in biotechnology R&D.

The governments of these four countries took an interest in biotechnology at different times. The governments of both the Federal Republic of Germany and Japan identified the life sciences in the early 1970's as an area worthy of special government and private sector assistance. Those of France and the United Kingdom, on the other hand, realized the industrial importance of biotechnology only recently, primarily as a result of the recent advances in molecular biology.

The centralization of government activities varies among countries. In France and the Federal Republic of Germany, the direction of all activities, from basic research to industrial development, is centralized in a single ministry: the Ministry of Industry and Research in France and BMFT in Germany. In the United Kingdom, the Department of Industry is responsible for articulating and executing the Government's policy to commercialize biotechnology, but it must work with other departments that are concerned with the development of science in specific fields. In Japan, at least three Government departments have major biotechnology policies of their own.

These four foreign countries have various processes by which industrialists are brought into the formulation of their commercial biotechnology policies. Japan, France, and West Germany have a long history of involving industrialists. The United Kingdom, on the other hand, has only been officially involving industrialists in the formulation of its biotechnology policy for a short period.

The mix of policy measures to encourage industrial innovation in biotechnology assumes a variety of forms within each country. In Japan and the Federal Republic of Germany, the governments carry out their policies partly in the form of joint R&D projects with industry. These projects concentrate the resources of the government and private companies to meet specific objectives set by the government. In some cases, the companies have exclusive rights to the resulting patents; in other cases, the patents are made available to all interested parties. The British and French Governments, in addition to providing support for specific projects, have adopted a different sort of approach: the organization and support of small firms, such as Celltech in the United Kingdom and Immunotech in France, to commercialize the results of government-funded basic and generic applied research.

At this early stage, any evaluation of the foreign targeting programs' probability for success is preliminary. History has shown that even the best thought-out targeting policies do not guarantee competitive success. Whether the targeting policies of Japan, the Federal Republic of Germany, the United Kingdom, or France are superior to the U.S. Government policy of funding basic research in the life sciences and encouraging R&D in all industries with tax credits remains to be seen. The United States currently leads the world in the commercialization of biotechnology. Although targeting policies may not be of great importance when compared with other competitive factors, they could tip the balance of equivalent competitive situations in the future.

Issue

ISSUE: How could the U.S. Government target biotechnology?

It is beyond the scope of this report to evaluate whether the commercialization of biotechnology is of sufficient importance to the U.S. economy as a whole to warrant targeting efforts by the U.S. Federal Government. If such efforts are undertaken, however, several targeting mechanisms might be considered.

The mechanisms for targeting biotechnology in France, the United Kingdom, the Federal Republic of Germany, and Japan range from highly coordinated to loosely organized, but all reflect some combination of the following:

- *Firm-specific assistance.* Firm-specific assistance involves choosing a single company or group of companies for assistance from the government in jointly agreed upon areas of high-risk R&D. The companies chosen sometimes perform the subsidized research in consortia.
- *Industrywide assistance.* Industrywide assistance involves providing government assistance to all companies that perform R&D in a particular area (or funding R&D in a national laboratory open to all interested industry participants). Low-interest loans or tax credits for R&D and procurement of new products are methods commonly used.
- *An interagency coordinating committee.* An interagency oversight committee without the authority to set goals or grant subsidies facilitates coordination of the policies and actions of government agencies and periodically recommends action through the appropriate agencies to address problems hindering the development of biotechnology.

The U.S. Government would probably have to avoid actions in the category of firm-specific assistance. If the U.S. Government were to select a few companies for subsidies, demands for equal assistance would probably arise from the companies that did not receive subsidies.

For U.S. Government policies in the category of industrywide assistance, there are historical precedents. The types of U.S. Government support that were provided for the U.S. semiconductor industry in its early years are described in *Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology*. As it did in the case of the U.S. semiconductor industry, the U.S. Government could provide or guarantee low-interest loans for high-risk R&D in biotechnology. It could also guarantee Government procurement of certain products to eliminate some market size uncertainties. A commitment by the Federal Government to purchase certain drugs developed by biotechnology could spur R&D that otherwise might not be undertaken.

The third mechanism, an interagency coordinating committee, would probably raise the fewest objections in the United States but would also be the least substantial. The defunct Interagency Working Group on Biotechnology of the White House Office of Science and Technology Policy temporarily served this function and presented its recommendations to the Office of Science and Technology Policy in June 1983 (11).

Earlier chapters of this report have outlined options that could improve U.S. competitiveness in biotechnology. The adoption of the most acceptable of these options in a coordinated fashion would be one way in which the U.S. Government could target biotechnology.

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Chapter 21

Public Perception

Contents

Chapter 21

Public Perception

Introduction

Public perception of genetic research and technology is a factor that could influence the rate of commercialization of biotechnology. This chapter considers the factors that may affect public *perception* of genetic research and technology. As it does not consider the many ways by which the public might *express* its perceptions, it does not describe various methods that have been or could be used for public *participation* in decisionmaking processes, nor does it consider the arguments advanced for each.

Most of the discussion in this chapter is centered on the United States. One of the final sections considers the relative influence of public perception on the commercialization of biotechnology in the United States and foreign countries. For issues and policy options, readers are referred to OTA's April 1981 report *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals* (29).

The discussion in this chapter goes beyond biotechnology as defined in the rest of this report, and, for that reason, uses the broader terms "genetic research" and "genetic technology." These broader terms include directed manipulation of genes in human beings. Biotechnology, as defined in this report, does not include directed change of genes in human beings and is limited to industrial applications of new genetic technologies to produce useful substances, to improve the characteristics of economically significant plants and animals, and to act on the environment in useful ways. Because the public does not always make a clear distinction between industrial applications of novel genetic technologies and the manipulation of genes in humans, biotechnology can elicit public concerns that are based on incomplete knowledge and sometimes erroneous assumptions. Regardless of the *accuracy* of public perceptions about biotechnology, however, these perceptions could influence the rate of commercialization.

Public perception in the United States

The discussion that follows begins by considering the U.S. policymaker vis-a-vis the public on issues related to science and technology. It then describes various factors that influence public perception of biotechnology in the United States. It also reviews some arguments frequently raised in debates over genetic research and technology, considers difficulties in assessing risks and benefits of genetic research and technology, discusses the influence of the media on public perception of biotechnology, and provides some survey data.

The public and the policymaker

In a democratic society, where decisions are made by elected representatives, the public plays a vital role in the acceptance of new technology and the directions in which it will be applied (2). That public beliefs can significantly influence U.S. policymakers with respect to biotechnology is illustrated by the changing attitudes of policymakers in Massachusetts. In 1976, Boston Mayor Alfred Vellucci argued strongly for major controls on research and development (R&D) using recombinant DNA (rDNA) technology in Boston and Cambridge. As a result, the Cambridge Experimental Review Board was established to determine whether additional protection for citizens was needed beyond that provided by the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).* Mayor Vellucci's position may be con-

*The NIH Guidelines for Research Involving Recombinant DNA Molecules are discussed along with the rDNA research guidelines of other countries in *Chapter 15: Health, Safety, and Environmental Regulation* and *Appendix F: Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety*.

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trasted with that taken by then Massachusetts Governor King when he addressed Harvard University's symposium on "New Partnerships in Biotechnology" in 1982. Governor King pledged his assistance to the establishment of commercial biotechnology firms in the State. The different positions taken by Mayor Vellucci and Governor King reflect, in part, the changes in public concern over the risks posed by rDNA technology.

Although the level of U.S. public concern about R&D involving rDNA appears lower now than it was in the late 1970's, it is not nonexistent. As of June 1982, two States and nine municipalities had passed laws and resolutions relating to control of rDNA R&D. The two States are New York and Maryland. With the exception of Princeton, N.J., the municipalities are located in Massachusetts (Amherst, Boston, Cambridge, Newton, Somerville, and Waltham) and California (Berkeley and Emeryville). It is interesting to note that all local municipalities involved in formulating laws or resolutions are the sites of, or located near, major centers of corporate and university research activity in rDNA. Although most of this legislative activity took place in the late 1970's, several municipalities in Massachusetts either amended or originated ordinances or laws in 1981. At a minimum, the laws extend the NIH Guidelines from institutions receiving NIH funds to all public and private institutions conducting rDNA research. Some of them also establish additional occupational and environmental safety requirements (15).

In light of the developments noted above, U.S. policymakers probably can expect to be increasingly involved in biotechnology issues. One issue in biotechnology is the amount of consideration that should be given to the unanticipated consequences of deliberately releasing into the environment products of rDNA technology (e.g., modified plants or microbes with improved capability for mineral leaching or pollution control). But this is just the opening wedge to a wider range of societal concerns that are emerging as new knowledge leads to new capabilities. The potential capabilities of genetic research and technology include human gene therapy, gene surgery, and estimation of differential susceptibility to disease based on differences in genetic traits.

An accident or perceived negative consequence involving genetic research or technology could stir up public fears and have a sizable impact on biotechnology's further development. This observation is true especially in the United States, where public involvement in the debates surrounding rDNA technology in its early years was very strong compared with public involvement in other Western democracies.

Factors influencing public perception of genetic research and technology

The Organisation for Economic Co-Operation and Development identified the following characteristics of science and technology issues that distinguish these issues from other public controversies (18):

- rapidity of change;
- the raising of *new* issues;
- scale, complexity, and interdependence among technologies;
- irreversibility of effects;
- strong public sensibilities about real or imagined threats to human health; and
- challenging of deeply held social values.

OTA's April 1981 report *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals* (29) noted that these factors were especially applicable to advances in genetics and that they helped to explain the public controversy over the safety of rDNA technology. The same factors remain applicable to advances in genetics today. Some are discussed below, along with other factors that may elicit positive, negative, or mixed public reactions to developments in genetic research and technology.

THE TECHNOLOGY IS PERCEIVED TO ENDANGER BASIC HUMAN NEEDS

Some new developments in science and technology are far more threatening to the societies in which they arise than are other developments. In an attempt to understand and predict which emerging technologies will be most threatening, and hence be most likely to raise issues for policymakers, E. W. Lawless makes the reasonable assumption that public concern with a new technology will vary in direct proportion to the degree

that the technology is perceived to affect basic human needs (16). The greater the importance of an individual or societal need, and the greater the impact of the new technology on that need, the greater will be public concern.

At the top of the list of important *individual* needs developed by Lawless are the functions controlled by the nervous system, and particularly by the brain. Genetic technology has the potential to alter the functioning of the human brain, affecting attitudes, emotions, learning, and memory. Besides the concerns associated with the technology's potential to alter these characteristics per se, genetic technology may arouse deeper concerns that relate to an individual's sense of self. Aspects of self derive from each person's most basic characteristics—tendencies to elation or depression, ambition or sloth, and extroversion or introversion, to name a few. If these characteristics can be modified, what happens to an individual's unique, inviolate self?

The most fundamental *societal* need identified by Lawless is sexual activity, reproduction, and family organization. He notes (16):

> . . . any events or practices which portend a threat to man's reproduction or care of children cause immediate and serious alarm. Technologically related cases involving materials which are mutagenic (cause genetic damage) or teratogenic (cause congenital deformities) receive wide coverage by the news media and attention by the public—the announcement that LSD may cause chromosome breakage apparently caused much more concern to its users than other stated hazards, and the thalidomide case is almost classic.

The application of genetic technology to the production of useful industrial substances is not always clearly distinguished from the genetic manipulation—or "genetic engineering"—of higher organisms. Following Lawless, if biotechnology is associated with the capability to alter human reproductive cells, and hence future human generations, it is likely to be perceived as threatening.

TERMINOLOGY

As has been pointed out by various authors (20,21), some of the terminology of applied genetics has negative overtones. The phrase "genetic engineering," for example, may raise Frankenstein-like subconscious fears when associated with human application. "Cloning" of genes, a basic technique of rDNA technology, can be confused in the minds of those who are not expert in the field with the cloning of individual human beings. Because language is widely understood to influence perception, the problem of terminology is not a minor one. Terms that are widely used, however, even though inaccurate, misleading, or imprecise, are not easily changed.

PERCEPTION OF BENEFITS FROM BIOTECHNOLOGY

Biotechnology appears to offer potentially major positive contributions to diverse aspects of life. Economic benefits (e.g., cheaper chemicals and drugs), health benefits (e.g., cures for cancer, schistosomiasis, and herpes; improved diagnostic tools), agricultural benefits (e.g., saline-tolerant or pest-resistant plants, a vaccine for foot-and-mouth disease), and even decreased dependence on foreign oil (e.g., substitution of biomass for petroleum feedstocks, production of fuel alternatives) are envisioned.* To the extent that these benefits are perceived by the public, their perceptions of biotechnology are likely to be positive.

NIH GUIDELINES FOR RECOMBINANT DNA RESEARCH

Biological scientists were instrumental in bringing about the NIH Guidelines for Research Involving Recombinant DNA Molecules that established safety procedures for rDNA research conducted with NIH funds. The NIH Guidelines apply only to work supported by NIH funds, but other U.S. Government agencies have adopted them voluntarily. As far as is known, private industry observes them as well.

On the one hand, the history of the NIH Guidelines should produce a positive perception of responsible action with regard to genetic research and technology by the scientists concerned and the Federal Government. On the other hand, NIH is in a position of potentially conflicting interests. It serves both as a quasi-regulator of genetic research through the NIH Guidelines and as a promoter of genetic research through its sizable

*For a review of the state of the art in achieving these benefits, the reader is referred to chs. 5 through 10 of this report.

funding of genetic research. The degree to which the public perceives a potential conflict of interest and its influence on public perception of biotechnology are unknown.

THE IMAGE OF THE SCIENTIST

Some members of the public appear to be dismayed by the fact that some scientific researchers have turned into entrepreneurs. The question of the appropriateness of private gain from research supported by public funds was aired as part of joint hearings in 1981 and again in 1982 by the Subcommittee on Investigations and Oversight and the Subcommittee on Science, Research, and Technology of the U.S. House of Representatives (26,27).

There is no reason that scientists should not share in financial rewards that accompany application of the results of their research, but the *deliberate* pursuit of profits makes a scientist also a businessman. It can be argued that a major reason for supporting research with public funds is that such research leads to commercial products that benefit society and also generates more public funds through taxes levied on new businesses. However, the fact that some scientists have become millionaires through corporations they have helped to establish has disturbed some people. Simple envy is not the sole reason for unease; more important may be the public image of the scientist. Although U.S. cultural tradition has supported, and even encouraged, the entry of engineers and inventors into the business world (e.g., Edison), it has not done the same for individuals with established careers in pure science.*

COMMENT

A fundamental reason that rDNA technology may be "so inflammatory" is that it elicits a *mixture* of concerns from many categories (9). These concerns range from perceived positive benefits to fears associated with research on human subjects. The point for the policymaker is that, because of the wide range of concerns, genetic research and technology is a volatile area, one where the smallest incident may raise heated public emotions.

*For a discussion of university/industry relationships in biotechnology, see *Chapter 17: University/Industry Relationships.*

Arguments raised in debates over genetic research and technology

Five broad categories of arguments that are frequently raised in debates over genetic research and technology are briefly summarized below. It should be noted that the discussion that follows is in the simplest possible terms. The purpose is to indicate some topics of controversy rather than to describe the considerable subtlety of some of the positions that have been taken.

FREEDOM OF INQUIRY

Some people argue that scientists should be free to pursue any inquiry they choose, and hence that genetic research should not be restricted in any way. Others disagree and feel that at least some forms of research are subject to restraint. H. Jonas takes the latter position and argues that unqualified free inquiry ceases as a preeminent right when science moves from *contemplation* to *action* (12). As soon as science involves action (e.g., conducting experiments with real apparatus and real subjects) rather than just thought, it is subject to legal and moral restraints, as all *actions* are.

RISK OF CATASTROPHIC CONSEQUENCES

Some people argue that genetic research should be banned unless the risk of catastrophic consequences can be shown to be zero. At the other extreme, some people argue that any level of risk is acceptable. Although either of these extreme positions may be taken by individuals, neither is likely to be taken by society. What constitutes an acceptable level of risk of catastrophic consequences, however, is a major societal issue, in part because of the difficulty of assessing both risks and benefits. The fundamental disagreement on both this and the preceding topic is where the line is to be drawn between two extreme positions that can be taken. The position of the line is a societal decision that is never permanent and that varies across cultures and over time.

THE TECHNOLOGICAL IMPERATIVE

Some people argue that what is technologically possible will eventually be done, regardless of

moral and ethical guidelines. Others disagree. As S. P. Stich points out, successful animal breeding has been carried out for centuries, yet controlled breeding is not done in humans even though it has been known for a long time that it could be (24). Thus, people have differing views on whether society is capable of deciding when genetic manipulation of traits is and is not permissible.

"WE SHOULD NOT PLAY GOD"

Some opponents of genetic research argue that humans should not "play God" by manipulating the genes of other organisms or themselves. Despite its use of the term "playing God," this argument is based on areligious as well as on religious grounds. Both types of arguments are briefly considered below.

To opponents of genetic research who argue on religious grounds that humans should not manipulate genes, proponents respond that humans have manipulated the genes of other organisms for thousands of years. Long before the laws of genetics were known, humans were successful in changing the characteristics of plants and animals by selectively breeding them for desired characteristics. In addition to altering the genes of other organisms, humans also have altered their own gene pool. Throughout history, because some persons are more desirable than others as mates, some genes have tended to increase in the gene pool while others have tended to decrease. More recently, medical advances have permitted persons with genetic diseases, such as hemophilia and phenylketonuria, to live and reproduce (17).

But, opponents argue, the genetic changes that have been brought about so far have been limited and *did not involve crossing fundamental species barriers*. So far, this argument is correct in that species are *defined* by the fact that fertile hybrids between them do not occur in nature. However, some opponents of research involving genetic manipulation further argue that the forces of evolution have led to separation of the species and that *breaking down the separation will be deleterious or separation would not have occurred in the first place*. The accuracy of this argument is not known.

As noted above, arguments for a prohibition against genetic research are sometimes based on religious grounds. Fundamentalist and religious objections have played a major role in U.S. debates over genetic research and technology in the past and are likely to continue to do so in the future. Recognizing the importance of religious views in such debates, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (hereafter referred to as the President's Commission) asked the General Secretaries of the National Council of Churches, the Synagogue Council of America, and the United States Catholic Conference to "elaborate on any uniquely theological considerations underlying their concern about gene splicing in humans" (21). The scholars concluded (21):

> . . . contemporary developments in molecular biology raise issues of responsibility rather than being matters to be prohibited because they usurp powers that human beings should not possess. The Biblical religions teach that humans beings are, in some sense, co-creators with the Supreme Creator.

Furthermore, Pope John Paul II, who has been critical of genetic manipulation, "recently told a convocation on biological experimentation of the Pontifical Academy of Science of his approval and support for gene splicing when its aim is to 'ameliorate the conditions of those who are affected by chromosomic diseases, because this offers hope for the great number of people affected by these maladies' " (21).

It should be noted, however, that the religious community's position is in a state of flux. As illustration, a resolution was issued on June 8, 1983, that urged the U.S. Congress to ban genetic changes affecting human reproductive cells. The resolution was signed by 64 religious leaders representing several faiths. The actual positions of the signatories of the resolution are difficult to decipher, because some church officials who signed the resolution appear to be in favor of genetic changes that would repair the effects of genetic diseases. Some forms of genetic defect, such as Tay Sachs disease, may be best eliminated through changes that affect the reproductive cells. Such changes would be banned by the resolution (3,11,14,19).

GENETIC DIVERSITY

Another area of controversy is the potential effect directed genetic manipulation may have on genetic diversity, i.e., the total number of different kinds of genes available to a population. All members of a given species can mate with any other member of that species, so the total number of genes available to the species population is the sum of all the different kinds of genes in all members of the population. Nevertheless, certain combinations of genes may be perceived as particularly desirable. In agriculture, for example, most farmers in a given location often plant the same strain of a particular crop that they perceive as especially desirable; then all members of that crop in a given location are genetically identical. When a new pest threatens the crop, much of the crop will be lost, because the genetic similarity of the plants results in a similar susceptibility to disease. The corn blight of 1970 is a case in point (10).

Opponents of directed genetic manipulation fear that it may result in increased genetic uniformity with a consequent loss of a species' resistance to future threats. Whether such fears are justified depends, of course, on how the organisms resulting from genetic manipulation are used.

COMMENT

Genetic technology, particularly when direct applications to humans are considered, raises strong public concerns. The degree to which public concerns about direct human applications of genetic research and technology are likely to influence the commercial development of biotechnology as defined at the outset of this report is unclear. Some influence is likely, however, because of a failure on the part of the public to make a clear distinction between human and nonhuman applications of genetic technology, a problem that is exacerbated by multiple uses of terms such as cloning.

Difficulties in weighing the risks, costs, and benefits of genetic research and technology

The central question raised by genetic research and technology is how risks, costs, and benefits are to be weighed. This is a question surrounded by problems.

One problem is that of establishing the probabilities that various risks and benefits will occur. Some probabilities can be estimated more accurately than others because of differences in the assumptions that must be made and in the availability of data that are useful in making estimates. Estimating the probability that an organism will escape from a laboratory, for example, involves different assumptions than estimating the probability that an organism released to the environment (e.g., a genetically modified plant or a microbe designed to control oil spills) will adversely affect that environment.

Then, there is the problem of measuring benefits, risks, and costs. First, it is necessary to decide whether the measure should be in economic terms (i.e., dollars) or human terms (e.g., lives saved or lost, illnesses prevented, or some measure of quality of life). If a measure can be selected, then there is the problem of applying it. Furthermore, if different measures are appropriate for costs, benefits, and risks, how should they be compared? Although methods have been developed to deal with these questions, including cost-benefit and cost-effectiveness analysis, they are always fraught with assumptions that become particularly acute with a new technology.*

Finally, like most new technologies, some applications of the new genetic technologies will have consequences that cannot be envisioned. These

*For a discussion of some of the limitations of techniques such as cost-benefit analysis and cost-effectiveness analysis, see OTA's 1980 report *The Implications of Cost-Effectiveness Analysis of Medical Technology* (28).

consequences may be high in benefit or high in cost, but some are certain to alter significantly any calculations that are made today.

In sum, assessment of benefits, risks, and costs, except where empirical data are available, is a subjective rather than an objective process, as is the assigning of relative value to various benefits, risks, and costs. Unfortunately, the most interesting and significant contributions of genetic research are those for which there are no empirical data. While risk assessment analysis was helpful several years ago when concern focused on the safety of laboratory research with rDNA, it may be of little use in considering many issues that may emerge as the technology matures, such as whether to release genetically modified organisms to the environment.

What, then, can be done? In a thoughtful analysis of gene splicing as applied to humans, the President's Commission recommends that an oversight group be established (21):

> . . . through which the issues generated by genetic engineering can continue to receive appropriate attention. These issues are not matters for a single day, deserving of only occasional attention. They will be of concern to the people of this country—and of the entire globe—for the foreseeable future; indeed, the results of research and development in gene splicing will be one of the major determinants of the shape of that future. Thus, it is important that this field, with its profound social and ethical consequences, retain a place at the very center of "the conversation of mankind."

The President's Commission suggests several objectives to guide the oversight group. Education, it states, should be a primary responsibility—education of the public about science and education of the scientific community about the social and ethical implications of emerging capabilities in genetic technology.

That Congress may perceive that the recommendation of the President's Commission for an oversight body reflects a broader public interest is suggested by the introduction of H.R. 2788 to the 98th Congress (Apr. 27, 1983) by Representative Albert Gore. H.R. 2788 would establish the President's Commission on the Human Applications of Genetic Engineering. The proposed Commission would review developments in "genetic engineering" that have implications for human application and examine the medical, legal, ethical, and social issues that might accompany such application. As of this writing, H.R. 2788 has been incorporated into the Health Research Education Act of 1983, H.R. 2350.

Influence of the media on public perception of genetic research and technology

The media bring knowledge of new discoveries and applications of genetic research to the attention of the public and thereby play a role in public perception of biotechnology. The role of the media extends beyond simple reportage of facts, however, because television, radio, and print media have time or space limitations that result in selective coverage. In selecting items for coverage, the media impose value judgments on the relative worth of possible news items. The media also determine how the items they consider newsworthy will be covered and thus vary the amount of coverage and the tone of coverage. Thus, it is helpful to explore the role of the media in public perception of biotechnology further.

June Goodfield, in an essay entitled "Reflections on Science and the Media" (8), traces the shifting relationship between scientists and the media in American society and the reasons for present day dissatisfaction between these two groups. Goodfield's orientation is to the public, which, she believes, both professions serve. The media and scientists, Goodfield observes, share a common aim in their respective spheres, namely, "the public expression of truth." Different pressures, however, constrain achievement of this ideal for each profession. Constraints on the print media include the need to create interest, the basic structure of newspaper reports, and the constant need for newness. The problems are exaggerated for radio and television. Scientists, on the other hand, are constrained by the nature of their work and their methodology. No scientist likes to "go public" before being sure that his or her findings are reproducible. The tendency among scientists, therefore, is toward caution. There is also, for a variety

of reasons, an aversion among scientists to popularization. Thus, the different forces acting on each profession tend to polarize scientists and the media rather than bring them together.

In considering the relationships among scientists, the public, and the media, Goodfield is particularly concerned with three aspects: 1) the obligation of science to inform, 2) the duty of the public to become informed, and 3) the appropriate role of the journalist relative to science and the public. The journalist, she believes, not only must help the public distinguish what is factual from what is speculative but also must help people judge between scientists who differ.

Some of Goodfield's observations are echoed by William Stockton, former Director of *Science Times* of the *New York Times*. At a recent New York Academy of Sciences meeting, Stockton cited an increasing number of science publications, such as *Science 80* and the *Science Times*, as indicators that scientific journalism is moving into an era of scientific interpretation (25).

The possible roles for the media vis-a-vis genetic research and technology include:

- reporting the facts;
- separating facts from speculation;
- presenting issues;
- indicating which individuals or groups have a stake in each side of an issue and why;
- promoting, or downplaying, specific aspects of genetic technology; and
- educating the public in genetic science and technology, both their methods and their content.

Although many media people would probably claim that their role is limited to reporting the facts and separating these from speculation, their role is clearly larger. The media promote or downplay a technology, if only by virtue of the fact that some news items are selected for print or featured in a radio or television spot while others are rejected. Furthermore, the media's promotional role is sometimes far more active than simple selection.

Surveys of public perception

Given all the above, it is reasonable to ask for actual data on public perception of biotechnology, or at least of the broader area of genetic research and technology. Unfortunately, such data are extremely limited.

Two early surveys of the U.S. population were conducted in the 1970's with the following results (6):

- In 1977, the National Assessment of Educational Progress surveyed the attitudes of adults 26 to 35 years in age toward rDNA technology. About two-thirds of the respondents opposed its use on any life form.
- In 1979, the National Science Board conducted a survey of 1,635 adults. Sixty-five percent of the respondents believed that studies relating to creating new life forms should not be conducted.

In the 1980's, Cambridge Reports, Inc., included five questions on "genetic engineering" in its survey for the first quarter report of 1982 (5) and one question on behalf of the American Chemical Society in its survey for the first-quarter report of 1983 (1). The responses to the five questions in the 1982 survey showed (5):

- About half the people surveyed either hadn't heard the phrase "genetic engineering" or wouldn't guess what it meant.
- Of those who had heard of private corporations "getting into the field of 'genetic engineering' or biotechnology" (roughly 40 percent), and who were willing to take a position as to whether this was good or bad, positive sentiments (15 percent) outweighed negative (8 percent) by almost two to one.
- Of those expressing an opinion about "genetic engineering," 25 percent believed it would bring major benefits to society; 11 percent believed it would endanger public health and safety; 44 percent didn't know; and 20 percent believed it would bring both benefits and dangers.

- Respondents with higher income levels and/or higher levels of education were more likely to expect major benefits from "genetic engineering" than those with lower incomes and/or less education.
- Of respondents able to choose between government regulation and self-regulation, 28 percent favored the former and 16 percent the latter. Combination of both government regulation and self-regulation and "don't know" made up the balance.

The single question in the 1983 survey by Cambridge Reports, Inc., asked what respondents thought of when the term "DNA" was mentioned. Sixty-three percent didn't know; 27 percent responded with relevant but incomplete answers; 2 percent gave an accurate definition; and 2 percent said it was "poison" (1).

In 1981 and 1982, Yankelovich, Skelly, and White surveyed the general public with regard to "genetic engineering" (13). Their survey population is a nationwide stratified random sample of 2,500 persons aged 16 and over. Results are considered predictive of the U.S. population as a whole at a confidence level of 98 percent. The results showed the following:

- The percentage of the general public believing that the benefits of "genetic engineering" outweigh the risks increased from 31 percent in 1981 to 39 percent in 1982.
- Seventy percent of the public had heard of "genetic engineering" in 1982.
- Sixty-two percent of the public were very or somewhat concerned about "genetic engineering" in 1982.
- In 1982, those who had heard of "genetic engineering" were asked how it would be applied (by responding to a list of possible application areas). Health was selected most frequently (61 percent), followed closely by test tube babies (58 percent), and farming (57 percent). Responses to other application areas were: food processing (33 percent), forestry (31 percent), waste management (30 percent), chemical research (28 percent), pollution control (20 percent), and energy (19 percent).

Yankelovich, Skelly, and White believe that, although the intensity of public concern with "genetic engineering" is low at present, there is a significant latent level of public concern that could surface if adverse consequences associated with applied genetics were reported (13).

The survey data just cited suggest several things:

- A relatively small fraction of the American public is fully informed about genetics in general and, undoubtedly, about biotechnology in particular.
- The more informed public is more likely to view applied genetics favorably than unfavorably.
- There are real concerns about applied genetics.

Implications of public perception for competitiveness in biotechnology

As a factor influencing competitiveness in biotechnology, the importance of public perception varies greatly both across and within countries. Considering first democratic v. nondemocratic countries, public perception as a factor influencing competitiveness will be more important in the democracies than in those countries without such forms of government, simply because of the greater public input permitted by democratic, representative forms of government and the independence of the media.

Among democratic nations, variability in the importance of public perception as a factor influencing the commercialization of biotechnology is a function of many cultural characteristics. Of these characteristics, the traditions of the media, the degree to which the public participates in deci-

sionmaking on scientific and technological issues, and the level of public education in science and technology are particularly important.

Of the six countries examined in this assessment—the United States, Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France—public perception appears to have the greatest importance in the United States. The basis for this statement is that public debate over the establishment of rDNA R&D laboratories in the late 1970's was much greater in the United States than in the other countries. The behavior of the public and the media in the United States and other countries in the years since has changed little, and thus, public involvement as a factor in competitiveness currently remains of greatest importance in the United States.

Public perception will be a factor in determining competitiveness of the United States in the commercialization of biotechnology primarily in the event that genetic research or technology results in actual or perceived adverse consequences. In the case of an accident or perceived negative consequence, several factors would operate to make public perception of genetic research and technology of particular importance in the United States compared to other countries: the role of the media, traditions regarding public participation in scientific and technological issues, and the public's level of education in such issues. In this context, "level of education" requires further elaboration.

A technologically literate public can discriminate between different uses of genetic research and technology; this is important because different uses are associated with different issues. Some uses do not raise any new issues; others do. Thus, use of rDNA technology to produce drugs and biologics that replace similar products produced by chemical synthesis or extraction is simply an alternate means of production and in itself raises no ethical issues (17). An ethical issue for the pharmaceutical industry may be allocation of resources to produce drugs using biotechnology with markets that are potentially large and profitable v. drugs for treating rare diseases or diseases endemic to the Third World, where profits are more limited. Ethical issues are also raised if rDNA technology permits the manufacture of drugs that influence learning, memory, and personality traits, for decisions will be needed on whether such substances should be produced and perhaps on how their distribution should be handled and controlled.

Use of normal DNA to treat the body cells of patients with genetic diseases such as sickle cell anemia is another area where rDNA raises no new ethical issues beyond those associated with other treatment of sick persons. As geneticist A. G. Motulsky points out, this therapy is (17):

> . . . conceptually no different from any therapy in medicine that attempts to improve the health of a sick patient. The only difference is that DNA, rather than other biologicals, drugs, or surgery, is used as the therapeutic modality.

An application of genetic research and technology that does involve new ethical issues is use of genetic markers for diagnosis of susceptibility to disease. This application raises questions pertaining to private v. societal goals and confidentiality. Similarly, any genetic manipulation that alters the reproductive cells is "a qualitative departure from previous therapies since this would affect future generations" (17).

Rational consideration of issues raised by genetic research and technology is often confounded by failure to discriminate between different types of applications. The problem is compounded, because, as pointed out in *Chapter 14: Personnel Availability and Training,* scientific education in the United States is falling behind that of many industrialized nations. These factors could act to the disadvantage of the United States in the worldwide commercial development of biotechnology should an accident or other adverse consequence occur.

Findings

Public perception of the risks and benefits of biotechnology is of greater importance in countries with representative, democratic forms of government than it is in countries with other forms of government, simply because of the greater attention paid to public opinion in the democracies, and the independence of the media. As a factor influencing competitiveness, public perception is probably of greater importance in the United States than it is in Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, or France.

A number of factors influence the relative importance of public perception as a factor influencing competitiveness. In all countries, the importance of public perception will be greatly increased in the event of an accident or perceived negative consequence of biotechnology. In such a case, the level of scientific and technological literacy in the various competitor countries becomes important, as judgments must be made concerning complex issues. Unfortunately, at least in the United States, survey data show that only a small fraction of the public is fully informed concerning genetics in general and therefore, undoubtedly, about biotechnology in particular. Survey data also suggest that there are real concerns in the public mind concerning applied genetics.

Given the lack of public knowledge, it is particularly important that the media play a responsible role with respect to biotechnology. The role of the media extends beyond mere reporting of the facts. How far the media should go beyond such reportage deserves consideration.

Issues and policy options

OTA's first assessment in the field of genetics, *Impacts of Applied Genetics: Micro-Organisms, Plants, and Animals* (29), was published in April 1981 and contained a chapter titled "Genetics and Society." The issues that arise from the material presented in the preceding pages are similar to the ones developed in the chapter on genetics and society. Since the issues in this report and OTA's earlier report are similar, the reader is referred to that earlier report for issues, options, and arguments relevant to them.

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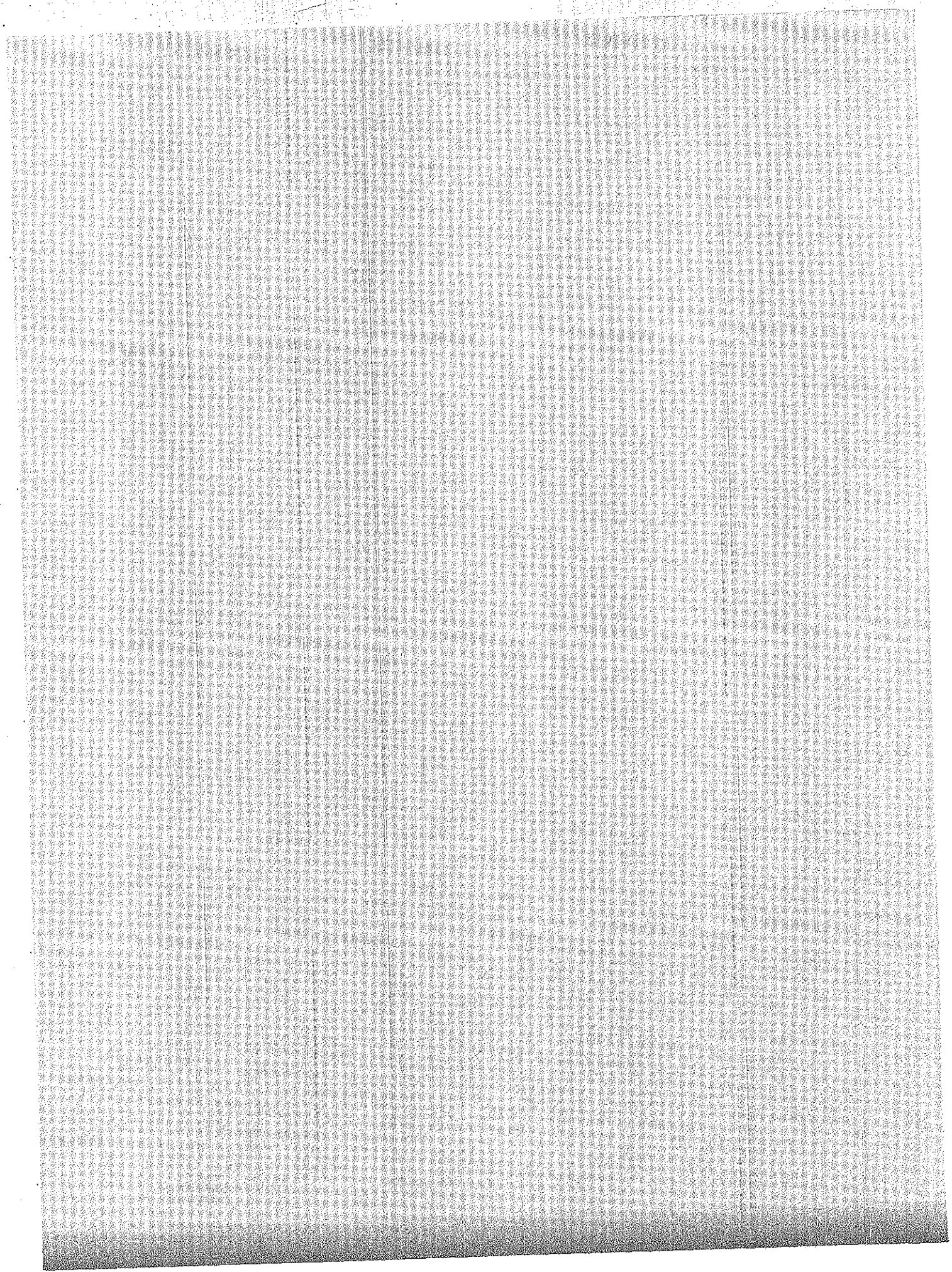
Appendixes



Appendix A

Definitions of Biotechnology

The following is a list of definitions of biotechnology used by the governments and organizations of various countries in assessments of the developing field within their jurisdictions. Most of these definitions encompass both old and new biotechnology.*

Australia

[Biotechnology is] "the devising, optimising, and scaling-up of biochemical and cellular processes for the industrial production of useful compounds and related applications. This definition envisages biotechnology as embracing all aspects of processes of which the central and most characteristic feature is the involvement of biological catalysts" (2).

"In its broadest sense, biotechnology encompasses industrial processes based on biological systems involving naturally occurring micro-organisms, micro-organisms that have been modified by genetic engineering, or isolated cells of plants or animals, and the genetic manipulation of cells to produce new strains of plants or animals" (4).

Canada

[Biotechnology is] "the application of biological organisms, systems, or processes to manufacturing or service industries" (9).

[Biotechnology is] "the utilization of a biological process, be it via microbial, plant or animal cells, or their constituents, to provide goods and services" (11).

European Federation of Biotechnology

[Biotechnology is] "the integrated use of biochemistry, microbiology, and engineering sciences in order to achieve technological (industrial) application of the capabilities of micro-organisms, cultured tissue cells, and parts thereof" (3).

Federal Republic of Germany

"Biotechnology deals with the introduction of biological methods within the framework of technical processes and industrial production. It involves the application of microbiology and biochemistry together with technical chemistry and process engineering" (5).

*The distinction between old and new biotechnology as used in this report is noted in *Chapter 1: Executive Summary*.

France

"Biotechnology consists of the industrial exploitation of the potential of micro-organisms, animal and plant cells, and subcellular fractions derived from them" (6).

International Unions of Pure and Applied Chemistry (1981)

[Biotechnology is] "the application of biochemistry, biology, microbiology, and chemical engineering to industrial processes and products (including here the products in health care, energy, and agriculture) and on the environment" (3).

Japan

[Biotechnology is] "a technology using biological phenomena for copying and manufacturing various kinds of useful substances" (7).

The Netherlands

[Biotechnology is] "the science of the production processes based on the action of micro-organisms and their active components, and of production processes involving the use of cells and tissues from higher organisms. Medical technology, agriculture, and traditional crop breeding are not generally regarded as biotechnology" (10).

Organisation for Economic Co-Operation and Development

Biotechnology consists of "the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services" (3).

Switzerland

The Swiss Government uses the same definition the European Federation of Biotechnology uses (8). (See definition above.)

United Kingdom

[Biotechnology is] "the application of biological organisms, systems or processes to manufacturing and service industries" (1).

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Appendix B
Country Summaries

OTA identified five foreign countries as the major potential competitors of the United States with respect to the commercialization of biotechnology: Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France. This appendix summarizes information about those countries presented elsewhere in this report. It also describes the activities in biotechnology of Sweden, the Netherlands, Australia, Israel, Canada, the U.S.S.R., and Brazil.

Japan

INTRODUCTION

The commercialization of biotechnology in Japan is accelerating over a broad range of industries, many of which have extensive experience in bioprocessing. Leading Japan's drive to commercialize biotechnology are large established Japanese companies such as Takeda Pharmaceutical, Shionogi Pharmaceutical, Mitsubishi Chemical, Sumitomo Chemical, Toray Industries, Suntory, and Ajinomoto. The general chemical and petrochemical firms especially are leaning strongly to biotechnology, and some of them are making rapid advances in research and development (R&D) through their efforts to make biotechnology a key technology for the future.

The Japanese Government, which fell behind in starting to form a national support structure, has embarked on building a foundation for R&D and is demonstrating ambitious movement by forming Government and private collaborative projects with the motto "catch up, get ahead" (8). As biotechnology product markets begin to develop, Japan's expertise in the art of bioprocessing will provide Japanese companies with significant competitive strengths.

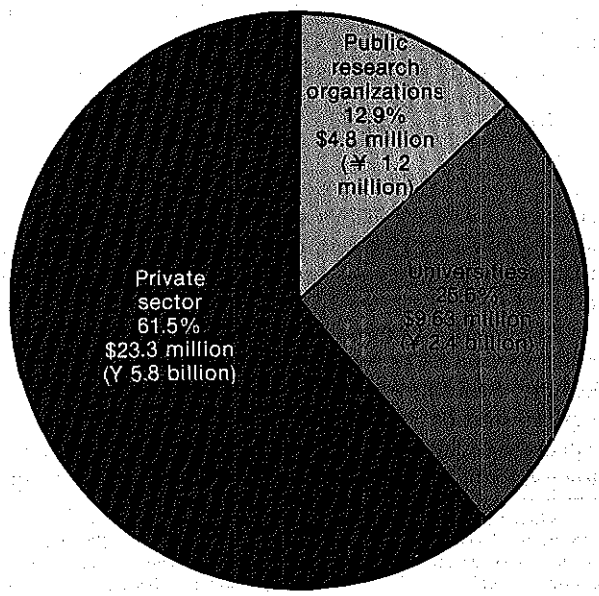
INDUSTRY

All of the large private sector Japanese companies using biotechnology have come from established industries. In this respect, Japan differs from the United States, where more than 100 new biotechnology firms (NBFs)* have been started specifically to exploit biotechnology.

Japanese companies did not start investing in new biotechnology until after 1980, when publicity spread about its potential applications to the pharmaceutical industry. Since then, led by the promise of interferon and monoclonal antibodies (MAbs) in cancer treatment and the potential of producing unlimited quantities of each through biotechnology, more than 150 Japanese companies have rapidly reorganized their R&D systems, equipped research institutes, and recruited new staff to evaluate the applications of biotechnology. The breakdown by funding sector of Japan's total expenditures for recombinant DNA (rDNA) related R&D for fiscal year 1981 is illustrated in figure B-1.

Japanese pharmaceutical companies, whose penetration of international markets heretofore has been low, show promise of becoming increasingly competitive with the United States in world pharmaceutical markets. The Japanese pharmaceutical market is currently second only to the U.S. market in size. In addition to the pharmaceutical companies, Japanese companies from the food, chemical, textile, and pulp and paper industries have also begun to further exploit their accumulated experience in bioprocessing by diversifying into newly developing pharmaceutical product

Figure B-1.—Breakdown of Japan's Expenditures for Recombinant DNA Technology R&D, Fiscal Year 1981



Total rDNA expenditure = $38.1 million (¥ 9.5 billion)

SOURCE: Office of Technology Assessment, based on data from *Science and Technology in Japan*, April/June 1983.

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are firms that have formed specifically to capitalize on developments in biotechnology.

markets.* The field of specialty chemicals will be another highly competitive area of Japanese involvement. Japan is already the dominant international force in amino acid production, and two of the largest amino acid producers, Ajinomoto and Kyowa Hakko Kogyo, have production plants in the United States. Japanese companies' current emphasis on research in specialty chemicals such as enzymes and amino and organic acids reflects efforts to pull the Japanese petrochemical industry out of its present decline in international markets. The urgency of this task is greater in Japan than in the United States, because Japanese petroleum-based industries such as chemicals and textiles are solely dependent on imported petroleum feedstocks. Although some specialty chemicals have traditionally been made by bioprocesses, opportunities for using bioprocesses to make specialty chemicals previously made from petroleum-derived feedstocks have arisen with biotechnology. Producing specialty chemicals using biotechnology offers Japanese companies in these industries an opportunity to reduce their dependence on petroleum and at the same time switch from the production of high-volume, low value-added products to products with higher profit margins.

GOVERNMENT TARGETING POLICIES AND FUNDING OF BASIC AND APPLIED RESEARCH

Within the Japanese Government, a consensus regarding the importance of biotechnology to the future health of the Japanese economy has been achieved. Three Government departments in Japan—the Science and Technology Agency (STA), the Ministry of International Trade and Industry (MITI), and the Ministry of Agriculture, Forestry, and Fisheries (MAFF)—have specifically targeted the development of biotechnology.

STA was the first to demonstrate an interest. As early as April 1971, STA's advisory group, the Science and Technology Council, composed of government, business, and academic leaders, stressed the importance of promoting life science on a nationwide basis because of its commercial potential (4), and STA responded in 1973 by establishing its Office for Life Science Promotion. This office, which is Japan's highest science and technology policymaking body, also manages and coordinates R&D projects in biotechnology. Until the early 1980's, STA's basic, generic applied research,* and applied programs in biotechnology were the largest and best funded Government programs in Japan, and even today STA's programs are comparable in scale to those of MITI (see below). The agency is currently funding corporate generic applied research projects to develop DNA synthesis techniques, bioreactors, immobilized enzyme processes, screening techniques for new micro-organisms, and new medicines.

MITI did not enter the biotechnology field until 1981. That year, MITI established its "System for Promotion of Research on Next-Generation Industrial Technologies," an overall plan to promote "next-generation" industrial technologies, including biotechnology (11). To focus MITI's overall biotechnology effort and to oversee its three next-generation biotechnology projects, an Office of Biotechnology Promotion was established within MITI's Basic Industries Division.

MITI's three next-generation projects in biotechnology— bioreactors, rDNA technology, and mass cell culture—are a part of a 10-year program that is specifically designed to develop and diffuse new biotechnology among Japanese companies.** MITI has invited 14 companies to participate in the projects and will provide allocations over 10 years of $43 million each to the rDNA and bioreactor projects and $17 million to $22 million for the mass cell culture project (2). Some 10 percent of the R&D work (by expenditure) for MITI's biotechnology projects is conducted in the national laboratories of MITI's Agency for Industrial Science and Technology. Ninety percent of the work is conducted in industry laboratories.

To facilitate coordination, the 14 companies that MITI has invited to participate in the biotechnology projects have been organized into the Biotechnology Development Research Association. This association has its own central office through which the various companies communicate with MITI, but otherwise maintains no intercompany institutions or laboratories. MITI subsidies to the companies cover 100 percent of all direct expenses (salaries and laboratory expenses) for biotechnology R&D, but no overhead is allowed, and any capital equipment purchased is nominally the property of the Japanese Government. Furthermore, all patents resulting from the work belong to the Japanese Government. MITI has assured both domestic and foreign companies access to the patents (11).

*The first Japanese companies to enter the field of rDNA-produced pharmaceuticals, Green Cross, Hayashibara, and Suntory, were led by pioneering entrepreneurial managers. For example, the Hayashibara venture into producing interferon with hamsters was possible only because the owner owns or controls 12 companies (hotels, gas stations, and candy manufacturing) and does about $150 million (¥ 37.4 billion) worth of business a year (14). Suntory's (a whiskey company) diversification into rDNA-produced pharmaceuticals is a similar situation.

*Basic, generic applied, and applied research are defined in *Chapter 13: Government Funding of Basic and Applied Research.*

**The Biotechnology Forum, a group of five major Japanese chemical companies that had organized independently after the announcement of the Cohen-Boyer rDNA process patent, was instrumental in lobbying for the establishment of the biotechnology projects.

The third Japanese Government agency that is taking an active role in biotechnology, MAFF, recently established the Committee on Biological Resources Development and Utilization, which compiled a report recommending actions MAFF could take to promote biotechnology development (7). Currently, MAFF is actively promoting cooperative biotechnology research with private industry at its laboratories and is funding work both with Nippon Shokuhin Kako and Oriental Yeast at the National Food Research Institute and with Kao Soap at the National Institutes of Agricultural Sciences. It is also planning cooperative research with Japanese seed companies in the areas of plant breeding and species improvement. Although achievements from the cooperative research are used jointly by Government and industry, these companies that participate in the research projects receive exclusive licensing rights to the patents resulting from these projects for a 3-year period (9). MAFF funding for biotechnology R&D is comparable to that of MITI and STA (11).

In addition to STA, MITI, and MAFF, three other Japanese Government agencies are funding basic and generic applied research in biotechnology: the Ministry of Health and Welfare, the Ministry of Education, and the Environmental Protection Agency. Total Japanese Government funding for biotechnology R&D in 1983 is $67 million (11). Although the level of Japanese funding may be slightly lower than Government funding in both the Federal Republic of Germany and the United Kingdom and is dwarfed by that of the United States, a far greater proportion of Japanese than U.S. funding goes to applied research.

The importance of the Japanese Government's investment in applied research relevant to biotechnology, however, should not be overstated. Of greater importance than the Government's investment in research per se is the Japanese Government's success in encouraging industry's involvement in and long-term commitment to biotechnology. The strength of Japan's biotechnology policy lies in its emphasis on the sensible development of mutually agreed on research strategies, horizontal organization and coordination within the private sector, and timely funding of the necessary high technologies (known in Japan as the "seed corn" policy).

FINANCING AND TAX INCENTIVES FOR FIRMS

Private sector financing in Japanese biotechnology is still mostly indirect and mediated through the Japanese banking system. At present, most Japanese firms using biotechnology are very thinly capitalized. The ratio of debt to equity is still far higher in Japan than it is in the United States. As far as can be determined, however, the financing of R&D efforts is not a major problem for the large companies in Japanese biotechnology. The Japanese companies involved in biotechnology R&D have either their own internal sources of funds or close relations with the banks (11).

Certain weaknesses in Japan's financial system have been especially evident in biotechnology. Despite many changes in recent years, capital remains heavily concentrated in the Japanese banking system, and stock markets play a relatively small role in allocating capital. Only 111 Japanese companies currently have their securities traded over the counter, and total venture capital investments amount to no more than $84 million (1).* Mostly because of the lack of venture capital and the cultural factors inhibiting risk-taking entrepreneurialism, Japan does not have a large class of startup companies that specialize in biotechnology R&D such as that found in the United States.

Japan's private sector has recently taken some initiative in developing a source of "venture capital" by pooling corporate resources. The Japan Associated Finance Corp. (JAFCO) is a private venture capital fund that was organized by Nomura Securities Co. One French, three Hong Kong, and 10 Japanese firms are involved in JAFCO, which plans to offer financial help to new businesses until they qualify for listing as a joint stock company. When the firm reaches this stage of maturity, its income gains will be distributed among the partners of the fund according to the ratio of the capital contribution to the fund (3). These new sources of venture capital may or may not succeed in increasing the supply of venture capital in Japan. In any case, the amount of venture capital these sources currently provide is very small when compared to the amount available in the United States.

The Japanese Government is interested in changing the country's financial system. In 1982, MITI set up a new Office of Venture Enterprise Promotion in parallel with the creation of the Office of Biotechnology Promotion (6). In fiscal year 1981, a Government-related organization called the Center for Promoting R&D Type Corporations guaranteed approximately $3.7 million (¥ 750 million) in loans (a total of 24 loans), and beginning in 1982, this center began making its own loans as well as guaranteeing other lender's loans. In an equally significant development, MITI and the Ministry of Finance (MOF) have recently begun discussing an "automated over-the-counter share transaction system" to make it easier for enterprising small and medium-sized firms that lack business experience to raise funds in the finance market. Currently, MOF's evaluation standards are so strict from the standpoint of protecting investors that venture businesses find

*Institutions such as Japan Godo Finance, Sogo Finance, and Universal Finance Corp. are viewed as nascent venture capital companies.

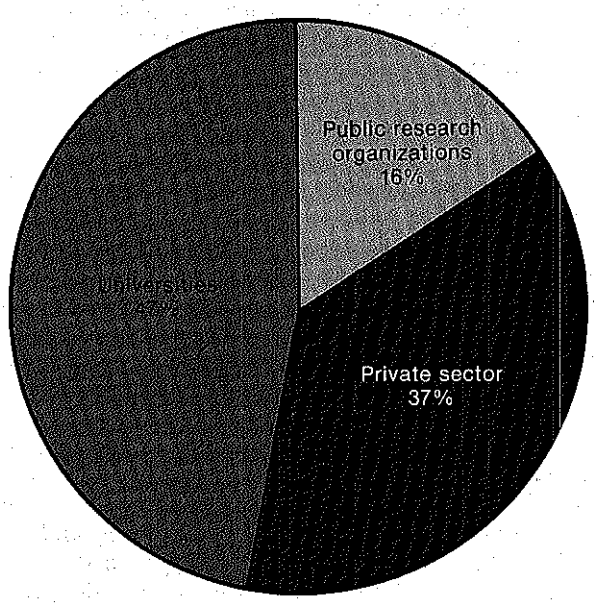
it difficult to have their shares sold when they want to go public.

In the past, Government-funded banks like the Japan Development Bank (JDB) have played a key role in providing large amounts of low interest loans to heavy industries. Certain funds within the JDB loan portfolio are targeted for "technology promotion," and loans from the fund are made at interest rates between 7.5 and 8.4 percent. Currently, however, these funds are not being channelled into biotechnology (11).

Japan's corporate tax code exhibits a uniformity across industrial sectors that is not evident in the United States. Furthermore, corporate taxes are generally lower in Japan than they are in the United States (13). A number of Japanese tax code provisions are aimed at benefiting R&D activity and technological innovation across the board.

One Japanese tax break of particular relevance to the development of biotechnology is the special depreciation schedule used for companies that are members of a MITI-approved National Research Association (e.g., the Biotechnology Development Research Association). Such companies can take an immediate 100-percent depreciation deduction on all fixed assets used in connection with their research association activities. Because of the decentralized character of most National Research Association R&D—90 percent of it is performed separately in corporate laboratories—the tax writeoffs directly encourage R&D activity within corporate laboratories.

Figure B-2.—Breakdown of Japanese Personnel Engaged in Recombinant DNA Technology R&D by Type of Research Organization, Fiscal Year 1981



Total 1,353 researchers

SOURCE: Office of Technology Assessment, based on data from *Science and Technology in Japan*, April/June 1983.

PERSONNEL AVAILABILITY AND TRAINING

Since World War II, the training of industrial microbiologists and bioprocess engineers has been encouraged by both Government and industry funding in Japan, and as a result, a steady supply of these personnel has been maintained. In fact, Japan is considered the world leader in this area. On the other hand, largely because of its weak basic biological science research base, Japan is experiencing a shortage of molecular biologists and immunologists. Some Japanese companies have addressed this problem by sending some of their personnel to the United States for training in molecular biology. Other companies have had success in repatriating Japanese workers already trained overseas. Figure B-2 gives a breakdown of Japanese personnel engaged in rDNA R&D by type of research organization.

Retraining of corporate workers in biotechnology is being pursued actively in Japan. In Japan, more than in any other industrialized country, worker training is the responsibility of the corporation. Japan's ability to adjust rapidly to weaknesses in its labor force, based primarily on the Japanese corporations' funding of worker retraining, is truly extraordinary. In 1981, for example, no more than 10 private Japanese companies had more than 10 researchers working on rDNA technology; a year later, surveys revealed that 52 out of the 60 leading companies surveyed had obtained 10 or more research workers in that area (11).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

In applied research areas such as bioprocessing and microbiology, Japanese university/industry relations and the transfer of information from universities to industry are generally very good. In basic research areas, however, the transfer of information from universities to industry is impeded by the fact that almost all university rDNA and hybridoma research in Japan takes place in "basic" science departments, and these departments pride themselves on independence from industrial influence. The Japanese Government has launched new programs designed to cross the barriers between university basic science departments and industry, but their future success is questionable (11).

The movement of knowledge across industrial sectors in Japan is facilitated by the unique "keiretsu"

structure (a group of companies with historical ties, which usually consists of a company from each industrial sector and a bank or trading company which plays a dominant role by virtue of its contact with other companies within the group). The transfer of information among companies within sectors, however, is inhibited by extreme secrecy and a lack of mobility of personnel from one company to another. MITI's "next generation" projects in biotechnology are designed in part to compensate for this problem and to diffuse knowledge among companies using biotechnology. In part because they suspect they would have to sacrifice proprietary positions in some commercially important research areas, however, some Japanese companies have not joined the MITI projects in the areas in which they have comparative advantages (11). For example, Kyowa Hakko, a leader in work on rDNA, is not participating in the "next generation" project in this area.

OTHER FACTORS

Historically, Japan's guidelines for rDNA research have been among the most restrictive in the world. Although the guidelines have recently been relaxed somewhat, they are still quite restrictive. Japanese companies have mounted intensive lobbying efforts to get the guidelines changed. Although companies have had extreme difficulty in obtaining approval to do work with more than 20 liters of culture, this situation is expected to change soon.

Although estimates are difficult to obtain, the cost of gaining approval for new pharmaceuticals is believed to be lower in Japan than the United States. In Japan, the cost of obtaining approval for a new drug is about $12 million to $20 million (¥ 3 billion to ¥ 5 billion), compared to about $87 million in the United States. The time required for drug development and approval is similar (about 10 years) in both the United States and Japan (5).

The basic law governing worker health and safety in Japan is the Industrial Safety and Health Law. This law imposes on employers the obligation of preventing health impairment caused by substances and conditions found in the workplace. Substantial criminal penalties and fines are imposed for violations. At the present time, no regulations are addressed specifically to biotechnology. Furthermore, specific measures governing environmental effects of biotechnology applications have not been prepared by the Japanese Government.

Because the United States is considered a world leader in the commercial applications of biotechnology, Japanese companies have been actively importing technology from the United States and other countries through R&D joint ventures and licensing agreements. NBFs in the United States in need of financial support widely accept research contracts from Japanese companies, often because U.S. partners cannot be found.

An issue brought up in recent U.S.-Japan trade negotiations was U.S. access to the technologies developed by the MITI-sponsored National Research Associations. MITI has promised to abandon its past policy and disclose the patents obtained in National Research Associations to foreign firms. MITI is also promising membership in National Research Associations to U.S. companies that have Japanese subsidiaries or substantial technological expertise.

Japan is engaged in international efforts to secure sources of biomass* in the event that biomass becomes the favored route to meeting energy needs. In cooperation with developing countries (mostly Asian), Japan is organizing biomass centers. This foresight may operate to Japan's advantage in the future.

Nontariff trade barriers in Japan, especially in the area of pharmaceuticals, may hinder U.S. companies' penetration of Japanese markets. The Japanese Ministry of Health and Welfare has not yet begun to accept clinical test data from the United States, although as of April 1983, Japan did begin accepting foreign test data on animals. Foreign stability test data and data on specifications and test methods will be accepted from October 1983 onward (10).

Unlike the United States, Japan has constraints inhibiting foreign acquisition of domestic companies. Foreign acquisitions in Japan require the unanimous approval of the Japanese company's board of directors and also the approval of MOF. Recently, however, the regulation surrounding the establishment of foreign subsidiaries in Japan has noticeably eased; large numbers of European pharmaceutical companies have established wholly owned subsidiaries in Japan during the past year. The ease of foreign acquisition of domestic companies in the United States is an important issue to consider, because Japanese companies very often acquire foreign companies to gain access to their technology, markets, and distribution networks.

CONCLUSIONS

Because of its present competitive strength in biologically produced specialty chemicals, Japan can be expected to be a major competitor in future specialty chemical markets defined by biotechnology. The fu-

*Biomass, discussed further in *Chapter 9: Commodity Chemicals and Energy Production*, is all organic matter that grows by the photosynthetic conversion of solar energy.

ture competitive position of Japanese companies in future pharmaceutical markets is more difficult to assess. Japanese companies traditionally have not had a significant presence in world pharmaceutical markets, but Government promotion of the pharmaceutical industry, rising investments in pharmaceutical R&D (including related biotechnology applications), and increased competition in the domestic pharmaceutical market all portend a greater role for Japanese companies in future international markets.*

Federal Republic of Germany

INTRODUCTION

A powerful private sector, a well-developed administrative infrastructure, an extensive research base, a generous funding program, and an adequate supply of personnel all contribute to the potential of the Federal Republic of Germany to compete with the United States and other industrialized countries in biotechnology. The overall West German effort does have certain deficiencies (e.g., an inflexible research grants system), however, and the ability to correct them will be a factor that influences the country's competitive position.

The ability to correct these deficiencies, however, will not by itself guarantee competitive success. Politics, for example, and its most powerful ally, public perception, could influence the course of biotechnology development more immediately in the Federal Republic of Germany than in any other country. The West German environmentalists, embodied in the political party of the Greens, have yet to focus their attention on risks specifically associated with biotechnology, but the leading German companies using biotechnology have already aroused public protest as major chemical polluters. The Greens, now incorporated in the Federal parliamentary process, represent a potential threat, especially in the event of a mishap, to the progress of biotechnology in the Federal Republic of Germany (24).

INDUSTRY

The Federal Republic of Germany's competitive position in biotechnology will be determined by the ability of large, established West German companies to develop and market biotechnologically produced goods and services. Responsibility for most of the development of the country's industrial capabilities in biotechnology to date rests largely with chemical companies such as Hoechst, Bayer, and BASF, three of the four largest in the world, and with the slightly smaller pharmaceutical companies such as Boehringer and Schering. Small and medium-sized West German companies have played no significant role in biotechnology innovation, despite the West German Government's efforts to encourage this through the provision, for example, of startup funding for high-risk undertakings (24).

To speed the transition to new biotechnological techniques and processes, the large West German companies that are developing biotechnology have sought outside expertise. Hoechst, for example, signed a 10-year, $70 million contract with Massachusetts General Hospital to support work in molecular biology (18). Hoechst, criticized in Germany for a breach of faith with national science and in the United States for the appropriation of U.S. technology, apparently entered into this agreement with the objectives of getting a "window on the technology" and gaining access to a large, state-of-the-art laboratory in which to train its scientists (18).

GOVERNMENT TARGETING POLICIES

A government policy for the commercialization of biotechnology rates as one of the Federal Republic of Germany's strengths. According to a 1979 statement by the Federal Ministry for Research and Technology (BMFT, Bundesministerium für Forschung und Technologie), the German Government has an obligation to establish the preconditions for industrial innovation in key areas of technology in order to strengthen the competitive performance and competitive capacity of the German economy in long-range growth areas, and in the process, correct weaknesses revealed through international comparisons (24).

The present biotechnology targeting policy has evolved from the West German Government's historical interest in the life sciences. In 1972, BMFT commissioned a report on old biotechnology from the German Society of Chemical Engineering (Deutsche Gesellschaft für Chemisches Apparatewesen) (19), and in 1979, BMFT presented its first official policy specifically for biotechnology (16). This "performance plan" (Leistungsplan) outlined biotechnology research programs with specific objectives, such as the development of unconventional feed and foodstuffs, bioinsecticides, and pharmaceuticals from plant cell cultures. BMFT's more recent statements continue to promote the development of specific product areas (e.g., pharmaceuticals, plant agriculture) and particular proc-

*For example, in 1981, Japanese companies ranked first in terms of the largest number of major new drugs introduced into world markets. In 1982, not only did Japanese companies account for over 16 percent of all U.S. patents issued for pharmaceutical and medicinal products, but 38 percent of all U.S. medicinal patents granted to foreign firms went to Japanese originators. See *Chapter 4: Firms Commercializing Biotechnology* for a more detailed description of Japanese pharmaceutical activity.

esses (e.g., cell culture), but they also focus attention on the importance of basic research and the need for greater interdisciplinary cooperation between biologists, chemists, medical experts, and engineers, disciplinary areas which are important to the development of biotechnology (24).

BMFT implements its policy primarily through a strong and varied funding program. Types of BMFT support fall into three broad categories: 1) funds specifically set aside for the development of biotechnology, 2) grants that fall into already existing schemes for industrial development work, and 3) funds distributed by third-party organizations to which BMFT contributes as part of more generalized funding programs for all areas of public research. For its own biotechnology program alone, BMFT in 1982 spent $29 million (DM70 million), up $5 million (DM12 million) from 1981. In 1981, BMFT also contributed to the German Research Society (DFG, Deutsche Forschungsgemeinschaft) (25) and to the Max Planck Society (Max Planck Gesellschaft) (15). It is impossible to calculate the exact proportion of these other funds dedicated to biotechnology research, but a reasonable estimate might range from $20 million to $40 million (DM50 million to DM100 million). Since data are unavailable to support this estimate, a total BMFT biotechnology funding figure of $50 million to $70 million (DM120 million to DM170 million) for 1982 should be regarded with caution.

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

The Federal Republic of Germany maintains an extensive public research base. Both basic and generic applied research are generally good. Three different types of nonindustry laboratories conduct basic research in biotechnology: 1) laboratories belonging to the universities, 2) laboratories dependent on BMFT for operating expenses and on DFG for project support, and 3) laboratories supported by the Max Planck Society (which, in turn receives support from BMFT).

The operating costs of the universities are supported by the individual States (Länder). Highly publicized deficiencies in German university research have resulted from budget cuts and university reform laws. With the current shortage of funds, grant allocations go to tenured professors (27) and to replace used equipment, not to the young researchers (29). University reform laws have created excessive administrative duties for university professors, making it difficult for them to dedicate sufficient time to their research (20). Despite such problems, however, universities such as those at Heidelberg, Munich, and Cologne continue to conduct research fundamental to the development of biotechnology (21).

Although laboratories supported jointly by BMFT and DFG, such as the Cancer Research Center at Heidelberg, carry out important biotechnology-related work, laboratories funded by the Max Planck Society are responsible for the bulk of the basic research advances in biotechnology. The Max Planck Institute for Plant Breeding Research in Cologne boasts some of the best plant genetics teams in the world (24). Other leading Max Planck institutes working in basic research related to biotechnology include those in biochemistry at Martinsried, biology and virus research in Tubingen, genetics in Berlin, and cell biology in Ladenburg (21).

Some of the Max Planck institutes conduct generic applied biotechnology research, but the center for such research is the Society for Biotechnological Research (GBF, Gesellschaft für Biotechnologische Forschung). GBF is a Government-supported though private institution that was originally founded to conduct generic bioprocessing research to meet the needs of industries (26). GBF employs 365 people (249 permanent and 116 temporary), and its 1982 budget was $13 million (DM31.6 million), of which 89 percent came from BMFT, 9 percent from the Länder, and 2 percent from its own earnings (Gesellschaft für Biotechnologische Forschung, 1982). GBF's current activities include the general development of bioprocess technology, the scale-up of laboratory processes, the screening of micro-organisms and plant and animal cell cultures, the support of other research groups in biotechnology, the participation in joint biotechnology projects with industry, and the advanced interdisciplinary training for scientists, engineers, and technicians. GBF suffers from the usual rigidity of a large German research organization—funds, once allocated, cannot be shifted from one area of research to another. Nevertheless this well-equipped and well-staffed Government-supported applied research facility in West Germany is one of Europe's best.

FINANCING AND TAX INCENTIVES FOR FIRMS

There is no parallel in the Federal Republic of Germany to the U.S. venture capital industry. The powerful and rather rigid banking structure in the Federal Republic of Germany virtually inhibits the formation of venture capital, though there is apparently little demand for it (24). Commercial banks provide most of the funds used for industrial expansion, and it is common for such banks to have equity participation in companies in which they invest. The commercial banking sector is dominated by three banks, and the linkages between the banking and corporate structures are so close that the Monopoly Commission in 1976 concluded that the banks effectively utilize management functions to the detriment of competition (24).

In 1975, a consortium of 28 banks recognized that the German banking system was not conducive to funding high-risk innovative, startup firms and formed a venture capital concern called the Risk Financing Society (WFG, Deutsche Wagnisfinanzierungs-Gesellschaft) (17). The principal objective of this organization was to aid small and medium-sized firms in commercializing their products. So far, however, this concern has not shown much interest in biotechnology companies, a major reason being that since 1980 it has been looking for innovations that could achieve success within 24 months. If this continues to be the criterion for a firm to receive funds from WFG, it would be surprising if many biotechnology startup firms were established in the Federal Republic of Germany with WFG funds.

Tax incentives are a less important source of financing for private sector innovation in the Federal Republic of Germany than direct Government subsidies. This country maintains the highest nominal corporate tax rate of the six countries analyzed in this report (56 percent on retained earnings and 36 percent on distributed earnings). Measures such as an investment grant provision allowing a company to recover up to 20 percent of the cost of R&D capital expenditures contribute to lower the effective tax rate, although the United Kingdom, Switzerland, and Japan still have the lowest effective tax rates of the competitor countries.

PERSONNEL AVAILABILITY AND TRAINING

The Federal Republic of Germany has sufficient personnel to compete with the United States and other competitor countries in biotechnology. Molecular biologists with expertise in rDNA and hybridoma research are in short supply, but the training of such specialists is now a high priority (24). Like Japan, the Federal Republic of Germany maintained a steady supply of both industrial and government funding for applied microbiology and bioprocess engineering after World War II. Thus, the supply of personnel in these areas appears to be adequate.

The Max Planck Society's senate and the present Minister of Research and Technology have indicated that there is a significant drain of German researchers from the Federal Republic of Germany to the United States (21,28). The "brain drain" of scientists from West Germany, however, appears to be less serious than that from the United Kingdom (see below).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

The Federal and State Governments and the private sector in the Federal Republic of Germany use several mechanisms to accomplish the transfer of technology developed in public research laboratories into domestic industries. The Max Planck Institute for Plant Breeding Research and GBF both have several contract arrangements with private companies. On a much larger scale, the pharmaceutical company Schering joined with the State of Berlin and its two universities to establish a biotechnology research institute (Biotechnikum). Though the institute will undertake primarily basic research in rDNA technology, it will also support industrial microbiology research and the production of hormones and amino acids (22). Bayer, BASF, and Hoechst have also established cooperative research programs with West German universities and other research institutes.

OTHER FACTORS

In general, the West German regulatory environment is comparable to that in the United States and poses no additional barriers to the commercial development of biotechnology for either domestic or foreign firms. Guidelines for rDNA research, food and drug testing regulations, intellectual property law, and international trade laws in West Germany are approximately equivalent to those in the rest of the competitor countries.

CONCLUSIONS

The Federal Republic of Germany could become one of the principal competitors of the United States in the commercialization of biotechnology. West Germany's extensive research base would be one of the most well-balanced in the world, were it not for the funding and administrative problems in the universities and the resulting effects on the quality of research. Another problem is that the Government bureaucracy for implementing biotechnology policy is somewhat inflexible. Once funding has been granted for specific projects, money cannot be shifted to other potentially more promising studies. One of the Federal Republic of Germany's strengths, however, is the country's private sector. The size and international market penetration of established German chemical and pharmaceutical companies suggests that these companies are likely to be competitive in the commercial use of biotechnology.

United Kingdom

INTRODUCTION

In many respects, the United Kingdom has the capabilities to compete in biotechnology on an equal basis with the United States, Japan, and the Federal

Republic of Germany. Government initiatives, national science and technology resources, both human and material, and efforts by a few individual companies to commercialize biotechnology place the United Kingdom on a par with these other competitor countries. A relative lack of experience in joint government, industry, and public research cooperation compared to the United States and, with some exceptions, a generally risk-averse private sector, however, could become obstacles to the smooth development of biotechnology in the United Kingdom.

INDUSTRY

A number of NBFs have been started to commercialize biotechnology in the United Kingdom. These include Celltech, Agricultural Genetics, Plant Sciences, Imperial Biotechnology, IQ (Bio), and other companies that were founded specifically to exploit results of basic research in biotechnology-related disciplines. Although the United Kingdom has more NBFs than do other European countries or Japan, the importance of NBFs to the commercialization of biotechnology in the United Kingdom does not generally rival that of their U.S. counterparts. The 1983 marketing by Celltech of MAbs to detect and isolate interferon (34) and of two blood-typing kits using MAbs (47), however, demonstrates a certain dynamism within the United Kingdom's NBF sector.

The large established U.K. companies such as ICI, Burroughs-Wellcome, G. D. Searle, Unilever, Glaxo, and others will play the major role in determining the United Kingdom's competitiveness in the commercialization of biotechnology. These companies, like established companies in the other competitor countries, are better equipped than the NBFs to absorb the high costs of large-scale production, health and safety testing, and marketing, in fields such as pharmaceuticals, food, or agriculture. Although they appear to be investing large sums in biotechnology R&D (44), it remains to be seen whether established companies in the United Kingdom can generate the same level of innovation from in-house research and arrangements with universities as the NBFs in the United States.

GOVERNMENT TARGETING POLICIES

Until recently, many analysts in the United Kingdom believed that biotechnology products would reach markets only after 10 to 20 years (36) and that the British Government should maintain its traditional functions with respect to developing technologies, i.e., limit itself to supporting basic R&D, training qualified personnel, and creating a propitious climate for industry to capitalize on discoveries made in public research facilities (35).

In 1980, a Government committee published a report that identified weaknesses in the development of biotechnology and recommended that the Government take specific corrective actions to assist the transfer of the results of public sector research to industry and to expand existing programs supporting training, research, and innovation (30). The British Government has responded to this report, commonly known as the Spinks' Report, by increasing funds both for the British Technology Group (BTG) for investment in innovative private sector projects in biotechnology and for the Research Councils and Government departments for the support of basic life science research.

In 1981, the British Government, through BTG and in association with four private investors, established Celltech, Ltd., to develop and market products made by some of the new technologies. In 1982, the Department of Industry launched a new 3-year, $30 million program of support for biotechnology in industry (31). The Government has also encouraged the creation of university centers of expertise in biotechnology to bring together experts in different disciplines within a single field and has established a Biotechnology Directorate at the Science and Engineering Research Council (SERC) to coordinate biotechnology R&D in all public sector research laboratories.

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

The United Kingdom has a strong and well-established basic research base. The Research Councils and the universities possess considerable depth in basic research fields such as immunology and plant genetics. Although the economic recession has forced cuts in both university and Research Council grants (46), the Government has attempted to protect the basic science research budget and to redirect resources within this budget to priority areas such as biotechnology. Research Council funds for biotechnology have actually increased. University funds have been reduced in some areas, but the Government has encouraged universities to protect basic research, and the University Grants Committee has been funding the establishment of new posts at many different universities (37).

Generic applied research in biotechnology has been receiving strong support in the United Kingdom. The British Government sponsors generic applied research at a number of locations, including the Centre for Applied Microbiology Research in Porton Down (bioprocess engineering); Warren Spring Laboratory in Harwell (downstream processing); and the Biotechnology Institute and Studies Centre Trust (enzymes). These and other programs all contribute to make develop-

ment a strength of the Government's support for biotechnology.

Definitional problems make it difficult to arrive at a figure for overall Government expenditures for biotechnology R&D. Though the British Government uses the Spinks' Report definition,* research institutes tend to classify work in scientific terms such as rDNA technology, hybridoma technology, and others. A conservative estimate of biotechnology funding for all phases of R&D would fall between $56 million and $60 million for 1982 (46), though the Government expects to increase this level substantially during 1983. The 1982 figure roughly equals spending in Japan, the Federal Republic of Germany, and France.

FINANCING AND TAX INCENTIVES FOR FIRMS

Views on whether there is a shortage of funds available for biotechnology firms in the United Kingdom vary depending on the source of information. Financial institutions say funds are not in short supply; rather, the shortage is in well-presented ideas with commercial value that are capable of earning the relatively high rates of return desired by investors with risk capital. Entrepreneurs say that there is a shortage of funds, because institutions demand more evidence than they can supply to prove that their products are capable of earning high profits.

Funds for the industrial development of biotechnology, especially for NBFs, are available from both public and private sources. The major public source of venture capital is BTG (see above). Private venture capital groups with either investments or plans to invest include Biotechnology Investments, Prutec, Advent Eurofund, Cogent, Technical Development Capital, and others. Of these, Biotechnology Investments, a branch of N. M. Rothschild Asset Management, is the largest, with an initial capital pool of $55 million (39). Most of the fund's investments to date have been in U.S. NBFs and in primarily foreign quoted companies (39), although the company recently purchased equity in Celltech (33) and is now considering more project proposals from British firms than from U.S. companies (43). Other sources of capital for NBFs include banks and other financial institutions, whose project loans are guaranteed by the Government, and the Unlisted Securities Market, for companies with profits of less than $1 million.

Tax law in the United Kingdom tends to favor established companies with programs in or plans to implement biotechnology R&D rather than NBFs. Most of the Government's tax incentives apply to companies earning taxable income (i.e., the large established companies) and are used primarily to encourage additional expenditures on R&D or on plants and equipment required for research or scale-up. The tax code allows the largest and most rapid depreciation allowance of capital expenditures for scientific research of all the competitor countries (100 percent in the first year of use). This provision contributes to making the effective corporate tax rate in the United Kingdom among the lowest of the countries analyzed by this report.

Few of the tax incentives in the United Kingdom, on the other hand, encourage the formation of capital, a necessary precondition for starting an NBF. Both the taxation of long-term capital gains (30 percent) and of income resulting from the sale of technology (in the form of patent sales or licensing royalties) are the most unfavorable of the competitor countries. The British Government recently introduced new measures designed to encourage the private sector to make equity investments in startup firms by offering tax relief at the top marginal rate to investors in new (up to 5 years old) qualifying trades, but the effect of this policy remains to be seen.

PERSONNEL AVAILABILITY AND TRAINING

Like the United States, the United Kingdom boasts both qualified personnel and excellent training and education programs for personnel in the basic life sciences. Personnel supported by the Medical Research Council are internationally prominent in the development of rDNA and hybridoma technologies.* Also like the United States, the United Kingdom is experiencing personnel shortages in areas related to scale-up. The shortage in the United Kingdom in part results from the fact that very limited opportunities in British universities have led some scientists to leave their posts in academia for positions in foreign biotechnology companies. Approximately 70 Ph. D.s have left the United Kingdom in the past few years. Slightly less than two-thirds of these scientists have come to the United States, though some of them may not be working exclusively in biotechnology. About 30 of the 70 have joined commercial enterprises (13 now work at Biogen S.A. in Switzerland). This "brain-drain" also affects another class of professionals, i.e., individuals skilled in applying the new technologies such as bioprocess and chemical engineers and masters-level microbiologists. Analysts estimate that a total of between 100 and 1,500 experts in some aspect of biotechnology have left the United Kingdom over the past several years (45).

The effects of this outflow on the overall British effort are difficult to determine; no one really knows

*This and other definitions of biotechnology are presented in *Appendix A: Definitions of Biotechnology*.

*British researchers Georges Köhler and Cesar Milstein at the Medical Research Council were the first to develop hybridomas.

whether the United Kingdom may be losing visionaries as well as scientists or whether 100 people represent a significant portion of the available specialized personnel in the United Kingdom (41). In an effort to correct a situation which often obliges some younger researchers and engineers to emigrate, the British Government has recently launched a program to make room for "new blood" in the life sciences in the universities. The creation of these new positions will raise the number of lecturers and create new openings for postdoctoral research and postgraduate courses. In addition, SERC maintains a list of British biotechnologists outside the United Kingdom and may be taking measures to encourage them to return (45).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

The universities in the United Kingdom have had very few ties with industry in biotechnology. As a result, the transfer of technology from public research to the industrial sector in the United Kingdom has not always been effectively accomplished. In 1975, for example, the Government failed to patent Kohler and Milstein's technique for making hybridomas, the specialized cells which produce MAbs, and the Americans were the first to recognize the commercial potential of MAbs (40).

With the growth of biotechnology and of public support for these technologies, however, the British Government has taken steps to encourage the process of domestic technology transfer. BTG, which encourages cooperative projects between industry and public sector research and serves as a public source of venture capital, has committed $21 million in support for biotechnology projects so far, with $6.5 million annual increases expected for the next few years (44). In addition, the Department of Industry launched in 1982 a new, 3-year, $30 million "Biotechnology in Industry" program, independent of BTG's activities. Directed by the Laboratory of the Government Chemist, this program sets aside funds for consultancies and project feasibility studies, supports demonstration plant construction, and sponsors joint industry-research centers (31). SERC has initiated several collaborative research programs and promoted, for example, the Leicester Biocentre. The British Government's establishment of NBFs such as Celltech and Agricultural Genetics Co. in association with private investors and BTG's loss of the rights of first refusal* on inventions in public research (32) may help stimulate direct relationships between researchers and industrialists.

*This is the right to choose whether or not to produce and market any good or service, without having to bid competitively with other firms.

OTHER FACTORS

The regulatory environment in the United Kingdom poses little threat to the development of biotechnology in that country. Approval for the marketing of a new drug in the United Kingdom, for example, occurs twice as quickly as in the United States (46).*

The public body that has been responsible for setting and enforcing the United Kingdom's guidelines for rDNA research is the Genetic Manipulation Advisory Group (GMAG). GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended the relocation of the group from the Department of Education and Science to the Department of Health and Social Security (42). GMAG, now called the Health and Safety Commission Advisory Committee on Genetic Manipulation, has been moved to the Department of Health and Social Security and will advise the Health and Safety Commission and Executive on general questions, giving advice, when requested, to Government departments. This change in status of the old GMAG reflects a belief by the Government that those responsible for agriculture, environment, and industry need the committee's advice now more than those in charge of education and science (44). Only in exceptional instances will the Advisory Committee on Genetic Manipulation actually review project proposals. The burden of this task has been passed on to Government officials (42).

British patent law in general conforms to European standards. The lack of case law specific to biotechnology inventions, however, precludes an assessment of whether certain patents that are issued in the United States would receive the same treatment in the United Kingdom. Antitrust laws are approximately equivalent to U.S. statutes.

CONCLUSIONS

The United Kingdom could be a major competitor of the United States in specific product markets in biotechnology. The country's strong basic and generic applied research base, the British Government's strong interest in direct measures to stimulate the commercial development of biotechnology, the excellent university system, and the relatively positive regulatory environment all contribute to allow domestic industries a competitive foothold in biotechnology. The future of commercial biotechnology will be decided in part by the speed, content, and scale both of political decisionmaking with respect to biotechnology and of industrial commitment to developing the technologies.

Although the number of NBFs has grown in the United Kingdom because of an increasingly positive

*For further discussion, see (38).

public attitude toward high technology in general, the development of high-technology fields in the United Kingdom may lack some of the dynamism of similar enterprises in the United States. The causes of what appears to be a lack of entrepreneurialism fall outside the scope of conventional modes of analysis and may be due in part to cultural factors which defy measurement.

The ability of all interested parties to adopt recent Government measures to encourage technology transfer from public institutions to industry and to solve other problems will, to a large extent, determine whether the country can challenge the United States, Japan, and West Germany in this new set of technologies. The United Kingdom's affinity with the United States and longstanding commercial ties to the Pacific Basin could very well be assets.

Switzerland

INTRODUCTION

Switzerland reveals an impressive national commercial potential in the area of biotechnology. It has a good university system and several renowned research institutions. A strong financial sector and a technology-based, export-oriented economy also contribute to Switzerland's potential competitiveness in biotechnology. Swiss companies produce 10 percent of the world's pharmaceuticals (53), and, by reinvesting large proportions of sales revenues in R&D, they achieve high rates of innovation essential to competitive success.

Switzerland is organized as a federation of 26 relatively autonomous regions (cantons), and a liberal economic tradition constrains the Federal Government's role in industrial policymaking. Consequently, the Swiss Federal Government has not developed a central policy for biotechnology. A number of steps have been taken to promote innovation through Government loans to highly focused, small-scale projects, but these have not been focused on biotechnology (53). In fact, in 1982, a proposal to establish a national research program specifically for biotechnology under the auspices of the Swiss National Science Foundation (Schweizerischer Nationalfund zur Forderung der Wissenschaftlichen Forschung) was voted down by this organization.

INDUSTRY

Private sector biotechnology R&D in Switzerland is concentrated among three large pharmaceutical companies (Ciba-Geigy, Hoffmann-La Roche, and Sandoz), an NBF (Biogen S.A.*), and, to a lesser extent, several companies involved with bioprocess engineering and biomass conversion for producing chemicals and for energy production (Bioengineering AG, Chemap AG (now owned by Alfa Laval), Petrotec Holding Co. AG, and Batelle Geneva Research Center (U.S. owned).

All of the three large Swiss pharmaceutical companies spend a substantial portion of their R&D expenditures abroad. Ciba-Geigy has made the greatest in-house commitment to biotechnology R&D by improving current production lines such as antibiotics with genetic manipulation. Ciba-Geigy's commitment to the development of biotechnology can be seen in its new $19.5 million biotechnology research center employing 150 people and in its extensive program of support for research in local universities and its own institute laboratories (53). Ciba-Geigy, spent about 8 percent of its 1981 total sales of $1.8 billion (SFr 3.8 billion), on overall R&D. Of this amount, almost 60 percent was spent within Switzerland, while expenditures in U.S. facilities comprised 23 percent and those in the rest of Europe and Asia accounted for 20 percent of the total outlays (49).

In comparison with Ciba-Geigy, Hoffmann-La Roche and Sandoz look more toward the United States for developing biotechnology expertise through contracts and R&D subsidiaries. Hoffmann-La Roche, in conducting biotechnology R&D in its research institutes throughout the world (especially New Jersey) and forming partnerships with NBFs in the United States, spent $59 million on biotechnology R&D in 1981 (50). Approximately one-third of Hoffmann-La Roche's biotechnology R&D budget goes to rDNA experiments (48). Similarly, Sandoz pursues biotechnology through a half-million dollar contract with the Wistar Institute (Philadelphia), a contract with NPI (Salt Lake City), a $5 million investment in the Genetics Institute (Boston), and the purchase of Zoecon (Palo Alto), in addition to research conducted in its Austrian institutes. Though only $5 million of the $226 million Sandoz R&D budget has been spent on biotechnology since 1977, biotechnology will account for an increasing share in the future (48). For example, a biotechnology research institute recently established by Sandoz at University College, London, a center of neurobiology and neuro-

*Biogen, S.A., a Swiss company, is one of the four principal operating subsidiaries of Biogen N.V., which is the parent company of the Biogen group and is registered in the Netherlands Antilles. Biogen N.V. is about 80 percent U.S. owned. The other three subsidiaries include: Biogen Research Corp. (a Massachusetts corporation) which conducts R&D under contract with Biogen N.V. and Biogen B.V. (a Dutch corporation) and Biogen, Inc. (a Delaware corporation) both of which perform marketing and licensing operations. Biogen's principal executive offices are located in Geneva, Switzerland. Biogen N.V. is largely U.S. owned.

chemistry, will receive $7.6 million over the next 3 years.

While the established pharmaceutical companies are beginning to explore new applications of biotechnology in the area of pharmaceuticals, the NBF Biogen S.A. is applying biotechnology to several industrial sectors with a diverse R&D program. Biogen was established in 1978, largely at the initiative of venture capitalists from the United States, with funds from International Nickel Co. Biogen currently has three other principal shareholders: Monsanto (U.S.), Schering-Plough (U.S.), and Grand Metropolitan Limited (U.K.). Biogen S.A. has yet to sell any products made from biotechnology, but it was the first firm to obtain expression of hepatitis B surface antigens, leukocyte interferon, and the viral antigen of foot-and-mouth disease from rDNA technology. The diverse background of its scientific board suggests a flexible R&D policy with widespread applications of biotechnology to mining and metals refining, pharmaceuticals, chemicals, energy, agriculture, and food and beverage production (54). In 1982, through $20.5 million generated from contract research (primarily with Schering [F.R.G.], Shionogi [Japan], and Fujisawa [Japan]), Biogen S.A. supported an $18.4 million R&D program (48).

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

Though the Swiss Federal Government has no specific biotechnology policy, its funding for biotechnology-related research is increasing (48). The Swiss National Science Foundation serves as a clearinghouse for Federal funds for the support of basic research related to biotechnology at specific universities and other institutions. Much of the fundamental research in the life sciences, however, is carried out in the largely canton-supported universities (52). Out of Switzerland's total biological and biomedical research budget of about $73 million (SF150 million), about 4 percent or $980,000 (SF2 million) goes to biotechnology.

The major Government source of applied research funds is the Commission for the Encouragement of Scientific Research (Kommission zur Forderung der Wissenschaftlichen Forschung). This commission provides grants for applied research projects of proven interest to industry, normally contributing 50 percent of the costs. The Department of Biotechnology (Institut für Biotechnologie) at the Swiss Federal Institute of Technology at Zurich (ETH-Zurich, Eidgenossische Technische Hochschule) receives strong support from the commission. ETH-Zurich, with an additional complex at Honggerberg, conducts research in the areas of basic biological research, bioprocess engineering, and water and sludge treatment. In addition to funding these activities, the Commission for the Encouragement of Scientific Research itself plays an active role in identifying potential industrial partners and interesting them in particular research projects (53). Given the proprietary nature of much of the work, funding figures are unavailable (52).

TAX INCENTIVES FOR FIRMS

Beause of low corporate tax rates, Switzerland provides a favorable environment for established companies in biotechnology. Though corporations conducting business in Switzerland are subject to both Federal and cantonal taxes, the Swiss effective corporate tax rate is the lowest in Europe (51).

PERSONNEL AVAILABILITY AND TRAINING

The access to distinctive universities and the high standard of living in Switzerland, attract highly qualified personnel from around the world to participate in Swiss biotechnology. Although the availability of personnel may not be important for the large pharmaceutical companies, which conduct a large proportion of their R&D in other countries, it is crucial to the Swiss advancement of biotechnology in other sectors. The attraction of talent from other industrialized countries may help the competitive efforts of Swiss companies in biotechnology in the future.

OTHER FACTORS

Swiss antitrust laws preventing monopolies present no serious problems for R&D joint ventures. In Government-industry joint projects, Swiss law assigns patents to industry, though holders of inventions whose R&D was supported by a Federal grant must repay the Federal contribution from license fees generated by the patent.

Health and safety laws in Switzerland do not generally impose barriers to biotechnology development. Although Switzerland is following a previous, and more restrictive version of the U.S. guidelines for rDNA research, there are no requirements covering large-scale work. The licensing of pharmaceuticals is more streamlined in Switzerland than in other countries. There is no requirement for Government approval before initiation of clinical trials, and the drug approval process generally takes from 6 to 10 months.*

*The Swiss pharmaceutical industry exports roughly 90 percent of its products. Thus, the drug and other product regulations of importing countries cause more concern to these companies than Switzerland's relatively relaxed regulatory framework (53).

CONCLUSIONS

The factors cited above and a growing commitment to biotechnology by the private sector suggest that biotechnology is advancing in Swiss industries. Both the Federal Government and most companies have been slow to initiate R&D programs in biotechnology, although the Swiss pharmaceutical industry and especially four companies have boosted their activities in these fields. For several reasons, Switzerland has only recently begun to dedicate its collective efforts to biotechnology (53):

- financial experts and bankers have lacked the technical expertise to evaluate high risk technologies;
- manufacturers have been averse to incorporating biotechnology into some Swiss industries because of the high financial risks and uncertainies caused by public and professional concern about the safety of rDNA research;
- Swiss industrial scientists have trailed Swiss and non-Swiss academic scientists in recognizing the widespread potential of biotechnology; and
- Swiss industries are highly oriented toward chemical synthesis and thus have underestimated the commercial implications of new biological processes.

In conclusion, the majority of Swiss biotechnological expertise rests in the large pharmaceutical companies and in Biogen S.A. and a few other small firms. The large companies generally conduct their R&D in foreign subsidiaries or in the form of proprietary research at in-house facilities and make no concerted effort to support domestic basic research outside industry (48). Thus, technology transfer between large Swiss firms and the universities is limited. Nevertheless, given the quality of Swiss educational institutions teaching the knowledge needed for the development of biotechnology, the attraction of foreign talent to Switzerland, and a new Government focus toward biotechnology development, the industrial use of biotechnology by Swiss companies is likely to become more widespread in the near future.

France

INTRODUCTION

France is currently in a less favorable position to compete with the United States than Japan and the other European countries analyzed in this report. The country's research system and industries generally lack a critical mass of qualified personnel in many disciplines important to the development of biotechnology. In addition, attempts by the socialist government to increase R&D expenditures have met with frustration because of an adverse macroeconomic situation in France during the last 2 years. However, the existence of isolated centers of excellence in scientific disciplines such as immunology, molecular biology, and bioprocessing, and of a few companies with bioprocessing expertise and a strong commitment to developing biotechnology, such as Elf Aquitaine and Rhone Poulenc, may help France to compete with other industrialized companies in selected product markets.

INDUSTRY

Three large French companies have R&D programs in biotechnology—Elf Aquitaine (67-percent Government owned), Rhône Poulenc (100-percent Government owned), and Roussel Uclaf (40-percent Government owned and a Hoechst subsidiary). Of these three, Elf Aquitaine has committed the most effort and money to biotechnology. It owns Sanofi, a pharmaceutical company that has the right of first refusal on all development research at Institut Pasteur Production (the scale-up branch of the Institut Pasteur), and has established Elf Bioindustries and Elf Bioresearch to develop biotechnology in the foodstuff and agricultural sectors. Medium-sized French companies, especially in the foodstuff sector, spend very little in overall R&D (about 0.1 to 0.2 percent of revenues) and have hesitated to devote their energies to biotechnology (62). Furthermore, France has only a few NBFs (e.g., Genetica, Transgene, Hybridolab, and Immunotech), and most of them are subsidiaries of large companies or commercializing arms of research institutes. Thus, the ability of large companies to commercialize biotechnology products will determine France's competitiveness in certain product markets.

GOVERNMENT TARGETING POLICIES

Official interest in the commercialization of biotechnology in France emerged only recently, with the appearance of the Pelissolo report in December 1980 (59). Since the election of the socialists, the French Government has resolved to push the development of several new technologies in its national industries and has accorded a privileged position to biotechnology within this scheme.

The French socialist government has established the most highly coordinated policy for the development of biotechnology of any of the six major competitor countries identified in this assessment. This policy rests on two cornerstones:

- a general research law (Loi de Programmation et d'Orientation) adopted by the French National Assembly in the first week of July 1982, and

- a program specifically for biotechnology ("Programme Mobilisateur: L'Essor des Biotechnologies") presented toward the end of the same month (58).

The general research law sets two objectives: 1) to stimulate French effort in new technologies by "guaranteeing" real increases in the overall civilian R&D budget of 17.8 percent per year, economic conditions permitting, and setting up seven technological "programmes," including one for biotechnology, on which a major portion of research funds are now to be directed; and 2) to open up French science to industry and education by encouraging scientists in research institutes to work in collaboration with private sector colleagues and to teach in universities (65). The Programme Mobilisateur, presented in July 1982 by the Biotechnology Mission of the newly organized Ministry of Research and Industry (now the Ministry of Industry and Research), outlines in detail the steps the Government should take to strengthen French biotechnology. This document calls for intervention from Paris through a myriad of organizations and committees in all aspects of research, education, technology transfer, and industrial development.

Both the research law and the Programme Mobilisateur demonstrate the French Government's determination to promote the necessary multidisciplinary approach to the various technologies and to establish vertical chains (filières) that incorporate all the relevant expertise in basic research, generic applied research, and large-scale production necessary to bring a product to market (60). The effectiveness of the French policy, however, will depend in part on the extent of voluntary cooperation among the various Government groups implementing the policy and the sectors the plans affect (i.e., public research centers, universities, and private industry).

GOVERNMENT FUNDING OF BASIC AND APPLIED RESEARCH

Most basic research in France is conducted in public research centers ("grands organismes"), similar in principle to the British Research Councils, or in a few university laboratories associated with these centers.* One of the three major "grands organismes," the National Center for Scientific Research (CNRS, Centre National de le Recherche Scientifique), conducts basic research related to biotechnology in three different divisions, and some of the projects CNRS sponsors overlap with similar work both at the center itself and at other centers and universities (62).

Little public sector generic applied research takes place in France. There are no national applied research laboratories, and with the exception of isolated programs at the universities at Compiègne (enzymology and bioprocess engineering) and Toulouse (biotechnology), the Government of France supports almost no generic applied research of benefit to its domestic industries.

Until recently, Government funding of both public and industrial R&D counted as a French strength. Although it should be noted that definitions of biotechnology differ from one organization to the next, funding estimates vary according to referred sources, and many research projects receiving biotechnology money have nothing to do with biotechnology (62), the French Government probably spent between $35 million and $60 million on biotechnology R&D in 1982.* Notwithstanding the Government's strong initial effort to fund biotechnology, increases planned for 1983 were effectively reduced. The National Assembly reduced the scheduled 17.8-percent real increase in the 1983 civil research budget to about 10 percent (66), and the reduction for researchers in biotechnology related fields was even greater. CNRS saw its original 1983 budget cut by 12.5 percent, and the Programme Mobilisateur research has lost a quarter of its allocation. These austerity measures allow research funding to keep pace with inflation, but little more. In spite of the reductions, the overall research budget still represents a 7.5-percent real increase over 1980 levels, and the Ministry of Industry and Research continues to support its policy of increasing allocations for science (56).

FINANCING AND TAX INCENTIVES FOR FIRMS

A new law enacted in February 1983 created a legal structure allowing the formation and investment of venture capital (67), but the venture capital market in France is poorly developed. Banks are the major source of financing in France, and have always hesitated to take major equity positions in industry. The financing that French banks provide, however, is designed for long-term projects, thus eliminating the problem, encountered by companies in the United States, of finding sources for second- and third-round financing.

With the exception of one provision, tax law in France generally conforms to European and American standards. A generous depreciation allowance in the tax code permits a company in France to write off 50

*For a more detailed description of the research infrastructure in France, see R. Walgate, "Great Schools, Great Contradictions" (63) and "CNRS—The Core of Research (64).

*This estimate is based on a 3-year (1983-85) projected total of $175 million, with a guaranteed (by law) 17.8-percent annual increase in the civil research budget, plus increased support for industry through existing schemes.

percent of its expenditures on R&D capital assets during the first year following the acquisition of these assets.

PERSONNEL AVAILABILITY AND TRAINING

France has a serious shortage of qualified personnel that could well undermine the country's basic and applied science base and prevent France and its industries from competing successfully in the world biotechnology marketplace. Specialists in the fields of general and industrial microbiology, rDNA and hybridoma technologies, enzymology, plant and animal cell culture, and bioprocess engineering are few (55). Although some French research centers boast internationally recognized teams, such as the enzymology and bioprocess technology teams at the technical University of Compiègne or the immunology groups at the Institut Pasteur (62), these are isolated clusters of expertise and will have difficulty matching the total output of the large and balanced national research bases of other competitor countries.

The scarcity of personnel in France cuts across several sectors of R&D in these technologies and applies equally to different categories of personnel, from scientists and bioprocess engineers with advanced degrees to skilled laboratory and production technicians. In order to correct this situation, the French Government has given special attention to the education and training of qualified personnel. The research law passed in July called for the active involvement in the educational process of public sector researchers outside universities (65), and the Programme Mobilisateur presents educational guidelines for all stages of schooling from secondary to postdoctoral levels, placing special emphasis on an interdisciplinary approach within the universities (58). The education of a specialist in rDNA technology, nonetheless, takes many years, as does the implementation of such training programs. As a short-term solution to its present lack of personnel, therefore, France imports foreign experts (58).

UNIVERSITY/INDUSTRY RELATIONSHIPS AND DOMESTIC TECHNOLOGY TRANSFER

Universities in France have had very few ties with industry in biotechnology. Large firms in France actively seek out developments in basic research, either by locating plants near research centers or through an office that monitors current developments in biotechnology research in France and other countries.

The French Government encourages domestic technology transfer through the National Agency for the Evaluation of Research (ANVAR, L'Agence National de la Valorisation de la Recherche). ANVAR, which has no right of first refusal on the results of research in public laboratories, acts as a catalyst for the direct interaction between these institutes and private firms (e.g., through publications on the status of innovation with applications in different industrial sectors).*

OTHER FACTORS

The French legal and regulatory environment, with one exception, poses no real barriers to the commercial development of biotechnology. France maintains the most rigid investment control laws in Europe (61). These regulations allow the French Government to prevent strategic companies from being acquired by foreign concerns and may well hinder foreign firms' ability to penetrate French markets.

Health and safety regulations, as well as patent and antitrust laws in France, however, are approximately equivalent to those in other European countries.

CONCLUSIONS

At present, France lags somewhat behind the United States, Japan, the Federal Republic of Germany, the United Kingdom, and Switzerland in the commercial development of biotechnology. If the country can solve its personnel problems, however, French industries could well gain a competitive footing in selected product markets. The Government's well-coordinated formal policy and adequate but precarious funding program represent a strong commitment to the development of biotechnology that needs to be completed with the necessary qualified personnel. Although the French private sector until rather recently has hesitated to develop its biotechnology capabilities, large companies do have the money and the means of uncovering the latest technological developments. Therefore, the ability of both the public and private sector to recruit and train scientists and technicians and the maintenance of sufficient Government allocations for R&D in the face of adverse macroeconomic conditions may ultimately determine the competitiveness of French biotechnology in the international marketplace.

Sweden

Sweden is a technologically progressive country, but adverse public opinion toward rDNA technology has resulted in the imposition of Government restrictions on the use of rDNA in research and industry. Furthermore, a lack of trained personnel in basic sciences has restrained the commercialization of biotechnology.

*For a general review of ANVAR's functions and activities, see "Commentary on the National Agency for the Evaluation of Research," *Le Monde* (57).

Swedish public opinion and Government policies may be changing to encourage biotechnology in Sweden. If this proves to be the case, Sweden may market products in areas such as the following:

- *Support sector.* Swedish scientific instrumentation, filtration, and industrial separation systems are used around the world and are important in the commercialization of biotechnology.
- *Bioprocess engineering.* A large portion of Sweden's combined public and private sector R&D efforts is devoted to heterogeneous bioprocessing systems, stabilization of immobilized cell systems, membrane technology, and downstream purification and regeneration (76).
- *Pharmaceutical industry.* Swedish pharmaceutical companies maintain aggressive export policies and are active in innovation. The five largest Swedish companies have a gross annual income of about $1 billion, with 70 percent derived from exports (76). It is not known to what extent Swedish pharmaceutical companies will use biotechnology, given Sweden's shortage of trained personnel in rDNA technology and other areas. In the near term, most Swedish companies will probably rely on licensing arrangements with NBFs in the United States to gain access to biotechnology (76).

Among the Swedish companies that appear to have the potential to use biotechnology for producing goods and services are Pharmacia AB, KabiGen/KabiVitrum, and Alfa-Laval.

Pharmacia AB concentrates on pharmaceuticals, separation products, diagnostics, and cosmetic products, and derives 90 percent of its revenues from exports; the U.S. subsidiary, Pharmacia, accounts for 25 percent of these sales. With demonstrated abilities to serve specialty markets, this company is a leader in separation science and is working to establish rDNA capabilities.

KabiGen/KabiVitrum, operated by the Swedish Government, is currently the world's largest supplier of pituitary-derived human growth hormone (hGH). In order to protect its hGH market from foreign competition, Kabi has entered into a licensing arrangement with Genentech (U.S.) to market rDNA-produced hGH outside of the United States. KabiGen is also moving to establish its own rDNA capabilities, intending to pursue projects on human insulin, methanol production, bacterial metal enrichment from ores, interferon, and anticoagulant pharmaceuticals (71,72). Furthermore, Kabi is involved with the development of support equipment, including a polynucleotide synthesizer (69).

Alfa-Laval has large-scale fermentation capabilities and is currently working to establish rDNA capabilities through its subsidiary AC Biotechnics, in which it shares ownership with Cardo Co. Biotechnics has a budget of $8 million to $10 million for an unspecified length of time to produce specialty chemicals and ethanol using rDNA technology.

Other Swedish companies interested in biotechnology include Sorigona AB, which produces chemicals and foods; Astra, which is working in collaboration with U.S. researchers to develop long-acting anesthetics (74); and approximately a dozen additional firms.

Funding for high technology in Sweden is available from several Government sources. Since each department of the Swedish Government establishes its own R&D budget, however, overall R&D funding estimates are difficult to obtain. Some degree of R&D coordination is maintained by the National Swedish Industrial Board (Statens Industri Verk), which is responsible for promoting technological development, organizing training, and orchestrating Government actions, and the National Swedish Board for Technical Development (STU, Styrelsen för Teknisk Utveckling). STU, which is the main source of Government funds for biotechnology, granted an estimated $4 million for biotechnology in 1982, and Swedish industry probably spent an additional $15 million (72).

The manner in which STU distributes R&D funds reflects a Swedish Government policy of directly promoting strategic industries. STU works through joint Government/private ventures with foundations established by Swedish and foreign companies interested in a particular field of development. STU provides half the R&D funding as provisional grants and the foundation provides the other half. If the venture is successful, the funding is treated as an interest-free loan; otherwise, it is considered a grant. Research grants/loans are limited to $100,000, and those for product development to $600,000. In 1973, 20 Swedish, 2 Danish, 2 Finnish, and 1 Norwegian company established a specific foundation to promote biotechnology called the Biotechnology Research Foundation (SBF, Stiftelsen Bioteknisk Forskning) (72). SBF, in conjunction with STU, is currently conducting research on heterogeneous bioprocessing systems, immobilized cell systems, membrane biotechnology, and regeneration of coenzymes (76).

Private industry R&D in Sweden is encouraged by corporate tax incentives, which include a 10-percent deduction for R&D and a 20-percent deduction for any increase in R&D from the previous year.

Sweden's Central Investment Bank and commercial banks provide risk capital in promising technological areas. Information about the banks' views toward new biotechnology is not available, but in 1982, $300 million for all R&D loans in Sweden were tendered. Capital for risk ventures from other sources is limited

in Sweden, and the larger Swedish companies, such as Fortia, rely primarily on internal funds and Biotechnology Research Foundation loans (73).

The Swedish Government has encouraged high-technology, export-directed growth for many years and has promoted relations among the Government, industry, and the universities. Seven Swedish universities have liaison officers with industry whose salaries are paid by STU. A 6-year, $7 million agreement has been established between the University of Uppsala, the University of Agriculture, the Swedish Veterinary Institute, and Fortia AB, that is intended to develop expertise in rDNA technology and to create the "... most intensive programme of biotechnology in the world" (68).

Although extensive interaction between the sectors is encouraged and funded, Swedish efforts to commercialize biotechnology suffer most from a shortage of certain types of trained personnel. Estimates of the number of Swedes working in biotechnology vary from 30 to 40 people (72) to as many as 200 workers at Uppsala alone (68), but shortages of personnel in key areas such as rDNA technology hamper wider commercial applications (75).

Personnel training for biotechnology has been largely inhibited by negative Swedish public attitudes toward rDNA experimentation. As a result of the restrictive rDNA guidelines, which required the Swedish National Recombinant DNA Advisory Committee's permission to conduct any rDNA research, there was little need for trained personnel, and Sweden's private sector relied on foreign companies for developing products requiring rDNA processes (70). In a joint project between KabiVitrum and Genentech (U.S.) to develop and produce hGH, for example, the first actual cloning of the hGH gene was performed in the United States by Genentech. Since the relaxation of the guidelines, however, the need for qualified engineers and scientists has increased, and some Swedish universities have instituted training programs in biotechnology.

The Swedish Government's identification of biotechnology as an industrially strategic area, as exemplified by the establishment of joint programs with SBF and other promotional activities for research, indicates that Swedish views may be changing. With Sweden's demonstrated ability to successfully exploit new technologies, Swedish companies may prove to be competitive in the future in the support and bioprocess sectors, as well as in pharmaceutical markets.

*Netherlands**

The Dutch Innovation Programme on Biotechnology, started in May 1981, is aimed at filling the gap between basic research and applied development work in Dutch universities. Funds supplied by the Government of the Netherlands will be used to develop research in areas where current national effort is insufficient. The program will be coordinated by the Dutch Programme Committee on Biotechnology. The program will last until the end of the 1980's, after which the existing research budgets of universities and institutes will furnish Dutch industry with the needed basic research.

The Programme Committee on Biotechnology (Programma Commissie Biotechnologie) requested $11.2 million (NLG30 million) to be spent on basic biotechnology research from 1983 until 1988. This amount is in addition to the $11.2 million to $15 million (NLG30 million to NLG40 million) which the Government spends yearly on research projects in the fields of molecular and classical genetics, microbiology, cell biology, biochemistry, enzymology, and bioprocess and bioreactor engineering.

In addition to the aforementioned sums, $2.6 million (NLG7 million) will be used by university/institute and industry groups in the Netherlands for multidisciplinary biotechnological research projects. According to the Programme Committee, these projects should be in the following areas:

- host vector systems for industrial and agricultural applications,
- somatic cell hybridization,
- second generation of biotechnological reactors and processes, and
- downstream processing.

Established Dutch companies that are setting up in-house R&D efforts in biotechnology include the following:

- Gist-Brocades N.V.
- Akzo-Pharma N.V.
- Unilever H.V.
- N.V. DSM
- Heineken N.V.
- Dupher N.V.

*This summary is based on a personal communication with Dr. Ir. R. R. Van der Meer, Secretary-Coordinator, Programme Committee on Biotechnology, Gravenhague, April 1983 (78).

Gist-Brocades N.V., one of the two companies in the world that supply more than 60 percent of the world's enzymes for industrial use, is devoting almost all of its $20.6 million (NLG55 million) budget for R&D to biotechnology. Intervet International, a subsidiary of Akzo-Pharma, was the first company to market vaccines produced through rDNA technology. Intervet's vaccines, introduced in March 1982, prevent scours (infectious diarrhea) in calves and piglets (77).

The Programme Committee on Biotechnology forecasts no personnel shortages. In fact, there is an excess of biochemical and microbiology students for the available Dutch jobs in industry. There are no tax policies aimed at encouraging biotechnology in Dutch industries. The Dutch have eased their regulatory guidelines for working with rDNA technologies to conform to U.S. guidelines.

*Australia**

The Australian Government supports a highly respected basic research system, especially in plant breeding and molecular biology, but it regards the development of biotechnological applications, including scale-up development and bioprocess engineering, as the responsibility of the private sector. Owing to a historic dearth of capital for high-risk ventures and a lack of trained personnel in applied technology, commercial biotechnology in Australia is not well developed. Australia's problems are exacerbated by the emigration of some of its top scientists to other countries where attractive jobs exist, although there is some indication that this situation might change in the future. The Australian Government is taking steps to implement incentives to help retain scientists and encourage venture capital formation to help foster promising applications of biotechnology.

Australian efforts are not expected to have an immediate impact on the markets discussed in this report. Nevertheless there is a strong possibility that, by using biotechnology to help solve local problems, Australia will find new markets for biotechnology products. Areas of biotechnology application in Australia being pursued include the following:

- plant improvement programs to develop agricultural species that are adapted for higher yields in Australian conditions;
- animal health products, particularly veterinary and nutritional products that improve the marketability of Australia's animals and animal products (especially wool) for export;*
- microbiological mineral recovery to reduce extraction and separation costs for certain minerals that Australia exports in great quantities;
- biomass conversion to ethanol and chemicals, based on Australia's large resources of grain crops and sugar cane residues.

Other applications of biotechnology in Australia include animal breed improvements through embryonic gene transfer, MAb-based diagnostic reagents for a number of human diseases, and, on a small scale, interferon and other rDNA projects to develop pharmaceutical products.

Government funding for biotechnology in Australia is administered through several Government agencies, including the Australian Science and Technology Council, which emphasizes expanded manufacturing and agricultural production with biotechnology, and the Commonwealth Scientific and Industrial Research Organization (CSIRO), the main research agency in Australia, which provided $4.6 million ($A4.5 million) for biotechnology research in 1981. Other sources are the National Health and Medical Research Council, which distributed $19.0 million ($A18.7 million) in research funds in 1980/81 (some of which benefited Australian biotechnology); the Energy Research, Development, and Demonstration Program which distributed $3.9 million ($A3.8 million) in 1980/81, partly for biotechnology project development; the Department of Health, which gave $1.88 million ($A1.85 million) to the Commonwealth Serum Laboratories to conduct research on interferon from 1980/81 to 1983/84; and the Australian Research Grants Scheme, which awarded $18.3 million ($A18 million) in 1982 to individual research scientists, some of whom use biotechnology in their work. In addition, financial assistance for general industry R&D projects is provided under the Australian Industrial Research and Development Incentives Scheme which in 1980/81, distributed $9.8 million ($A9.7 million) in commencement grants and $36.6 million (A$36.1 million) in project grants.

Other Australian incentives include tax policies that give minor benefits to firms undertaking R&D activities. Buildings used solely for scientific research purposes are depreciable over a 3-year period, compared to general industry's 40-year depreciation schedule. New equipment used for scientific research is also depreciable over a 3-year period, as opposed to a 5-year period for general industry equipment.

*This summary is based on information presented in "Biotechnology Research and Development, the Application of Recombinant DNA Techniques in Research and Opportunities for Biotechnology in Australia" (79) and "Genetic Engineering—Commercial Opportunities in Australia" (80).

*To date, most rDNA efforts have centered on cloning the genes that encode sheep wool keratin and other wool constituents in an effort to improve wool quality and lessen treatment costs of wool.

In addition to basic research funding and tax incentives to businesses, liaisons between Australian universities and industry are encouraged. In some cases, academic researchers have financial equity in biotechnology firms. In other cases, the relationship is through contracts with the universities. One example is an agreement under which Agrigenetics Research Association, Ltd. provided $2 million for biotechnology research at Australian National University.* Although Australia has the infrastructure to support healthy biotechnology development, lack of capital for high-technology firms retards growth. The Government and Australian banks make loans available to small businesses at low interest rates, but these loans are not generally available to high-risk enterprises such as NBFs. High-risk ventures are hampered by a smaller capital base in Australia than in the six major competitor countries. With increased Government interest in commercial biotechnology, more capital may become available. This increase in capital might in turn encourage increased efforts by existing NBFs to find applications for new biotechnology, as well as the formation of more NBFs. It should be noted, however, that Australia has some of the most restrictive drug licensing laws in the world, and these regulations may impede Australian applications of biotechnology to the pharmaceutical industry.

Biotechnology companies in Australia include the following:

- Biotechnology Australia Pty., Ltd. (a subsidiary of CRA Ltd.). Projects include animal feed additives and health care products, specialty chemicals, biomass conversion, and mineral extraction schemes.
- Austgen Pty., Ltd. (includes Biojet International [Australia] Pty. Ltd.). Projects include nutritional additives and waste treatment systems. Much of Biojet International's R&D is oriented towards products that can be exported.
- Australian Genetic Engineering Pty., Ltd. Projects focus on MAbs for diagnosis (a $5 million per year market for MAbs for diagnosis currently exists in Australia; a $15 million market is expected by 1986).
- Bioclone Australia Pty., Ltd. This firm markets MAbs made by the Garvan Institute and CSIRO on a worldwide basis. Its best known product is an antiprolactin MAb. Eleven additional MAb products have been or will soon be marketed.
- Australian Monoclonal Development Pty., Ltd. This company supplies MAbs primarily for research purposes.
- Fielder Gillespie, Ltd. This milling company funds MAb and biomass conversion projects.

In conclusion, Australia has the potential to develop and commercialize several applications of biotechnology successfully. A good Australian research base exists, but increased infusions of capital are necessary for new commercial startups if the potentials of biotechnology in Australia are to be realized. Australian Government policies have targeted the development of biotechnology, but the effect of the policies remains to be seen. Some Australian products, such as MAb diagnostic products, may prove to be competitive in world markets, but overall, major competition in the pharmaceutical and specialty chemical industries is unlikely.

Israel

For several reasons, Israel may be unique among developed nations in fostering a strong basic and applied research capability in biotechnology without having a large industrial infrastructure to exploit the successes of research endeavors. Israeli scientists train in U.S. institutions prominent in biotechnology and have become well-versed in molecular biology and immunology. Except for small brewery plants and one bioprocess plant (Gadot, which manufactures about 7,000 tons of citric acid per year), however, Israel does not have companies using old biotechnological techniques. Furthermore, Israel's tax and financial structures do not encourage financial risk-taking or the formation of new firms. Therefore, there are few industrial positions available for scientists trained in biotechnology.

As a result of the lack of depth in industrial expertise in Israel, Israeli universities, through their University-Connected Research and Development Organizations (UCRDOs),* turn to foreign companies that have the expertise to evaluate Israeli research and the resources needed to commercialize the results of this research. The number of joint ventures between Israeli UCRDOs and foreign firms is fairly large.

Noteworthy basic research in biotechnology is taking place at several Israeli universities and institutes, among them Hebrew University, Technion Institute at the Israel Institute of Technology, the Center for Biotechnology at Tel-Aviv University, and the Weizmann Institute of Science.

At Hebrew University, 12 departments in the medical school are conducting biotechnology-related research projects, ranging from cellular biology to can-

*The goal of this research is to incorporate the nitrogen-fixing genes of bacteria into plants adapted to Australian conditions.

*UCRDOs are set up by Israeli universities to promote commercialization and applied research. These organizations may enter into joint ventures or own equity in spinoff firms.

cer research. The agriculture department has initiated several projects and has received over $410,000 (more than DM1 million) from the Minerva Fund in the Federal Republic of Germany for cooperative projects on improving plant tissue culture techniques, rDNA and protoplast fusion in plant breeding, nitrogen fixation and control of soil-borne plant pathogens by microorganisms, and new uses of algae (84). Hebrew University's UCRDO Yissum signed a $5 million agreement on nitrogen-fixation research with Biotechnology General (Israel), Ltd. (82), an Israeli NBF, and another $3 million agreement has been signed with International Genetic Sciences Partnership (U.S.) (85).

Technion Institute, at the Israel Institute of Technology, is doing research on biotechnology instrumentation and on blood and blood plasma substitutes (82). Tel-Aviv University, Center for Biotechnology, conducts research on MAbs, enzyme systems of anaerobic bacteria, and immobilized enzymes (82).

The Weizmann Institute of Science is Israel's main center for rDNA research and is especially noted for its work with interferons. Additionally, research is proceeding with MAbs, antiviral vaccines, synthetic antigens, and new genetic forms of wheat, within seven departments.

Applied research using new biotechnology began in Israel in 1978. As of 1981, 17 universities, institutes, and venture firms in Israel had been identified as performing or funding applied research in biotechnology. Of the 17, perhaps 10 use the new technologies in their work (87). The four universities and institutes cited above, in addition to conducting basic research, also do applied work.

Israeli companies noted for their applied R&D include Biotechnology General, Interpharm, Inter-Yeda, Kibbutz Beit Ha'Emek. Biotechnology General develops research findings from the Weizmann Institute and Hebrew University. Its main emphasis is on foot-and-mouth disease vaccine, bovine growth hormone, biological disease control agents, and nitrogen fixation (82).

Interpharm, a subsidiary of Applied Research Systems (ARES), a Dutch multinational firm based in Geneva, sold over 1.15 million shares of common stock on the United States over-the-counter market in 1981. At the time of offering, Interpharm had a contract to supply ARES with hGH. Further, Interpharm may soon market human fibroblast interferon for labial and genital herpes, depending on results of clinical trials, produced by its R&D susidiary Inter-Yeda (83). Other projects with commercial possibilities include an immunoassay separation technology, extraction technologies for follicle-stimulating hormone and luteinizing hormone, and research on hybridomas (81).

Inter-Yeda, a joint venture firm owned 60 percent by Interpharm and 40 percent by Yeda, will concentrate on four areas: production of interferon using rDNA techniques, identification and isolation of interferon-associated proteins, artificial production of interferon, and MAb research (82). Inter-Yeda is shipping human fibroblast interferon to the Serono Corporation in the United States (81).

Kibbutz Beit Ha'Emek hired researchers in order to use advanced tissue culture techniques to "develop plant varieties resistant to herbicides, diseases and other environmental hazards" (86). The kibbutz claims a $1 million income from "tissue-culture-derived products," of which 65 percent are exported, mainly to the Netherlands and the Federal Republic of Germany.

At present, there is no central planning of any R&D by the Israeli Government, and thus the Government has no national targeting policy for biotechnology. Each Ministry within the Israeli Government determines and funds the R&D it deems necessary. The major source of Government funds for biotechnology R&D is the Office of the Chief Scientist in the Ministry of Industry and Trade. The Israeli Ministry of Industry and Trade plans to invest $25 million in biotechnology R&D over the next 5 years (85).

Canada

Canada's economy relies greatly on its natural resources such as agriculture, livestock, mining, and forestry. In the past 3 years, Canada's Federal and Provincial governments, as well as a few Canadian companies, have worked to incorporate biotechnology specifically as it relates to the development and exploitation of the country's natural resources. A focus on improving domestic capabilities in the necessary technologies and avoiding dependence on imported products and processes, however, represents an attempt by both the public and private sectors in Canada to compete in selected world markets. Whether Canada becomes internationally competitive in areas of biotechnology such as agricultural plant strain development, mineral leaching, or lignocellulose conversion, for example, will depend to a large extent on the rapidity with which it can exploit national expertise before other countries with extensive R&D programs in these fields.

Interest in the commercial development of biotechnology has evolved slowly in Canada. In June 1980, the Canadian Federal Government commissioned a Task Force on Biotechnology to evaluate the opportunities available to Canada in this area. This task force, in its report to the Minister of State for Science and Technology, identified specific weaknesses in

Canada's research base, Federal Government programs, regulations, and industry, and made specific recommendations to help correct these deficiencies (96). The Canadian Federal Government took more than 2 years to act on these recommendations. In early May 1983, it announced two separate yet complementary initiatives to help promote biotechnology in Canada.

First, as part of a broader plan to support the development of emerging technologies in general, the Ministry of State for Science and Technology designated biotechnology as one of the priority technologies targeted for development (94). The plan to support emerging technologies consisted of five basic components. The first was identification of strategic areas of development most important to Canada. Adopting the recommendations of the Task Force on Biotechnology, the Federal Government will concentrate efforts on research in nitrogen fixation, plant strain development, cellulose utilization, mineral leaching and metal recovery, and animal and human health care products. The second component was creation of research networks. Individual Federal departments will establish and promote networks of research projects in biotechnology and researchers in areas relevant to their mandates. The third component of the plan was establishment of a cost-sharing program. Under the program, and with $7.7 million per year, the Federal Government will match funds invested by industry in universities or Provincial research organizations. The funds could be used for purposes such as specific biotechnology research projects, the replacement of equipment, and the establishment of research chairs. The fourth component of the plan was strengthening of overall Federal research capacity in biological sciences ($3.1 million). The funds will be used to establish and promote networks, to promote interactions between Federal departments and universities and industry, and to strengthen existing programs within Government research organizations. Finally, the fifth component of the plan was the creation of advisory and coordinating committees. A National Biotechnology Advisory Committee, chaired by a member from the private sector with 25 representatives from industry, academia, and Federal Government departments, will monitor the course of the biotechnology policy and advise the Minister of State for Science and Technology on the program's progress. An Interdepartmental Committee on Biotechnology, which functions at the Deputy Ministry level, will control the allocation of funds to departments participating in the Federal plan and will deal with a wide range of issues such as patenting and regulation in biotechnology (92).

Parallel to and coordinated with the five-pronged program outlined above, the Ministry of State for Science and Technology has charged the National Research Council (NRC)* with responsibility for the promotion of centers of expertise in biotechnology. Under this program, NRC will undertake three separate projects:

- construction in Montreal of a $61 million biotechnology institute which will probably conduct generic applied research on bioprocessing and enzyme technology (95);
- refurbishment and reorientation of the Prairie Regional Laboratory in Saskatoon (95); and
- strengthening of the NRC Biological Sciences Division in Ottawa.

In addition to the Canadian Federal Government, many Canadian Provinces have begun to promote the development of biotechnology. Quebec, Ontario, Saskatchewan, Alberta, and British Columbia have shown an increasing interest in the commercial opportunities offered by biotechnology. Quebec, for example, has developed an explicit policy which gives high priority to biotechnology. Sasketchewan is also in the process of developing such a policy. Quebec and Ontario have invested in commercial ventures in biotechnology (Bio-Endo and Allelix, respectively).

Several problems may limit the commercial development of biotechnology in Canada. First, there is a generalized shortage of personnel trained in the relevant technologies (only 200 to 300 Ph. D.s), and many of those who do graduate with degrees, for example, in molecular biology or biochemical engineering are lured to the United States to work in the private sector (97). Furthermore, very few private firms have directed their efforts to developing an expertise in new biotechnology; most rely instead on more traditional techniques in research, development, and production.**Canada also has very little experience in joint university, industry, and Government cooperation (93), though current Federal initiatives are addressing this problem.

*NRC is an independent Crown Corp. with considerable influence on Federal science and technology policy. Though not a Government Department, the Council is funded primarily by the Federal Government. Because of the scientific expertise NRC possesses, it will administer $120 million for the technology support program (of which biotechnology forms a part). NRC currently employs a total of over 600 persons (including support staff) in biotechnology alone when their program is in full operation.

**Allelix Corp. appears to be one of the few companies devoted entirely to developing new biotechnology. Started by the Provincial Government of Ontario, the Canadian Development Corporation, and John Labatt Ltd. with a total initial capitalization of $105 million (89), this company is currently concentrating on the development of new plant strains, using both cell-fusion and rDNA techniques (88). For further information on private sector activities in biotechnology in Canada, see "Biotechnology Research and Development in Canada" (90).

The current Canadian patent law requires compulsory licensing of all human therapeutic drugs developed by one company to other general generic pharmaceutical companies (92). As a result of the implementation of this law in 1969, all multinational pharmaceutical companies in Canada closed their research operations (91). There is no equivalent in Canada to the U.S. Plant Variety Protection Act, even though certain mechanisms do exist in Canada to protect the ownership of new plant strains (88).

Canadian tax law favors the development of biotechnology. One provision allows for a 100-percent, first year deduction on all current and capital expenditures for R&D. Additionally, corporations in Canada may deduct a further 50 percent for incremental R&D expenditures (calculated from a moving 3-year average). R&D expenditures are also eligible for a 10 percent investment tax credit (small businesses and investments in some provinces receive a higher percentage rate) up to a limit of $12,200 ($C15,000). R&D limited partnerships are also permitted in Canada (94).

U.S.S.R.

It is extremely difficult to obtain information on development plans for biotechnology in the U.S.S.R. Although it is known that biotechnology R&D is carried out in the Soviet Union, information about the extent of these activities is unavailable to the general public. The following summary formed part of the report on competitive and technology transfer aspects of biotechnology by a working group for the White House Office of Science and Technology Policy (98):

> The Soviet Union is actively supporting biotechnology R&D and has established an Interagency Technical Council to organize and stimulate its progress across a broad spectrum of disciplines. There is no information regarding the budget for biotechnology R&D. However, the rate of growth of the Soviet research establishment mirrors that which occurred in the United States 3 to 5 years ago. Their stated interests are directed toward domestic concerns such as the development of medical/pharmaceutical preparations and agriculutural applications. Soviet establishment of U.S. patents covering an amino acid producing organism and the enabling technology suggests an interest in international commercial competition as well.
>
> Although Soviet research is often hampered by difficulties in obtaining equipment and reagents, the Soviet system offers one major advantage over the free enterprise system of the United States; i.e., R&D is supported from inception through production and distribution. The financing gap between completion of basic research which has potential for application, and actual development, the costs of which in the United States must be borne by industry, receives full support of the Government in the Soviet Union. The advantages of this system are:
>
> - risks are taken by the Government;
> - costs of development are borne by the Government;
> - the Government's financial base can support an extended period of development; and
> - the Government can support long-term price control to facilitate international market entry.

It is too early to project potential Soviet success in the international biotechnology market. Much depends on successful completion of research programs now underway, and, most importantly, continued support by the Soviet Government.

Brazil*

Brazil is the only developing country that has a formal government policy for biotechnology. This policy was developed because relations among the university, industry, and government sectors in Brazil tend to be adversarial, inhibiting communication among the sectors. Brazilian industry tends not to fund risky projects, concentrating its efforts instead on already existing products and processes. Historically, Brazilian industry has relied on the purchase of foreign technology and on joint ventures with foreign companies. Brazil's universities have little contact with either industry or the Government and conduct little multidisciplinary research. These historical relationships suggest that the government (both Federal and State) will have to play a strong role in Brazil to develop the R&D infrastructure necessary to develop biotechnology and to aid the commercialization of biotechnological applications.

In general, the major weaknesses for biotechnology development in Brazil are as follows:

- Brazil's human resource base trained in advanced biotechnology techniques is limited. In 1982, six qualified and experienced researchers in the field of rDNA and MAbs were identified.
- Brazil's national industrial sector is fairly underdeveloped and has little in-house R&D capability and little inclination to pursue high-risk, new product operation.
- There is uncertainty about the interpretation of Brazilian patent statutes with respect to biotechnological products and processes.
- Import and bureaucratic delays make it difficult for both public and private laboratories to obtain the necessary R&D equipment and supplies not available on the Brazilian market.

*This summary is based on "An Analysis of Current and Projected Biotechnological Activity in Brazil," a contract report prepared for the Office of Technology Assessment, U.S. Congress, by Robert Goodrich, July 21, 1982.

- Adequate analyses of market needs and opportunities are lacking, leading to inadequate orientation of research activities.

Three major Federal agencies in Brazil are involved in the funding of biotechnology: 1) the National Research Council, now known as the Council for the Development of Science and Technology (CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico); 2) the National Funding Agency for Studies and Projects (FINEP, Financiadora de Projetos); and 3) the Secretariat of Industrial Technology of the Ministry of Industry and Commerce. CNPq will devote about 5 percent of its annual budget to biotechnology or $1.12 million (BCr200 million) during 1982-83. FINEP will spend approximately $1.5 million to $2 million (BCr270 million to BCr360 million) during 2 years to aid the commercializing of R&D in biotechnolgy by supporting economic analyses, commercialization ventures, and marketing studies. The Secretariat of Industrial Technology of the Ministry of Industry and Commerce is responsible for the National Alcohol Program and is already funding extensive R&D in bioprocesses and enzymology.

The Brazilian Federal Government plans to fund the development of two biotechnology research centers. The first, in Sao Paulo, will be an educational facility for multidisciplinary training. Its research program will focus on bioprocesses and enzyme research. The second center, the Biotechnology Center in Porto Alegre, will receive $0.97 million (BCr175 million) in funding and will concentrate on microbiology and applied genetics with little or no concern for product development. It will have an initial staff of four Ph. D. and four M.S. researchers and trainees.

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Appendix C

A Comparison of the U.S. Semiconductor Industry and Biotechnology*

Introduction

A parallel is sometimes drawn between the early development of the U.S. semiconductor industry and biotechnology. There are similarities. Semiconductors and biotechnology each showed promise for major advances. Whereas semiconductors immediately showed promise for major advances in electronics, biotechnology shows promise for major advances in many industries, from agriculture to oil recovery. Furthermore, developments in semiconductors and in biotechnology have both been characterized by the pioneering efforts of small startup companies, which have played a major role in technological innovation. Another reason for drawing a parallel between the U.S. semiconductor industry and firms using biotechnology is probably the hope that the development of biotechnology will be accompanied by the same kind of intense competition, continuing innovation, wide commercial diffusion, and spectacular financial returns that characterized the U.S. semiconductor industry.

As will be seen in this appendix, the early history of the U.S. semiconductor industry and the history of biotechnology to date are in fact characterized more by differences than by similarities. Nevertheless, studying the history of the U.S. semiconductor industry may aid the healthy development of biotechnology in the United States. Some of the actions that fostered the development of the U.S. semiconductor industry could be applied to the further development of biotechnology, thereby increasing its similarity to the semiconductor industry. The clear success of the U.S. semiconductor industry suggests that such actions deserve consideration for their applicability to biotechnology, although biotechnology is not an industry, but a set of technologies that can potentially be used by many industries.

The purpose of this appendix is to clarify the similarities and differences between the early history of the U.S. semiconductor industry and the development of biotechnology, to identify factors contributing to the successful development of the semiconductor industry, and to consider the relevance of these factors to the further development of biotechnology.

*The primary source for this comparison was a contract report prepared for OTA by Michael Borrus and James Millstein (2).

Semiconductor devices: terminology and evolution

Semiconductors are materials such as silicon and germanium with electrical conductivities intermediate between good conductors, such as copper, and insulators, such as glass. By appropriate manipulations, these materials can be made into *semiconductor devices* that have special properties. Such devices include diodes and transistors.

One of the most important properties of a *transistor* is its ability to amplify an electrical current flowing through it. A transistor is a compact, reliable replacement for the vacuum tube, which was the foundation of the early electronics industry. While transistors substantially improved the reliability and performance of electronic devices such as computers, they were simply components in electrical circuits connected by wires to other components.

Integrated circuits were the next major advance in semiconductor technology. Integrated circuits are "chips" or single components that perform functions that had previously required groups of components wired together.

The next step in semiconductor technology involved increasing the density of circuit elements on each chip. The integrated circuit era began in the early 1960's. By the end of the decade, medium-scale integration (MSI) had been achieved (10 to 100 digital logic gates on one chip). Large-scale integration (LSI) (100 to 1,000 gates) was achieved in the mid-1970's, and the industry is now working on very large-scale integration (VLSI) (circuit complexity exceeding 1,000 gates) (9).

Advances in semiconductor technology have resulted in extraordinary gains in reliability and performance, with simultaneous reductions in component size and cost. In the 1950's, for example, the cost of computer memory capacity was about $1 per bit, but by 1981, a bit could be purchased for only $0.0001 (9).

The U.S. *semiconductor industry* is comprised of the companies that manufacture semiconductor devices such as transistors and integrated circuits. Two types of firms can be differentiated: 1) firms that develop and manufacture semiconductor devices for sale to other firms that use them to manufacture computers and other end products; and 2) firms that develop and manufacture semiconductor devices for in-house use

in the manufacture of final products. Both types of firms have been important to the development of the industry.

The following material describes the early development of the U.S. semiconductor industry and compares it to the short history of biotechnology. For the semiconductor industry, the period covered is from 1947 (the invention of the transistor) to the early 1960's. For biotechnology, which began in the mid-1970's, the period covered is from the mid-1970's to the present. In part because of the different time periods in which the semiconductor industry and biotechnology initially developed, an immediate difference between the two can be identified. The early development of the U.S. semiconductor industry occurred primarily in the context of the U.S. domestic market, whereas biotechnology is evolving in a world marketplace. International competition, which is an important factor in the development of biotechnology, is a far more important factor in the semiconductor industry now than it was in the early history of the industry. Both differences and similarities between the development of the U.S. semiconductor industry and biotechnology are indicated in the material that follows.

Development of the U.S. semiconductor industry

Two major influences in the development of the U.S. semiconductor industry were Bell Telephone Laboratories (Bell Labs) and the U.S. Government. These two influences are intimately related, because the Federal Government played a major role in shaping Bell Labs' contribution to the preeminence of the United States in high-technology electronic products including semiconductors, lasers, and computers. These industries have been built, in large measure, on the results of research undertaken at Bell Labs.

The role of Bell Labs in the development of the U.S. semiconductor industry is briefly described below. The multifaceted role of the Federal Government is discussed in the section that follows.

THE ROLE OF BELL TELEPHONE LABORATORIES

As part of the American Telephone & Telegraph Co. (AT&T), Bell Telephone Laboratories does fundamental and applied research in many areas to benefit its parent company. Bell Labs also serves a broader constituency. During World War II, for example, Bell Labs undertook about 2,000 research and development (R&D) projects for the U.S. Army, U.S. Navy, and National Defense Research Council (11). Federal funding of research at Bell Labs and AT&T's manufacturing arm Western Electric from 1949 to 1959 amounted to about $609 million—or about 48 percent of all AT&T research (17). The quality of research at Bell Labs and the level of funding available from corporate and Government sources attracted the most competent electronics scientists and engineers to work there.

In the late 1930's, the electronics industry depended on the vacuum tube for amplification of electric currents. The advantages of a smaller, more reliable device that would generate less heat were obvious, however, and because of military and aerospace needs, there was strong motivation to invent an alternative. Also clear was the potential importance of the transistor to commercial communications and computer applications. It is not surprising, given Bell Labs' commanding position in fundamental and applied electronics research, that the first new device that could compete with the vacuum tube in the marketplace, i.e., the transistor, was invented in 1947 at Bell Labs. This invention gave Bell Labs a lead in what would ultimately become the semiconductor industry.

Semiconductor R&D by Bell Labs was supported with corporate funds from AT&T. Between 1946 and 1964, Bell Labs' annual expenditures on semiconductor R&D rose from less than $1 million to about $22 million. In 1959, the funding of semiconductor R&D at Bell Labs represented about 30 percent of all privately funded semiconductor R&D in the United States (14).

The fact that Bell Labs was part of AT&T also contributed to Bell Labs' leadership in the semiconductor industry (2). The research done at Bell Labs was linked to real-world problems through AT&T's manufacturing arm, Western Electric. Western Electric involved Bell Labs in the solution of engineering problems associated with conversion from vacuum tube to semiconductor technology in communications systems. Western Electric also involved Bell Labs in research to improve *production* of semiconductor devices. In addition to conducting research that led to new devices, therefore, Bell Labs did research that led to process innovations. It was these process innovations that dramatically decreased the cost of semiconductor devices (2).

Federal and corporate investment in Bell Labs produced significant return. Between 1947 (invention of the transistor) and 1959 (invention of the integrated circuit at Texas Instruments and Fairchild), Bell Labs obtained 339, or more than 25 percent, of the patents related to the development of semiconductors. During this period, Bell Labs also was responsible for a disproportionate share of the most important product and process innovations (14).

In summary, market pull for an alternative to the vacuum tube favored the development of the semicon-

ductor industry. The key invention, the transistor, arose from fundamental R&D in an industrial laboratory. That laboratory was an arm of a major corporation that also would be a significant user of the new technology.

The history of biotechnology is quite different from the early history of the U.S. semiconductor industry. Biotechnology arose from basic research in universities—research supported by Federal funds for basic biomedical research. Probably most significant were Federal funds for research associated with the "war on cancer." Because of the "war on cancer," a great deal of research was done on tumors and tumor viruses. One of the simplest viruses, SV40, causes tumors in hamsters and mice. Researchers went to great effort to locate the genes in SV40 that enabled it to cause tumors. A need to improve on tedious genetic selection procedures for mapping genes led to the identification and use of restriction enzymes that cut DNA in specific locations, and thus enabled physical mapping of genes. Restriction enzymes also produce the "sticky ends" that are fundamental to recombinant DNA (rDNA) experiments. Physical mapping of an entire genome (an organism's complete set of genes) using restriction enzymes was first accomplished with SV40. And it was a proposed rDNA experiment using SV40 that gave rise to the Asilomar meeting that eventually led to the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules.*

Other researchers concentrated on myelomas (neoplastic growth of certain white blood cells). Thus, cancer research probably also contributed to the discovery of hybridomas** and the monoclonal antibodies they make possible.

In summary, cancer research played a significant role in the history of biotechnology and is another example of how fundamental research may produce unexpected results. In the development of biotechnology, "science push," rather than the "market pull" that gave impetus to the U.S. semiconductor industry, was particularly important.

THE ROLE OF THE U.S. GOVERNMENT

The actions of the U.S. Government that influenced the development of the U.S. semiconductor industry were many and diverse. Undoubtedly, not all the effects of the Federal Government's actions were intended or anticipated. With the benefit of hindsight, however, it is apparent that these actions helped to produce a dynamic, healthy U.S. semiconductor industry. Similar actions by the Federal Government could encourage the development of companies in other high-technology fields such as biotechnology.

Federal Funding of Semiconductor Research and Development To Encourage Competition.—In the late 1940's, the U.S. Department of Defense (DOD) wanted to miniaturize and increase the reliability of electronic devices so that a new generation of defensive weapons could be developed. Defensive missile systems, in particular, required these advances. To ensure achievement of its objectives, DOD distributed R&D funds to many research houses, including Bell Labs. The provision of funding to many research houses encouraged the competitive development of semiconductor technology throughout the U.S. electronics industry. It also had the effect of leveraging private funding of semiconductor R&D (2).

The same forces driving military interests—miniaturization and reliability—also applied to the U.S. aerospace program. In addition to DOD, therefore, the National Aeronautics and Space Administration (NASA) also became a major source of funding for semiconductor R&D.

It is important to note that the early development of semiconductor technology was dominated by the interests of the U.S. military and NASA (2). Civilian applications followed. This early predominance of military interests driving the development of semiconductors contrasts with the development of biotechnology, for although there are military applications of biotechnology, civilian commercial interests have driven its development.

Federal Funding of Demonstration Projects, Production, and Consumption of Semiconductor Devices.—Demonstration projects using semiconductor technology were financed by the Federal Government. The U.S. Air Force, for example, funded a demonstration in which a small digital computer using integrated circuits was built by Texas Instruments (1). Demonstration projects such as this convincingly demonstrated to both military and civilian users the feasibility of using integrated circuits in electronic systems (2).

In addition to funding demonstration projects, the Federal Government funded the development of semiconductor production capability and provided a market for semiconductor products under industrial preparedness contracts in 1952-53 and 1956-57. In 1952-53, $11 million of DOD funds were used to build pilot transistor production lines at five sites operated by Western Electric, General Electric (GE), Raytheon, RCA, and Sylvania (10). In 1956, DOD provided major assistance to production technology with $40 million

*These U.S. guidelines for rDNA research are discussed in *Chapter 15: Health, Safety, and Environmental Regulation.*

**Hybridomas are made by fusing an antibody-producing spleen cell with a myeloma cell.

in transistor production contracts to 12 firms. Because early production was often faulty and about 90 percent of the devices produced could not meet Federal specifications, the 12 firms had to build production facilities potentially capable of manufacturing 10 to 12 times the number of devices the Government wanted, thus assuring the Government of the number of devices it needed (19). As processes improved, more and more usable devices came off each assembly line, and the search for new commercial markets was stimulated by the need to absorb increases in production capacity.

The actions of the Federal Government just outlined helped to demonstrate the value of semiconductor technology to users other than the Federal Government, greatly reduced the risk of developing and producing semiconductor devices, and helped to develop industry capacity to produce semiconductor devices at levels that would meet the needs of new users as well as those of the Federal Government.

The Federal Government could support in biotechnology, just as it did in the semiconductor industry, the development of process and production technology. These are the very areas in biotechnology where needs for funds and for innovation are high. It is also in process and production capability and capacity that the United States is least competitive with Japan, its major competitor in biotechnology (2). One area of biotechnology that might be stimulated by a bioprocess production and demonstration project is the production of commodity chemicals. Large-scale bioprocess facilities, and hence large financial investments, will be necessary for U.S. firms using biotechnology to successfully enter the commodity chemical market. Cetus Corp. made an attempt to enter this market with its fructose-alkene oxide process using Standard Oil of California (SOCal) as financial backer. The attempt was frustrated when SOCal decided to terminate its backing (2). Federal funds could help new biotechnology firms (NBFs)* enter commercial markets requiring large-scale production. Alternately, rather than funding specific projects at particular firms, the Federal Government could support R&D in generic technology underlying bioprocessing. Regardless of the particular form of support, the Government should ensure that new knowledge of bioprocess technology gained with the assistance of Federal funding is made available to other potential users.

Federal Government support of field and clinical trials necessary for approval of some products of biotechnology by the U.S. Department of Agriculture (USDA) and the Food and Drug Administration (FDA) would be somewhat analogous to the federally funded semiconductor demonstration projects. Such trials are very expensive and beyond the financial resources of many small firms.

The 1956 Consent Decree.—In the development of the semiconductor industry, the Federal Government provided more than dollars, useful as these were to fund R&D, build production lines, demonstrate their products, and provide a first market. Substantial Federal dollar investments were accompanied by less direct policy decisions that helped shape a highly competitive U.S. semiconductor industry. The 1956 consent decree is a case in point.

In 1949, the U.S. Department of Justice initiated an antitrust suit against AT&T. Resolved in 1956, the consent decree (20) required AT&T's manufacturing arm Western Electric to license existing Western Electric patents to U.S. firms without royalty and to establish reasonable rates for licenses under future patents. AT&T was permitted to retain its vertically integrated structure but was prohibited from entering new product markets; in other words, AT&T was restricted to its existing markets of basic common carrier communications and Government defense and aerospace. Thus, AT&T was prohibited from using the results of research at Bell Labs to enter additional commercial markets that semiconductor technology promised to advance, such as commercial electronic computers.

Given the consent decree, one option for AT&T would have been to redirect Bell Labs' research so that it would not benefit fields AT&T could not enter. However, semiconductor R&D directed to enhancing AT&T's major interests in the telecommunications, military, and aerospace markets was not separable from R&D applicable to areas such as commercial computers from which AT&T was prohibited. In addition, Bell Labs had a history of open communication regarding its research. As a result, AT&T conformed not only to the letter but also to the spirit of the 1956 decree. The effect was to transform Bell Labs, for a time, into a sort of national laboratory for semiconductor R&D.

Continuing its open practices begun prior to the consent decree, Bell Labs actively contributed to the diffusion of the technology that it helped develop. Symposia to educate Government users and small and large firm licensees were begun in 1951, and a liberal license policy was begun in 1952. Also important, Bell Labs and Western Electric personnel moved freely to new employment in firms exploiting the results of Bell Labs R&D without fear of suit for theft of trade secrets (18). Such movements transferred know-how developed at Bell Labs and Western Electric to other firms.

*NBFs, as defined in *Chapter 4: Firms Commercializing Biotechnology*, are new, generally small firms that have been formed specifically to capitalize on new biotechnology.

Liberal licensing, the educational activities of AT&T, and personnel mobility encouraged by Federal antitrust activity resulted in wide diffusion of semiconductor technology. Diffusion was facilitated by the fact that data acquired under DOD R&D contracts were subject to unlimited use by the Government, including their supply to other contractors working in related areas. Various DOD offices and agencies, and DOD-funded centers at universities, served as information centers for research findings. The U.S. Department of Commerce (6), National Science Foundation, National Bureau of Standards (4), and NASA (13) served as clearinghouses for semiconductor information and transferred knowledge derived from military contracts to civilian users. Government agencies held symposia and colloquia to inform industrial contractors of the results of federally funded research and of future military and space requirements. The result was an acceleration in the pace, and hence the competitiveness, of the U.S. semiconductor industry, in civilian as well as military markets. In 1961, the Army Signal Corps estimated that defense R&D had made possible many civilian applicatons of semiconductor technology in a period perhaps 75 percent shorter than that which would have occurred without Government support (17).

In biotechnology, there is no institutional equivalent to Bell Labs, which served as a national resource for semiconductor research, development, education, and personnel. Furthermore, the scope and magnitude of Federal actions facilitating diffusion of knowledge and know-how in the area of semiconductors have no parallel in biotechnology at present. Finally, the diffusion of technology by personnel mobility that occurred in the semiconductor industry because of the commanding position of Bell Labs, which was restrained by the 1956 consent decree, is unlikely to occur to the same degree in biotechnology, where knowledge is spread among many competing firms.

Federal Loan and Tax Policies.—In the 1950's and 1960's, the U.S. Government also encouraged the development of the U.S. semiconductor industry through Federal loan guarantees and tax policies. Although not developed specifically for the semiconductor industry, these general policies made funds available for operations, plant investment, and new equipment.

The Defense Procurement Act of 1950 established the V-loan program and was a major source of Federal loan guarantees to defense contractors from 1950 to 1958. This act provided Federal loan guarantees that obligated the Federal agency guaranteeing the loan to purchase a stated percentage of the loan if the borrower defaulted. Thus, the Federal agency shared any potential losses up to the amount of the guaranteed percentage (16). Such guaranteed loans accomplished several things:

- They encouraged private investors by decreasing their risk of loss.
- Because they were granted at lower than prevailing interest rates, they decreased the cost of capital.
- They served as a system of revolving credit. Guarantees were not tied to particular loans but instead were guarantees against loss of a particular level of debt. As periodic repayments reduced outstanding debt, therefore, additional loans could be taken out as long as repayments kept debt within the face amount of the authorization. Thus, authorizations of only $2.9 billion allowed loans totaling about $11.6 billion to be made to defense contractors.
- They returned a net profit to the Federal Government of about $24.5 million (15). This profit resulted because the Federal guaranteeing agent was entitled to a portion of the interest paid on the loan.

Most of the funding leveraged by the V-loan program was used for working capital rather than facilities. Other Government financial aids produced additional working capital. Progress payments, advance payments, and direct loans were made to companies involved in defense production (16).

A particularly important financial instrument encouraging investment in defense production capability was a program permitting accelerated depreciation. In the 1950's, the Office of Defense Mobilization awarded Certificates of Necessity that provided a 5-year writeoff (compared to the usual 20- to 25-year amortization schedule) of the percentage of the cost of certified production facilities that could be attributed to major defense production needs. From November 1950 through April 1957, 21,925 Certificates of Necessity permitted the accelerated writeoff of almost $23 billion on facilities costing $39.2 billion (15). Although these figures include more than semiconductor firms and data do not permit isolation of their share, semiconductor firms definitely received Certificates of Necessity and their writeoff was surely substantial (5).

The growth of the U.S. semiconductor industry was further spurred in 1962 by two changes in general U.S. tax policy (2). One change was that the Revenue Act of 1962 permitted all manufacturing industries an investment tax credit of up to 7 percent of qualified investment in machinery and equipment. This investment tax credit stimulated investment in semiconductor production capacity just when integrated circuit

procurement began to expand. The second change was adoption by the U.S. Treasury Department in 1962 of new regulations that shortened depreciation guidelines by 15 to 20 percent.

Clearly, Federal tax and loan policies can stimulate substantially the growth of emerging industries. Consideration might be given to whether current tax and loan policies are stimulating development of biotechnology adequately or whether additional Government financial instruments are needed.

Defense Laboratory Research.—During the 1950's and early 1960's, each branch of DOD developed intramural programs for semiconductor R&D. Although these defense facilities produced relatively few significant semiconductor discoveries (with some major exceptions) (21), they nonetheless played a major role in the development of the semiconductor industry. In addition to serving as centers for information and technical liaison, these laboratories tested theories and ideas considered too speculative by private industry. Those that turned out to be practical were then developed by industry (7). Furthermore, personnel movements from defense establishments to private industry served to transfer knowledge, sometimes at critical points in the development of the U.S. semiconductor industry (23). Especially important, defense laboratory researchers provided the Federal Government with an independent view of the state-of-the-art of semiconductor technology and the capacity to verify, assist, and at times lead industrial efforts.

In terms of level of expertise and dynamic interaction between Federal agencies and industry, the closest analogs in biotechnology are NIH and FDA. Because it issues the U.S. guidelines for rDNA research, however, NIH is a quasi-regulator of biotechnology. This role puts NIH in a conflict of interest position vis-a-vis both its substantial funding of basic research in biotechnology and any additional role it might assume in commercialization. NIH, which has been forced to be aware of developments in the commercialization of biotechnology by the guidelines, however, nevertheless has a major potential role in biotechnology transfer. The degree to which and how best to involve NIH in commercial development of biotechnology deserve consideration.

FDA has developed expertise in biotechnology because of its regulatory function. Its major contribution to the development of biotechnology to date has been in providing a favorable regulatory climate for new products. However, the present regulatory climate is highly subject to administration views on industry regulation. Whether U.S. regulatory agencies should be better insulated from the effects of changes in administrations so that biotechnology evolves in a relatively stable environment deserves thought. In any case, an increased role for FDA in fostering the development of biotechnology is probably prohibited by conflict of interest with its significant regulatory responsibilties.

Other relevant U.S. Government agencies, such as DOD, the Environmental Protection Agency (EPA), the National Bureau of Standards, the National Science Foundation, the Occupational Safety and Health Administration (OSHA), and USDA have so far been less involved in the development of biotechnology than either NIH or FDA.

In sum, the substantial role that DOD and NASA played in encouraging the early development of the U.S. semiconductor industry is a role that is not being played by the U.S. Government in the commercial development of biotechnology.

THE ROLE OF UNIVERSITIES

During World War II, the successful funding of defense developments at universities gave rise to a conscious national policy of U.S. Government funding of university basic research. Although Federal funds for joint research at universities and industrial laboratories in solid-state physics and materials helped provide the basis for the U.S. semiconductor industry (22), the key discovery leading to the transistor was made in an *industrial* laboratory.

In the early 1950's, university electrical engineering departments lagged behind industry in the area of semiconductors by a considerable margin.* Federal funds were provided to universities to help reduce this gap and build the university expertise and training capacity that would be needed to support the expansion of the U.S. semiconductor industry.

These Government expenditures were fruitful. By roughly 1960, the major research universities in the United States had highly trained electronics personnel, creative basic research programs, and faculty members who served as expert consultants to industry.

Furthermore, the U.S. semiconductor industry became concentrated geographically around the major university recipients of Federal dollars, in particular, in Boston and San Francisco. The geographic proximity of semiconductor firms and these universities fostered productive interchange and insured the continued buildup of university expertise.

Increasingly cooperative ties between U.S. universities and the semiconductor industry resulted in the part-time employment by the industry of significant numbers of students. Many university faculty mem-

*Massachusetts Institute of Technology's Lincoln Laboratories is an exception.

bers served as directors of semiconductor corporations, and some even held positions such as board chairman and part-time company president (2). Some faculty members became millionaires through equity participation in the companies with which they were associated (2). In comparison with the protests that have been raised in reaction to similar arrangements in biotechnology, public protests against these arrangements were small.

In sum, in the early history of the U.S. semiconductor industry, few innovations emerged from federally funded university research. The universities used Federal dollars to bring their expertise up to a level commensurate with industry's and to become geographic foci for the development of the new semiconductor industry. In the case of biotechnology, by contrast, innovations have emerged directly from university research. New semiconductor firms tended to locate near major university research institutions. This colocation occurred fairly gradually as Federal dollars flowed to universities and helped build their expertise. In the case of biotechnology, the colocation of new firms and universities occurred immediately, because the universities were the site of biotechnology expertise (2).

The lack of public and congressional concern over equity ownership of semiconductor companies by university professors is in stark contrast to the reaction to similar arrangements in biotechnology. Some of the factors that may account for the differences include the following:

- The locations from which biotechnology and semiconductor technology emerged and the source of their expertise, coupled with patterns of Federal spending, are different. Semiconductor R&D was dominated by industry, especially in its early years, and Federal funds went to industry for the development of the technology. Federal funds to the universities were used very differently from Federal funds to industry, namely, to build the scientific infrastructure necessary to support the new industry. Thus, the roles played by universities and industry and the use of Federal funds in the two sectors were more distinct in the early years of the semiconductor industry than they have been in biotechnology.
- Many recent advances in research in biotechnology immediately suggest commercial products. Although there are many problems to be solved between, for example, cloning the gene for human insulin and market success, the potential marketability of the product of the research is obvious immediately. In addition, the DNA organism that makes insulin, is, in a sense, itself the product. A transistor, on the other hand, is of no value unless it is used with other electronic components to make an end product such as a missile guidance system. Thus, in biotechnology, the contributions of the universities and industry are less distinct than they were in the semiconductor industry.
- The semiconductor industry had obvious contributions to make to aerospace and defense. Defense and aerospace are seen as national objectives and national commitment to them tends to be stronger and more focused than commitment to other sectors of the economy, where biotechnology is making its first contributions. Actions that would be protested otherwise may be tolerated when they relate to meeting defense and aerospace needs.

Structure of the U.S. semiconductor industry

Industries develop unique structures in response to their own characteristics and the effects of external forces acting upon them. The forces that have been described in this appendix shaped the U.S. semiconductor industry so that its particular structure evolved from a myriad of possible structures, much as biological systems evolve in response to pressures of selection. The structure that emerged in the semiconductor industry consisted of three types of companies:

- small, new entrepreneurial firms that developed and manufactured semiconductor devices, the so-called "merchant" firms;
- generally larger, established companies that obtained most or all of their semiconductor devices from the merchant firms and incorporated them into electrical systems; and
- one very large, vertically integrated company, AT&T, that manufactured semiconductor devices for use in its telecommunications systems but was constrained by antitrust policy from dominating other markets.*

The role of AT&T, along with its affiliates Bell Laboratories and Western Electric, has already been discussed. The rest of this section describes the relationships between the other two groups of firms.

The emergence of new entrepreneurial firms in the U.S. semiconductor industry was facilitated by U.S. Government policies and actions, such as the 1956 consent decree and military and aerospace demands. Information on semiconductor technology was widely available, and personnel mobility was not effectively discouraged. AT&T's liberal licensing policy, a U.S.

*Later in the history of the semiconductor industry, a second vary large, vertically integrated firm, IBM, was added to this group. IBM manufactured semiconductor devices for its own use in the computer industry.

Government market for new products, and the fact that transistors could be *substituted* for vacuum tubes meant that an entrepreneur could start a new semiconductor firm and move immediately to market with a few million dollars of capital, a license from AT&T, and a DOD or NASA contract.

Larger U.S. companies were helped in establishing their position in the semiconductor industry by the patterns of DOD development and procurement established during World War II that favored large corporations. "Even as late as 1959 the old-line vacuum tube companies were awarded 78 percent of the federal R&D funds devoted to improving the performance and reducing the cost of the transistor although they accounted for only 37 percent of the product market" (3). In contributing to the development of transistors and integrated circuits, the large defense electronics companies were speeding the obsolescence of a technology in which they had a very large investment, vacuum tubes. The large companies were forced into this position, however, by the presence of small entrepreneurial firms that managed to obtain DOD funds by their more flexible and rapid response to DOD's demands for miniaturization and reliability. The small, new firms undoubtedly contributed to the speed of entry of the large companies into semiconductor technology.

Small entrepreneurial firms did contribute to innovation in semiconductors, but preeminence in that role went to Bell Laboratories. In the development of the U.S. semiconductor industry the major contributions of small firms were to diffuse semiconductor technology and to stimulate competition. Diffusion of semiconductor technology occurred because the small firms exploited new markets. It was they who most "quickly and successfully (took) new technology from the laboratory and adapted it for large-scale production" (14). The small firms also stimulated competition. In effect, the small firms, as independent sources of advanced semiconductor technology, introduced an element of dynamic uncertainty into the U.S. semiconductor industry. And because Federal policies helped them to *produce and market* their products, the small firms stimulated semiconductor R&D among all companies in the industry, large and small.

Biotechnology, as it now stands, presents a very different picture. Small NBFs in the United States, in order to spread risk and raise capital, have had to turn to complex cooperative arrangements with large domestic and foreign companies.* On the surface, the arrangements between NBFs and established companies may appear analogous to the relationship between the small new semiconductor firms and the Federal Government. An essential difference, however, is that small new semiconductor firms and the Federal Government did not compete for markets; NBFs *would* like to compete with established companies.

In the absence of support from the Government for producing and marketing its products or processes, an NBF is likely to turn to a large established company that has expertise in scale-up technology and regulatory clearance procedures. The established company is likely to have gained this expertise by developing a product similar to the one the NBF wants to bring to market. If the new product threatens an existing product of the established company, the established company's marketing of the new product is likely to be less than optimal. This is not to say that the established company will refuse to undertake the clinical trials, marketing, and distribution of the new product developed by the NBF. Indeed, the motivation of the established company is just the opposite. By obtaining a license for the NBF's new product, the established company ensures that another large competitor does not obtain the biotechnology product that threatens its own market. Furthermore, the established company can control the market environment of the new product. By entering into an agreement with an NBF, the established company also gains access to the new technology.

The arrangements between Eli Lilly and the NBF Genentech with respect to the new biotechnology product Humulin® are illustrative.* Eli Lilly has licensed this rDNA-produced human insulin product from Genentech. Humulin® is a competitor of insulin obtained from animals, and Lilly currently holds about 85 percent of the U.S. insulin market. Thus, the pace of market development in Humulin® can be controlled by the very company whose monopoly position Humulin® sales otherwise might challenge. A consequence of arrangements of this kind could be to slow market development and to reduce the flow of royalties to NBFs. Yet royalties may be necessary to NBFs' survival and certainly are anticipated by the new firms to assist them in expansion. Arrangements like that between Eli Lilly and Genentech in biotechnology go against the lessons to be learned from the evolution of the U.S. semiconductor industry. Both the pace of technological development and the growth of small, innovative semiconductor firms such as Texas Instruments might have been quite different had Texas Instruments found it necessary to license GE or RCA to get its transistor products on the market.

*These arrangements are discussed in *Chapter 4: Firms Commercializing Biotechnology*.

*These arrangements are discussed in *Chapter 5: Pharmaceuticals*.

Like the semiconductor industry in its early stages, biotechnology currently is restricted by its need for process technology. The history of process development in the evolution of the U.S. semiconductor industry is of relevance to biotechnology. As has been shown, large electronic defense contractors such as GE were assisted in developing production lines for semiconductor devices by large infusions of DOD dollars. But the history of the U.S. semiconductor industry demonstrates that small firms are not automatically foreclosed from process advances. Thus, the early growth of Fairchild Semiconductor, for example, was tied largely to its development of the planar process, which dramatically increased the firm's production yield and helped compensate it for its lack of production experience.

In the case of biotechnology, firms that exploit possibilities in both new product development and process innovation clearly will have more growth opportunities than those that restrict themselves to one or the other. In biotechnology, as in semiconductors, process know-how is probably transferable across a range of potential products and markets. Thus, if NBFs can surmount the financial hurdles to commercial production, the pace of technological advance and market development likely will be accelerated significantly, and the competitiveness of U.S. firms using biotechnology probably will be increased.

Other differences

Two other differences between the early history of the U.S. semiconductor industry and biotechnology are noteworthy. The first difference is the range of economic sectors each technology was perceived potentially to affect. For semiconductors, military, aerospace, communications, and computer applications were foreseen. All these draw primarily on the disciplines of electronics and engineering. The applications of biotechnology are perceived to be broader—pharmaceuticals, plant and animal agriculture, chemicals, pollution control, energy production, mining, oil recovery, and biosensors/biochips are areas where applications are being pursued. Not only is the array of sectors expected to be affected by biotechnology broader, the technical disciplines required for effective application of biotechnology are more numerous. Developing an effective infrastructure to support the commercialization of biotechnology, therefore, may be more complex than was developing an infrastructure to support the semiconductor industry.

The second difference is the prominent role of Federal regulation in biotechnology. NIH, through the rDNA research guidelines, is in a quasi-regulatory position with regard to both R&D and scale-up to commercial production. And for specific products of biotechnology, FDA, which regulates food ingredients and human drugs and biologics, and USDA, which regulates animal biologics, are particularly important. EPA and OHSA also may have significant regulatory authority, although their exact authority is somewhat unclear.* U.S. Government regulation in research, development, and marketing of many products of biotechnology, for which there is no parallel in the semiconductor industry, makes effective commercialization of the products of biotechnology relatively more complex.

Conclusions

Certain differences between the early history of the U.S. semiconductor industry and biotechnology are particularly important from a policy perspective:

- The U.S. semiconductor industry arose from a fundamental invention (the transistor) made at a major industrial laboratory, AT&T's Bell Telephone Laboratories, in 1947, and most of the subsequent product and process innovations in the period from 1947 to the early 1960's also were made by industry. Biotechnology arose from fundamental biomedical research in universities, and its early subject matter experts were primarily university professors.
- The need for development of the U.S. semiconductor industry to meet military and aerospace needs was clear. The tie between biotechnology and national objectives is less clear. The U.S. Government's role in support of basic biomedical research has been, and remains, clear, but its role in the commercialization of biotechnology is far less defined.
- At Bell Labs, early commercial exploitation of semiconductor discoveries was strictly limited to one industrial sector, communications (despite the much wider applicability of semiconductor technology). In effect, Bell Labs became, for a time, something like a national laboratory for the semiconductor industry. There is no equivalent in biotechnology.
- Many new semiconductor firms in the United States were formed to market a definite product, and, because of the availability of Federal contracts, relatively little capital was required to enter the market. Most NBFs were started as R&D houses, with the objective of determining how to make a product. With certain exceptions (e.g., in vitro monoclonal antibody diagnostic products),

*This issue is discussed in *Chapter 15: Health, Safety, and Environmental Regulation*.

the capital required to produce a biotechnology product and bring it to market will be greater than that needed by early semiconductor firms. For NBFs attempting to commercialize a new drug or biological for human use, capitalization requirements may be $50 million to $100 million.*
- The early U.S. semiconductor industry was characterized by multifaceted Federal encouragement of commercialization through a variety of policies ranging from antitrust to Federal loan and tax policies. There is no parallel to this in biotechnology.
- Biotechnology differs from the U.S. semiconductor industry in that the Federal Government is not providing substantial funds for process engineering and development of pilot and production facilities. Nor is the Federal Government serving as a "creative first market" for the products of biotechnology as it did for the semiconductor industry.
- Biotechnology also differs from semiconductor technology in the wider array of economic sectors it is perceived potentially to affect and in the larger role of the Federal Government in regulating many products of biotechnology.

Thus, NBFs currently face a very different, and much more complex, market environment than did the new entrants in the semiconductor industry. The industrial sectors in which biotechnology appears to be making its first contributions are human and animal health care, and the pharmaceutical sector has special characteristics. The market for a particular pharmaceutical product is often dominated by one or a few major corporations, as, for example, the U.S. insulin market is dominated by Eli Lilly.** The product of the dominant corporation is supported by extensive advertising in medical journals, by a complex distribution system involving detail men who provide product samples and are recognized by the physicians they serve, and by the reluctance of physicians to switch to a product with less familiar properties. The established company is also skilled in the clinical testing procedures necessary to obtain market approval. An NBF with a competing product, but without production capacity, experience in regulatory compliance, and an established marketing and distribution system within the medical community, has little choice but to license the new product to an established company that already produces a similar product. Such licensing, however, will tend to reduce the competitive stimulation to the industry that the NBF might otherwise provide.

The Federal Government was clear about its role in the development of the U.S. semiconductor industry. DOD and NASA funded the industry to produce products needed in military and aerospace applications. The Federal Government has funded basic biomedical research in university settings, but as yet it has no explicit role in the commercialization of biotechnology. Unlike semiconductor technology, biotechnology has sprung primarily from academia. As biotechnology moves to the market, universities of necessity have played a role in commercializing the fruits of public funding of research, because they were the sole source of basic knowledge. Moreover, the role of the universities has been further complicated in biotechnology by the close association between basic and applied research in this area. The traditionally distinct roles of the university as source of research and training and of industry as source of commercialization, which were clear with respect to semiconductors, are blurred for biotechnology.*

In the early history of the U.S. semiconductor industry, the Federal Government and industry were partners, with industry providing know-how and the Federal Government supplying public funds for R&D, demonstration projects, production, and consumption of semiconductor devices. Direct returns to the Federal Government, in the form of advances in defense and aerospace electronics, were obvious. In the case of biotechnology, however, not the Federal Government but the public health organizations and universities that were the sources from which biotechnology arose have been industry's partner in commercialization. As a result, an impression is left that the public is ceding the biotechnology research infrastructure and discoveries brought about by public moneys to private industry without corresponding return. The problem has been exacerbated because biotechnology emerged so quickly from the academic setting. Basic biomedical research nourished by Federal dollars is applicable suddenly to the development of commercial products.

Consideration of the differences between the early history of the U.S. semiconductor industry and biotechnology suggests several areas of need for biotechnology:

- One need is for the Federal Government clearly to distinguish basic research from commercialization and to define its different roles with regard to each.

*For discussion of the financial needs of firms using biotechnology, see *Chapter 12: Financing and Tax Incentives for Firms.*

**A profile of Lilly's share in U.S. and foreign insulin markets is presented in *Chapter 5: Pharmaceuticals.*

*University/industry relationships in biotechnology are explored at greater length in *Chapter 17: University/Industry Relationships.*

- A second need, suggested by the successful history of the U.S. semiconductor industry, is for the Federal Government to facilitate the development of NBFs so that they can compete effectively in the marketplace. As in the semiconductor industry, small firm competition would stimulate innovation by all companies, large and small.
- Related to the above is the need to develop effective mechanisms for the diffusion of knowledge developed in biotechnology.

The last is very important and is really the central issue with respect to ensuring a return to the public for the financial investment that the public has made in biotechnology.

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Appendix D

Firms in the United States Commercializing Biotechnology

Table 4 in *Chapter 4: Firms Commercializing Biotechnology* listed firms in the United States commercializing biotechnology and their product markets. Their names and addresses are provided below. In order for a company to be listed in table 4, the existence of the company and the fact that the company is pursuing the development of biotechnology as defined by OTA had to be confirmed by at least two sources (e.g., company directories, individuals, trade journals). The existence and commercial application areas of many of the companies listed also were confirmed through the survey of firms' personnel needs conducted by the National Academy of Sciences and OTA.*

The number of companies listed in table 4 is a very conservative estimate of the number of companies commercializing biotechnology in the United States. More than five established companies thought to be applying novel bioprocessing technology (e.g., G. B. Fermentation Industries, Inc.) are missing from the list, because sufficient information to confirm their activities could not be obtained. Like the biotechnology research of established companies, the existence of new biotechnology firms (NBFs) is often difficult to confirm. More than 10 new companies, not included here, are thought by OTA to be operating but with very little public visibility. Some established companies and NBFs regard the application of their biotechnology research to be proprietary, and others will not even publicly confirm whether or not they are involved in biotechnology. Approximately 10 companies are not listed for this reason. Various other companies are not listed, because their existence and involvement in biotechnology were not confirmed by at least two sources.

Most support firms are not included in the table, because they are not applying biotechnology to the production of their products. Those support companies that, in addition to supplying support products (e.g., restriction enzymes and oligonucleotides), are applying biotechnology to the development and production of such products as vaccines and monoclonal antibodies are included.

*All but 33 of the firms listed were sent the OTA/NAS survey questionnaire, which is reproduced in *Appendix E: OTA/NAS Survey of Personnel Needs of Firms in the United States.*

Abbott Laboratories
14th St. & Sheridan Rd.
North Chicago, Ill. 60064

Actagen
Rm. 802
99 Park Ave.
New York, N.Y. 10016

Advanced Biotechnology Associates, Inc.
177 Post St., Suite 700
San Francisco, Calif. 94108

Advanced Genetic Sciences, Inc.
42 Maher Ave.
Greenwich, Conn. 06830

Advanced Genetics Research Institute
2220 Livingston St.
Berkeley, Calif. 94606

Advanced Mineral Technologies, Inc.
P.O. Box 1339
Socorro, N. Mex. 87801

Agrigenetics Corp.
3375 Mitchell Lane
Boulder, Colo. 80301

Allied Chemical Corp.
Columbia Rd. & Park Ave.
P.O. Box 4000R
Morristown, N.J. 07960

Alpha Therapeutic Corp.
5555 Valley Blvd.
Los Angeles, Calif. 90032

Ambico, Inc.
P.O. Box M, Route 2
Dallas Center, Iowa 50063

American Cyanamid Co.
One Cyanamid Plaza
Wayne, N.J. 07470

American Diagnostics Corp.
1600 Monrovia Ave.
Newport Beach, Calif. 92663

American Qualex
14620 Firestone Blvd.
La Mirada, Calif. 90638

Amgen
1892 Oak Terrace Lane
Newbury Park, Calif. 91320

Angenics
100 Inman St.
Cambridge, Mass. 02139

Animal Vaccine Research Corp.
3333 Torrey Pines Ct., Suite 120
La Jolla, Calif. 92037

Antibodies, Inc.
P.O. Box 442
Davis, Calif. 95617

Applied DNA Systems, Inc.
4415 Fifth Ave.
Pittsburgh, Pa. 15213

Applied Genetics, Inc.
5 Jules Lane
New Brunswick, N.J. 08901

ARCO Plant Cell Research Institute
6560 Trinity Ct.
Dublin, Calif. 94568

Atlantic Antibodies
10 Nonesuch Rd.
P.O. Box 60
Scarborough, Maine 04074

Axonics
1500 Salado Dr., Suite 202
Mountain View, Calif. 94043

Baxter-Travenol Laboratories, Inc.
One Baxter Parkway
Deerfield, Ill. 60015

Becton Dickinson & Co.
Corporate Research Center
P.O. Box 12016
Research Triangle Park, N.C. 27709

Bethesda Research Laboratories, Inc.
P.O. Box 577
Grovemont Circle
Gaithersburg, Md. 20760

Biocell Technology Corp.
220 East 23rd St.
New York, N.Y. 10010

Biochem Technology, Inc.
66 Great Valley Parkway
Great Valley Corporate Center
Malvern, Pa. 19355

Bio-con, Inc.
3601 Gibson St.
P.O. Box 5277
Bakersfield, Calif. 93388

Biogen, Inc.
241 Binney St.
Cambridge, Mass. 02142

BioGenex Laboratories
6529 Sierra Lane
Dublin, Calif. 94566

Biological Energy Corp.
P.O. Box 766
2650 Eisenhower Ave.
Valley Forge, Pa. 19482

Bio Response, Inc.
550 Ridgefield Rd.
Wilton, Conn. 06987

Biotech Research Laboratories, Inc.
1600 East Gude Dr.
Rockville, Md. 20850

Biotechnica International, Inc.
85 Bolton St.
Cambridge, Mass. 02140

Bio-Technology General Corp.
280 Park Ave.
New York, N.Y. 10017

Brain Research
46 East 91st St.
New York, N.Y. 10028

Bristol-Myers Co.
Industrial Division
P.O. Box 657
Syracuse, N.Y. 13201

BTC Diagnostics, Inc.
61 Moulton St.
Cambridge, Mass. 02138

Calgene
1910 Fifth St.
Davis, Calif. 95616

California Biotechnology, Inc.
2450 Bayshore Frontage Rd.
Mountain View, Calif. 94303

Cambridge Bioscience Corp.
495 Old Connecticut Path
Framingham, Mass. 01701

Campbell Institute for Research and Technology
Campbell Soup Co.
Campbell Rd.
Camden, N.J. 08101

Celanese Research Co.
86 Morris Ave.
Summit, N.J. 07901

Cellorgan International, Inc.
300 Park Ave.
New York, N.Y. 10010

Celtek, Inc.
102 West Eufala
Norman, Okla. 73069

Centaur Genetics Corp.
120 South LaSalle St., Suite 825
Chicago, Ill. 60603

Centocor
3508 Market St.
Philadelphia, Pa. 19104

Cetus Corp.
600 Bancroft Way
Berkeley, Calif. 94710

Cetus Immune Corp.
3400 West Bayshore Rd.
Palo Alto, Calif. 94303

Cetus Madison Corp.
2208 Parkview Rd.
Middleton, Wis. 53562

Chiron Corp.
4560 Horton St., Suite 0214
Emeryville, Calif. 94608

Ciba-Geigy
444 Saw Mill River Rd.
Ardsley, N.Y. 10502

Clonal Research
1598 Monrovia Ave.
Newport Beach, Calif. 92630

Codon
430 Valley Dr.
Brisbane, Calif. 94005

Collaborative Genetics, Inc.
128 Spring St.
Lexington, Mass. 01273

Collagen, Inc.
2455 Faber Pl.
Palo Alto, Calif. 94303

Cooper Diagnostics, Inc.
1230 Wilson Dr.
West Chester, Pa. 19380

Cooper-Lipotech, Inc.
1030 Curtis St.
Menlo Park, Calif. 94025

Corning Glass Works
Corning Biotechnology Department
Baron Steuben Plaza
Corning, N.Y. 14830

Crop Genetics International
7170 Standard Dr.
Dorsay, Md. 21076

Cutter Laboratories, Inc.
2200 Powell St.
P.O. Box 8817
Emeryville, Calif. 94662

Cytogen Corp.
201 College Rd., East
Princeton Forrestal Center
Princeton, N.J. 08540

Cytox Corp.
954 Marcon Blvd.
Allentown, Pa. 18103

Dairyland Foods Corp.
620 Progress Ave.
Waukesha, Wis. 53187

Damon Biotech, Inc.
115 Fourth Ave.
Needham Heights, Mass. 02194

Dart & Kraft, Inc.
2211 Sanders Rd.
Northbrook, Ill. 60062

Davy McKee Corp.
10 South Riversider Plaza
Chicago, Ill. 60606

DeKalb Pfizer Genetics
Sycamore Rd.
DeKalb, Ill. 60115

Diagnon Corp.
225 Main St.
Westport, Conn. 06880

Diagnostic Technology, Inc.
240 Vanderbilt Motor Parkway
Hauppauge, N.Y. 11788

Diamond Laboratories
2538 S.E. 43rd St.
Des Moines, Iowa 50316

Diamond Shamrock Corp.
T. R. Evans Research Center
P.O. Box 348
Painesville, Ohio 44077

DNA Plant Technology
2611 Branch Pike
Cinnaminson, N.J. 08077

DNAX Corp.
1454 Page Mill Rd.
Palo Alto, Calif. 94304

Dow Chemical Co.
2030 Dow Center
Midland, Mich. 48640

Ean-tech, Inc.
699-A Cerramonte Blvd.
Dale City, Calif. 94015

Eastman Kodak Co.
343 State St.
Rochester, N.Y. 14650

Ecogen, Inc.
c/o Johnston Associates, Inc.
1101 State Rd., Bldg. O
Princeton, N.J. 08540

E. I. du Pont de Nemours & Co.
Central Research and Development Department
1007 Market St.
Wilmington, Del. 19898

Electro Nucleonics Laboratories, Inc
12050 Tech Rd.
Silver Spring, Md. 20904

Eli Lilly & Co.
Lilly Research Laboratories
307 East McCarty St.
Indianapolis, Ind. 46285

EnBio, Inc.
Union Ave. #408A
Fairfield, Calif. 94533

Endorphin, Inc.
1000 Seneca St.
Seattle, Wash. 98111

Engenics, Inc.
2 Palo Alto Sq., Suite 500
Palo Alto, Calif. 94304

Enzo Biochem, Inc.
325 Hudson St.
New York, N.Y. 10013

Enzyme Bio-systems, Ltd.
Box 8000
Englewood Cliffs, N.J. 07632

Enzyme Center, Inc.
33 Harrison Ave.
Boston, Mass. 02111

Enzyme Technology Corp.
783 U.S. 250 East, Route 2
Ashland, Ohio 44805

Ethyl Corp.
P.O. Box 341
Baton Rouge, La. 70821

Exxon Research & Engineering Co.
180 Park Ave.
Florham Park, N.J. 07932

Fermentec Corp.
301 Saratoga Ave.
Los Gatos, Calif. 95030

FMC Corp.
2000 Market St.
Philadelphia, Pa. 19103

Frito-Lay, Inc.
Frito-Lay Tower
Exchange Park
P.O. Box 35034
Dallas, Tex. 75235

Fungal Genetics, Inc.
14721 Cottonwood Pl.
Bothell, Wash. 98011

Genencor
Baron Steuben Pl.
Corning, N.Y. 14870

Genentech, Inc.
460 Point San Bruno Blvd.
South San Francisco, Calif. 94080

General Electric Co.
Research and Development Laboratories
One River Rd.
Schenectady, N.Y. 12345

General Foods Corp.
555 South Broadway
Tarrytown, N.Y. 10591

General Genetics
15400 West 44th Ave.
Golden, Colo. 80403

General Molecular Applications
1834 Elmwood Ave.
Columbus, Ohio 43212

Genetic Diagnostics Corp.
160 Community Dr.
Great Neck, N.Y. 11021

Genetic Replication Technologies, Inc.
1533 Monrovia Ave.
Newport Beach, Calif. 92663

Genetic Systems Corp.
3005 First Ave.
Seattle, Wash. 98121

Genetics Institute
225 Longwood Ave.
Brookline, Mass. 02115

Genetics International, Inc.
50 Milk St., 15th Floor
Boston, Mass. 02109

Genex Corp.
6110 Executive Blvd.
Rockville, Md. 20852

Gentronix Laboratories, Inc.
15825 Shady Grove Rd.
Rockville, Md. 20850

Genzyme
1 Bishop St.
Norwalk, Conn. 06851

W. R. Grace & Co.
Research Division
7379 Route 32
Columbia, Md. 21044

Hana Biologics, Inc.
626 Bancroft Way
Berkeley, Calif. 94710

Hem Research
12220 Wilkins Ave.
Rockville, Md. 20852

Hoffmann-La Roche, Inc.
340 Kingsland St.
Nutley, N.J. 07110

Hybridoma Sciences, Inc.
4761 Hugh Howell Rd., Suite D
Tucker, Ga. 30084

Hybritech, Inc.
11085 Torreyana Rd.
San Diego, Calif. 92121

Hytech Biomedical, Inc.
1440 Fourth St.
Berkeley, Calif. 94710

IBM Corp.
Thomas J. Watson Research Center
Yorktown Heights, N.Y. 10598

IGI Biotechnology, Inc.
9110 Red Branch Rd.
Columbia, Md. 21045

Immulok, Inc.
1019 Mark Ave.
Carpinteria, Calif. 93013

Immunetech, Inc.
8950 Villa La Jolla Dr., Suite 2132
La Jolla, Calif. 92037

Immunex Corp.
51 University Bldg., Suite 600
Seattle, Wash. 98101

Immuno Modulators Laboratories, Inc.
10511 Corporate Dr.
Stafford, Tex. 77477

Immunogen
c/o T. A. Associates
111 Devonshire St.
Boston, Mass. 02109

Immunotech Corp.
11 Blackstone St.
Cambridge, Mass. 02139

Imreg, Inc.
P.O. Box 56643
New Orleans, La. 70156

Indiana BioLab
Palmyra, Ind. 47164

Integrated Genetics, Inc.
51 New York Ave.
Framingham, Mass. 01701

Interferon Sciences, Inc.
783 Jersey Ave.
New Brunswick, N.J. 08901

International Genetic Engineering, Inc. (INGENE)
1701 Colorado Ave.
Santa Monica, Calif. 90404

International Genetic Sciences Partnership
155-25 Styler Rd.
Jamaica, N.Y. 11433

International Minerals & Chemical Corp.
Biochemical Division
1401 South Third St.
Terre Haute, Ind. 47808

International Plant Research Institute
853 Industrial Rd.
San Carlos, Calif. 94070

Kallestad Laboratories, Inc.
Austin National Bank Tower, Suite 2000
Austin, Tex. 78701

Kennecott Copper Corp.
One Stanford Forum
Stanford, Conn. 06904

Lederle Laboratories
One Cyanamid Plaza
Wayne, N.J. 07470

The Liposome Co., Inc.
1 Research Way
Princeton Forrestal Center
Princeton, N.J. 08540

Liposome Technology, Inc.
1030 Curtis St.
Menlo Park, Calif. 94025

Litton Bionetics
5516 Nicholson Lane
Kensington, Md. 20895

3M Co.
3M Center
St. Paul, Minn. 55144

Mallinckrodt, Inc.
675 McDonald Blvd.
P.O. Box 5840
St. Louis, Mo. 63134

Martin Marietta
1450 South Rolling Rd.
Baltimore, Md. 21227

Meloy Laboratories, Inc.
6715 Electronic Dr.
Springfield, Va. 22151

Merck & Co., Inc.
Merck Sharp and Dohme Research Laboratories
P.O. Box 2000
Rahway, N.J. 07065

Microlife Genetics
P.O. Box 2399
1817 57th St.
Sarasota, Fla. 33578

Miles Laboratories, Inc.
1127 Myrtle St.
Elkhart, Ind. 46515

Miller Brewing Co.
3939 West Highland Blvd.
Milwaukee, Wis. 53201

Molecular Biosystems, Inc.
1118-A Roselle St.
San Diego, Calif. 92121

Molecular Diagnostics
400 Morgan Lane
West Haven, Conn. 06516

Molecular Genetics, Inc.
10320 Bren Rd., East
Minnetonka, Minn. 55343

Monoclonal Antibodies, Inc.
2319 Charleston Rd.
Mountain View, Calif. 94043

Monsanto Co.
500 N. Linbergh
St. Louis, Mo. 63167

Multivac, Inc.
P.O. Box 575
Seal Beach, Calif. 90740

Nabisco, Inc.
River Rd. and De Forest Ave.
East Hanover, N.J. 07936

National Distillers & Chemical Co.
99 Park Ave.
New York, N.Y. 10016

Neogen Corp.
Nisbet Bldg., Suite 22
1407 S. Harrison Rd.
East Lansing, Mich. 48824

New England Biolabs
32 Tozer Rd.
Beverly, Mass. 01915

New England Monoclonal Resources
267 Plain St.
Providence, R.I. 02905

New England Nuclear Corp.
85 Wells Ave.
Newton Center, Mass. 02159

Norden Laboratories
601 West Cornhusker Highway
Lincoln, Nebr. 68521

Novo Laboratories, Inc.
59 Danbury Rd.
Wilton, Conn. 06897

NPI
417 Wakara Way
University Research Park
Salt Lake City, Utah 84108

Nuclear & Genetic Technology, Inc.
172 Brook Ave.
Deer Park, N.Y. 11729

Ocean Genetics
1990 N. California Blvd., Suite 830
Walnut Creek, Calif. 94596

Oncogen
3005 First Ave.
Seattle, Wash. 98121

Oncogene Science Inc.
Nassau Hospital
Professional Bldg., Suite 330
222 Station Plaza North
Mineola, N.Y. 11501

Organon, Inc.
375 Mt. Pleasant Ave.
West Orange, N.J. 07052

Ortho Pharmaceutical Corp.
Route 202
Raritan, N.J. 08869

Petrogen, Inc.
2452 East Oakton St.
Arlington Heights, Ill. 60005

Pfizer, Inc.
25 East 42nd St.
New York, N.Y. 10017

Phillips Petroleum Co.
Research Center
Bartlesville, Okla. 74004

Phytogen
101 Waverly Dr.
Pasadena, Calif. 91105

Phyto-tech Lab
21822 South Vermont Ave.
Torrance, Calif. 90502

Pioneer Hybrid International Corp.
1206 Mulberry St.
Des Moines, Iowa 50308

Plant Genetics, Inc.
1930 Fifth St., Suite A
Davis, Calif. 95616

Polybac Corp.
1251 S. Cedar Crest Blvd.
Allentown, Pa. 18103

PPG Industries
One Gateway Center
Pittsburgh, Pa. 15222

Purification Engineering, Inc.
9505 Berger Rd.
Columbia, Md. 21046

Quidel Home
11077 North Torrey Pines
La Jolla, Calif. 92037

Replicon
P.O. Box 27053
South San Francisco, Calif. 94127

Repligen Corp.
101 Binney St.
Cambridge, Mass. 02142

Ribi Immunochem Research, Inc.
P.O. Box 1409
Hamilton, Mont. 59840

Rohm & Haas Co.
Independence Mall
West Philadelphia, Pa. 19105

Salk Institute Biotechnology/
Industrial Associates, Inc.
3333 Torrey Pines Ct., Suite 140
La Jolla, Calif. 92037

Sandoz, Inc.
Route No. 10
East Hanover, N.J. 07936

Schering-Plough Corp.
2000 Galloping Hill Rd.
Kenilworth, N.J. 07033

SDS Biotech Corp.
7528 Auburn Rd.
Painesville, Ohio 44077

G. D. Searle & Co.
Box 1045
Skokie, Ill. 60076

Serono Laboratories, Inc.
280 Pond St.
Randolph, Mass. 02368

SmithKline Beckman
One Franklin Plaza
P.O. Box 7929
Philadelphia, Pa. 19101

E. R. Squibb & Sons, Inc.
P.O. Box 4000
Princeton, N.J. 08540

A. E. Staley Manufacturing Co.
2200 Eldorado St.
Decatur, Ill. 62525

Standard Oil Co. of California
225 Bush St.
San Francisco, Calif. 94104

Standard Oil Co. of Indiana
Amoco Research Center
P.O. Box 400
Naperville, Ill. 60566

Standard Oil Co. of Ohio
1424 Midland Bldg.
Cleveland, Ohio 44115

Stauffer Chemical Co.
Nyala Farm Rd.
Westport, Conn. 06881

Summa Medical Corp.
4272 Balloon Park Rd., N.E.
Albuquerque, N. Mex. 87109

Sungene Technologies Corp.
3330 Hillview Ave.
Palo Alto, Calif. 94304

Sybron Biochemical
Birmingham Rd.
Birmingham, N.J. 08011

Synbiotex Corp.
348-B Rancho Dr.
San Marcos, Calif. 92069

Syncor International
12847 Arroyo St.
Sylmar, Calif. 91342

Synergen
1885 Thirty Third St.
Boulder, Colo. 80301

Syngene Products & Research, Inc.
225 Commerce Dr.
P.O. Box 2211
Fort Collins, Colo. 80524

Syntex Research
c/o Syntex Corp.
3401 Hillview Ave.
Palo Alto, Calif. 94304

Syntro Corp.
11095 Torreyana
San Diego, Calif. 92121

Syva Co.
900 Arastradero Rd.
Palo Alto, Calif. 94303

Techniclone International Corp.
3301 South Harbor Blvd., Suite 104
Santa Ana, Calif. 92704

Unigene Laboratories, Inc.
110 Little Falls Rd.
Fairfield, N.J. 07006

Universal Foods Corp.
433 East Michigan St.
Milwaukee, Wis. 53202

University Genetics Co.
537 Newtown Ave.
Norwalk, Conn. 06852

U.O.P., Inc.
10 UOP Plaza
Des Plaines, Ill. 60016

The Upjohn Co.
7000 Portage Rd.
Kalamazoo, Mich. 49001

Viral Genetics
10 Cutter Mill Rd., Rm. 403
Great Neck, N.Y. 11021

Wellcome Research Laboratories
3030 Cornwallis Rd.
Research Triangle Park, N.C. 27709

Worne Biotechnology, Inc.
Medford Medical Bldg.
Stokes Rd., Box 458
Medford, N.J. 08055

Xenogen, Inc.
557 Wormwood Rd.
Mansfield, Conn. 06250

Xoma Corp.
3516 Sacramento St.
San Francisco, Calif. 94118

Zoecon
975 California Ave.
P.O. Box 10975
Palo Alto, Calif. 94304

Zymed Laboratories
P.O. Box 1856
Burlingame, Calif. 94010

Zymos Corp.
2121 North 35th St.
Seattle, Wash. 98103

Appendix E

OTA/NAS Survey of Personnel Needs of Firms in the United States

As noted in *Chapter 14: Personnel Availability and Training,* OTA and the National Academy of Sciences' (NAS) Committee on National Needs for Biomedical and Behavioral Research Personnel cosponsored a survey of the personnel needs of U.S. firms using biotechnology. The purpose of the OTA/NAS survey was twofold. First, OTA was interested in identifying the companies that were using new biotechnology as defined at the outset of this report. Second, OTA and NAS were interested in the number of employees engaged in industrial biotechnology, how that number would grow, and where shortages of personnel, if any, are occurring. The cover letter and survey questionnaire reproduced in this appendix were sent to 286 U.S. companies. Of the 133 firms that responded, 18 indicated that they were not engaged in biotechnology activities, and 20 others were determined not to be engaged in biotechnology from their answers to the questionnaire. The remaining 95 indicated that they were engaged in biotechnology activities. The responses of these 95 firms, which are tabulated on the survey questionnaire reproduced in this appendix, are the basis of the characteristics described for the respondents. The distribution of size of firms was not significantly different between respondents and nonrespondents. Because the survey response rate was low, however, only general trends in the data have been used in the discussion of personnel needs in chapter 14.

Cornell University
Ithaca, New York 14853

March 4, 1983

Dear :

The Congressional Office of Technology Assessment (OTA) and the National Academy of Science's (NAS) Committee on National Needs for Biomedical and Behavioral Research Personnel have a mutual interest in determining the nation's need for research personnel. I am chairman of the NAS Committee's Panel on Basic Biomedical Sciences. We are particularly concerned that there be an adequate number of people trained in areas of the new biotechnology.

I am writing to ask your assistance in collecting some information on this issue. You could help us greatly in our efforts to get a profile of current employment opportunities and a sense of future demand in biotechnology and related industries by responding to the three questions on the attached page. To be useful in our report to the Congress, we need your answers before March 14, 1983. The tabulated data from the questionnaire will be published. Only OTA and the NAS panel will have access to the individual responses.

If you have additional comments or suggestions that you think would assist us, please include them with your response. A self-addressed envelope is enclosed. Also, if you have any questions concerning the questionnaire, don't hesitate to call me at (607) 256-3374.

With thanks for your help.

Yours sincerely,

Robert Barker, Ph.D.
Director, Division of Biological Sciences
Cornell University

RB:db
Enclosures

COMPANY NAME AND ADDRESS:

PERSON COMPLETING THIS FORM:
Name:

Phone Number:

For the purpose of this questionnaire, Biotechnology is defined as the application of novel biological strategies (rDNA, cell-fusion, mobilized cells or enzymes) for biochemical processing.

1. What year did your company begin research or development in activities related to the new biotechnology? _____

2. Please check all areas of biotechnology application in which your company is involved:

a) ____ fine chemicals
b) ____ bulk chemicals
c) ____ pharmaceuticals
d) ____ animal agriculture
e) ____ biomass conversion
f) ____ human diagnostics
g) ____ plant agriculture
h) ____ mineral leaching and mining
i) ____ pollution control
j) ____ enhanced oil recovery
k) ____ other; specify _____

PLEASE INCLUDE ANY COMMENTS ON REVERSE

3.

SPECIALTIES	(1) Check if you are experiencing personnel shortages in any of these specialties.			(2) No. scientists currently on staff (list each employee only once).			(3) No. you intend to retain during next 18 months.			(4) Expected No. of scientists to be hired in next 18 months.			(5) For vacant positions, do you expect to:		
	Ph.D.	MS	BS	Ph.D.	MS	BS	Ph.D.	MS	BS	Ph.D.	MS	BS	Hire from Industry	Hire from Academia	Retrain current Staff
a) Recombinant DNA/molecular genetics	10	7	4	293	126	167				143	65	92	22	43	4
b) Hybridomas/monoclonal antibodies	6	5	6	89	50	108				38	29	79	16	30	9
c) animal reproduction/embryotransplantation	1	0	0	1	1	1				0	0	0	1	1	1
d) classical genetics	1	1	1	30	8	12				6	5	3	4	4	1
e) gene synthesis	10	5	3	26	5	14				18	7	17	9	18	3
f) enzymology/immobilized systems	6	3	3	97	36	86				23	17	19	10	13	4
g) industrial microbiology	7	2	2	58	34	43				34	17	17	16	18	3
h) bioprocess engineering	12	4	3	71	47	68				44	31	25	21	15	2
j) analytical biochemistry	2	3	3	37	20	28				21	6	5	8	16	4
k) biochemistry, general	3	2	5	117	41	83				30	19	44	14	25	5
l) Cell culture	5	5	7	42	47	98				17	24	25	14	22	5
m) Cell fusion	3	2	2	11	4	11				6	3	8	3	5	2
n) Cell biology/physiology	4	1	3	18	7	18				10	5	10	3	9	1
o) plant molecular biology	8	0	1	40	18	18				31	12	20	7	17	2
p) plant biology/physiology	3	1	0	30	7	20				8	5	3	1	8	3
q) pharmacology	1	0	0	9	7	14				16	7	11	2	3	0
r) toxicology	1	0	0	13	2	16				2	2	1	3	1	0
s) microbiology, general	3	0	1	82	33	84				22	14	20	14	15	1
t) physiology	0	1	2	8	3	15				1	1	5	4	1	0
u) Other biotechnology specialties (specify)_____	4	3	4	51	23	44				8	7	9	8	11	2

THIS SAME AS (2)

Appendix F

Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety

Chapter 15: Health, Safety, and Environmental Regulation discussed the regulatory policies of the United States, the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan as they pertain to biotechnology. This appendix elaborates on the material presented in that chapter.

Recombinant DNA research guidelines

UNITED STATES

The National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules" (NIH Guidelines) apply to all research involving recombinant DNA (rDNA) in the United States or its territories conducted at or sponsored by any institution receiving support for rDNA research from NIH (28). All Federal agencies require their own scientists to comply with the guidelines, and Federal agencies other than NIH funding rDNA research also require their grantees to comply. Compliance is enforced by the authority of the agency to suspend, terminate, or place restrictions upon its financing of the offending project or all rDNA projects at the institution receiving support.

Although the NIH Guidelines are not legally binding on private companies (unless the company receives Federal funds), the private sector has espoused voluntary compliance. Some States and localities have required industry to comply by law.

Administrative Framework.—The NIH Guidelines create an administrative framework for oversight that specifies the responsibilities of scientists, their institutions, and the Federal Government. The primary responsibility for ensuring compliance lies with the institutions and scientists doing the research. The institution must establish an Institutional Biosafety Committee (IBC) meeting certain requirements, appoint a biological safety officer if certain experiments are done, ensure appropriate training, and implement health surveillance, if appropriate. The principal investigator has the initial responsibility for determining and implementing containment and other safeguards and for training and supervising the staff.

The IBC oversees all rDNA work at the institution for compliance with the NIH Guidelines. The IBC must consist of at least five members who collectively have the expertise to assess the safety of rDNA experiments. Two members must be otherwise unaffiliated with the institution and must represent the community's interest with respect to health and the environment. Institutions are encouraged to open IBC meetings to the public, and minutes of IBC meetings and certain other documents must be made available to the public on request. The institution must register the IBC with NIH by providing information about its members.

At the Federal level, the responsible parties are the Director of NIH, the NIH Recombinant DNA Advisory Committee (RAC), the NIH Office of Recombinant DNA Activities, and the Federal Interagency Advisory Committee on Recombinant DNA Research (Interagency Advisory Committee). The Director of NIH is the final decisionmaker under the guidelines. For major actions, he or she must seek the advice of the RAC and must provide the public and other Federal agencies at least 30 days to comment on proposed actions. Every action taken by the Director of NIH must present "no significant risk to health or the environment." RAC is a diverse group of experts that meets three or four times a year to advise the Director of NIH on the major technical and policy issues.* The NIH Office of Recombinant DNA Activities performs NIH's administrative functions under the guidelines. Additional oversight is provided by the Interagency Advisory Committee. This committee, which is composed of representatives of approximately 20 agencies, coordinates all Federal rDNA activities, and its members are nonvoting members of RAC.

Substantive Requirements.—The NIH Guidelines classify all experiments into four categories: 1) exempt, 2) those requiring RAC review and NIH approval before initiation, 3) those requiring IBC approval before initiation, and 4) those requiring IBC notification at the time of initiation. The first cate-

*In accordance with its charter, RAC is composed of not more than 25 members. At least eight must specialize in molecular biology or related fields; at least six must be experts in other scientific disciplines; and at least six must be authorities on law, public policy, the environment, public or occupational health, or related fields. As of June 30, 1983, RAC was composed of 10 molecular biologists, 6 experts from other scientific disciplines, and 9 persons in the third category (6). An industry trade association has requested that an industry representative be appointed to the RAC as a nonvoting member.

gory—exempt—covers an estimated 80 percent to 90 percent of all rDNA experiments. Examples include work with *E. coli* K-12, *S. cerevisiae,* and asporogenic *B. subtilis* host-vector systems.

NIH approval is required for experiments involving formation of rDNA containing genes for the synthesis of certain toxins lethal to vertebrates, deliberate release of recombinant organisms into the environment, and transfer of drug resistance to certain micro-organisms under certain conditions.

IBC approval is required for experiments involving certain pathogenic organisms, whole organisms or plants, or more than 10 liters of culture (except for certain exempt experiments). The last category—experiments requiring IBC notification—is a catch-all category. Containment levels are specified for each category except the one requiring NIH approval, where containment is set on a case-by-case basis.

Application to Industry.—In the absence of legal authority over industry's work with rDNA, NIH has taken several steps to encourage voluntary compliance and provide a modest degree of Federal oversight. Part VI of NIH Guidelines, added in January 1980, sets up a mechanism for voluntary compliance. It creates a parallel system of project review and IBC registration, modified to protect proprietary information.* In addition, RAC established a subgroup in May 1979 to deal with large-scale work. "Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules" (Large-Scale Recommendations) (27) developed by that subgroup, RAC, and NIH specify physical containment requirements, suggest the appointment of a biological safety officer, and suggest the establishment of a worker health surveillance program for work done at higher containment levels. (They were added to the NIH Guidelines as Appendix K in June 1983.)

According to industry spokespeople, the NIH Guidelines are accepted and followed by the private sector.** Compliance with the Large-Scale Recommendations also appears to be widespread, but there have been few, if any, definitive statements by industrial spokespeople on this point. Regarding present Large-Scale Recommendations, one industry group stated that its experience has indicated that "the present [recommendations] are reasonable and workable, although they are quite stringent for work at the P1-LS level. The design requirements in the Recommendations make sense to us and are consistent with other regulations relating to the manufacture of products for use with human subjects" (4). The group went on to state that it also saw difficulties arising from the recommendation that the primary containment system not be opened until all micro-organisms are inactivated because that could compromise that product in some cases (4).

Impact on Biotechnology.—The impact of the NIH Guidelines on biotechnology appears to be minimal. As essentially voluntary codes of practices that are fairly consistent with previously established good laboratory and manufacturing practices, they add little in the way of additional restrictions. Moreover, an estimated 80 to 90 percent of the experiments are exempt. On the basis of past history and what experts continue to learn about risks, the NIH Guidelines are likely to be further liberalized and may even disappear. In fact, whatever burdens they impose are probably offset by the gains in public confidence and the likelihood that they have headed off more restrictive mandatory controls.

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.—The European Economic Community (EEC) has considered at length the problems and prospects for rDNA research and the need for common Communitywide action to regulate and promote its development (13), but only a nonbinding recommendation has been made by the Council of the European Communities to member states on the question of guidelines applicable to rDNA research. The nonbinding EEC Guidelines were adopted in June 1982 (2). By that time, most of the individual member states with any significant amount of rDNA research had already adopted their own national guidelines. The EEC Guidelines impose no stricter requirements on rDNA research than those of the individual member states. They principally provide that any laboratory wishing to conduct rDNA research notify the competent national or regional authority in the member state and that the member states adopt a common definition of work involving rDNA (secs. 1-3).

More particularly, the EEC Guidelines suggest that notification of any rDNA research be given before work is commenced, except for research of very low-risk potential.* The notification should include infor-

*Proprietary information is protected in several ways. First, there is a presubmission review of data as to availability under the Freedom of Information Act. Second, NIH must consult with institutions applying for exemptions or approvals about the content of any public notice to be issued, if the application contains proprietary information. Finally, applications involving proprietary information are considered by RAC in nonpublic sessions.

**Although there is no means for NIH to monitor compliance with the NIH Guidelines or Large-Scale Recommendations, there is no evidence suggesting noncompliance.

*The EEC Guidelines do not define the term "very low risk potential," but indicate that this be determined by the competent national authorities. The United Kingdom, France, and the Federal Republic of Germany have adopted somewhat different methodologies in their guidelines for defining risk potential.

mation about the experimental protocol, the protective measures to be taken, and the general education and training of the staff working on the experiment or monitoring it. Such notification is thought desirable because it creates records that will be helpful in what the Commission of the European Communities believes to be the highly unlikely event of an accident or other misfortune involving rDNA (2). The authority receiving the notification must also, under the recommendation, protect the confidentiality of the information submitted (2). The EEC Guidelines do not call for specific approval of rDNA research of any type. As is discussed below, certain member states do require specific approval.

The EEC Guidelines do not address many issues which national guidelines, including those of the United States, have attempted to cover. The EEC Guidelines do not discuss the question of whether private laboratories should be subject to regulation, leaving this decision to the discretion of national authorities. Neither do they address how large-scale rDNA research should be regulated.

The fact that the EEC issued its rDNA guidelines despite the existence of more comprehensive guidelines in the member states reflects both the continuing concern over the safety of rDNA research and the difficulty in obtaining agreement on such matters. It is clear that the EEC has not yet determined its proper role in the regulation of rDNA research. Although discussions concerning rDNA as well as biotechnology generally are continuing within the EEC, it is likely to be some time before any agreement is reached concerning the respective roles of the EEC and the member states.

Federal Republic of Germany.—The Federal Republic of Germany has issued guidelines for rDNA research (3) that borrow heavily from the NIH Guidelines of the United States. The West German guidelines are theoretically broader than the NIH Guidelines because the German guidelines nominally apply to all research activities involving DNA. The only enforcement mechanism, however, is control over research funding from the German Federal Government.

The West German guidelines, like the NIH Guidelines, provide that the physical and biological containment measures required for particular experiments be determined according to the risk of the experiment. Risk is evaluated largely in terms of the source of the DNA. The German guidelines also prohibit certain specified experiments in the host organism *E. coli* K12 and other *E. coli* strains discussed in the NIH Guidelines (and the corresponding bacteriophages and plasmids of these strains), thereby requiring that the higher biological containment measures be used, regardless of the source of the DNA.* The guidelines also specify the appropriate containment methods required for various rDNA experiments. Physical and biological containment measures are divided into four and two levels (L1 to L4 and B1 to B2), respectively.

The German guidelines for rDNA research are administered by the Central Commission for Biological Safety (Zentrale Kommission für die Biologische Sicherheit),** a biological safety officer or committee at each laboratory, and a project leader for each experiment.*** The guidelines specify that the Central Commission must be notified of all rDNA experiments except those at the lowest physical containment level. For research at the next level, the Central Commission must authorize one of its scientist members to supervise the work and to keep the Commission informed. Experiments using mid-level containment measures require the prior approval of two members of the Commission. Prior approval must be sought from the Central Commission for all experiments using vertebrate cells as the host and for experiments using DNA from pathogenic organisms. In the case of the latter, the Central Commission must find that the expected benefits clearly outweigh the conceivable hazards. On request, the Central Commission will also authorize the use of new host-vector systems not enumerated in the German guidelines. The Central Commission also gives advice on research and safety measures.

United Kingdom.—The U.K. guidelines for rDNA research (26)† are similar to the NIH Guidelines in broad conceptual terms but differ with respect to

*These specially restricted experiments are: 1) the production of recombinant DNA for the biosynthesis of powerful bacterial exotoxins such as botulinus toxin, tetanus toxic, diphtheria toxin, and snake toxin; 2) the use of genomes of extremely pathogenic viruses such as Lassa, small pox, and hepatitis B; and 3) the transmission of genes which confer resistance to an antibiotic between micro-organisms that do not naturally exchange genes when the resistance gene has not previously been known in the receptor cell.

**West Germany's Central Commission for Biological Safety, the only Government body, has 12 members, 4 rDNA experts, 4 experts from related field of biology, and 4 "outstanding individuals" from unions, industry, or research-promoting organizations, all appointed by the Federal Minister for Research and Technology.

***The officer or at least one member of the committee must have the appropriate license, if the research work involves pathogenic or toxin-producing organisms. The project leader must possess adequate experience in microbiology and, for certain higher containment level work, knowledge about pathogens. The project leader is responsible specifically for planning and conducting the research, health monitoring of laboratory workers, informing the Central Commission and the biological safety officer or committee of the research and the planned safety measures, implementing Commission instructions, making regular reports to the Commission, maintaining a record of safety instruction, and training laboratory personnel.

†The term used in the United Kingdom to describe rDNA research is "genetic manipulation." Genetic manipulation is defined in the Genetic Manipulation Regulations as: the formation of new combinations of heritable material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid, or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.

scope, risk assessment, and enforcement. Like the NIH Guidelines, the U.K. guidelines have been gradually relaxed. Nevertheless, the guidelines in the United Kingdom are still regarded as more restrictive than those of the United States.

The guidelines for rDNA research in the United Kingdom are promulgated and administered by the Genetic Manipulation Advisory Group (GMAG) under the Health and Safety at Work Act of 1974 (24).* The guidelines apply to all research in the United Kingdom, not just that funded by the Government. Enforcement is the responsibility of the Health and Safety Executive (HSE), which is comparable to the U.S. Occupational Safety and Health Administration. HSE has taken no enforcement action to date.

As do the guidelines in all of the competitor countries, the GMAG guidelines establish four progressively more restrictive physical containment levels based on the perceived hazards of the research.** Facilities for the highest two levels must be examined by HSE inspectors before any rDNA research can be conducted to ensure that the GMAG requirements are met.

The GMAG guidelines also adopt the two-level biological containment approach of most of the other countries*** which is based on the degree of disability of the host-vector system being used. However, GMAG has also developed special rules for rDNA research involving experimental animals† and for work that involves the introduction of foreign nucleic acid into higher plants or into any plant pest.*

GMAG asssess the degree of potential hazard in a way somewhat different from the other countries, including the United States. GMAG considers three factors: access, expression, and damage.* As a general matter, the British classification system appears to require less stringent containment measures for some types of research than would be required in other countries. For example, the damage factors associated with interferon and insulin are quite low and work with these products would be classified as less risky in the United Kingdom than in some other countries (22).

The administrative framework for implementing the GMAG guidelines relies on institutional and governmental oversight. GMAG and HSE must be given advance notice of work involving rDNA except for certain self-cloning experiments.** Most work at the lowest two physical containment levels can go forward after notice. Although no express provision prohibits work at containment levels three and four before GMAG issues its advice, such premature work might violate the Health and Safety at Work Act, which carries criminal penalties. In addition, each institution conducting rDNA research is required to have certain personnel responsible for the research*** review, to forward notifications of proposed rDNA research to GMAG, and to suggest other health and safety actions that the institution might take.

Industrial or large scale applications of rDNA—that is, research involving the growth of self-propagating products of genetic material in volumes of 10 liters or more—are subject to special rules. GMAG reviews proposals to conduct such large-scale research on a case-by-case basis and visits each site, commenting on the safety measures proposed. GMAG expects that this review will involve "integration" of questions about physical and biologic containment. Whether this means that review of large-scale work will be stricter or more relaxed is unclear. GMAG has stated, however, that vaccine and antibiotic production can be done safely using ordinary chemical engineering measures—measures probably more relaxed than the containment-level measures required for small-scale research (20).

GMAG has recognized the potential commercial and industrial importance of genetic manipulation by establishing special confidentiality requirements for work that raises questions about commercial proper-

*The Government department with responsibility for GMAG policy is the Department of Education and Science, although this department has little expertise in such areas, particularly in comparison to the Department of Health and Social Security, which has a very limited role, via the Medical Research Council, in the oversight of genetic manipulation safety (25). GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended the relocation of the group to the Department of Health and Social Security (12). GMAG, now called the Health and Safety Commission Advisory Committee on Genetic Manipulation, has been moved to the Department of Health and Social Security.

**Certain DNA research is considered so safe as to not require containment. Laboratories conducting this research must instead follow simply the Guidelines for Microbiological Safety.

***France has four levels of biological containment.

†These require isolation of the animal, safe disposal of refuse and waste, and stricter rules for research in category III and IV laboratories (23).

*Plant pest is defined as "any living organism, other than a vertebrate animal, or any pathogen which is injurious to any plant, and includes any culture of such organism or pathogen." The work requires a special license from the Agricultural Ministries. The license will be issued only if the research is conducted according to the containment recommendations of GMAG, which include special rules for the handling of plants and preventing the dissemination of pollen and seed. The special plant rules do not cover experiments involving the introduction of plant nucleic acid into bacteria or other microorganisms (except plant pests), which are covered by the existing GMAG guidelines (21). It should be noted that the United Kingdom has adopted specific restrictions on the importation of such pests.

*"Access" is the possibility that escaped organisms will enter the human body and eventually reach susceptible cells. "Expression" is the possibility that a foreign gene incorporated into the gene sequence of an organism will be able to carry on or "express" its normal function, such as secretion of a toxin that the organism formerly did not secrete. "Damage" is the chance that a new gene sequence will cause physiological damage in the body to which it gains access once it is expressed (15,18,19,22).

**These include experiments using *E. coli* K12, *B. subtilis*, and *S. cerevisae* (17).

***These include a Biological Safety Officer familiar with the safety procedures for rDNA work and a Safety Committee to consider the containment and other safety measures proposed for genetic manipulation.

ty or patents. While confidentiality arrangements may vary from case to case, GMAG generally treats as confidential any material so labeled. Members of GMAG who have commercial interests in DNA work are prohibited from seeing such material or taking part in the discussion about it (17,20).

France.—The French guidelines for rDNA research (5) largely follow those of the United States. The guidelines were promulgated and are administered by the National Control Commission (Commission de Controle), which reports to the General Delegation of Scientific and General Research (Delegation Generale de la Recherche Scientifique et Technique). The French guidelines apply only to Government-funded research and require that scientists conducting such research notify the Control Commission of the planned research and in some cases obtain approval of the research. Local safety committees monitor ongoing research. The principal sanctions for failure to comply with the French guidelines are loss of Government funding or denial of approval to conduct research.

As in the United States, rDNA experiments in France must be conducted using certain physical and biological containment measures. The degree of containment depends on the risk of the work. Risk is assessed using a method very similar to that used in the United States. Research with DNA from oncogenic or highly pathogenic viruses is reviewed on a case-by-case basis but generally must be conducted according to the most stringent containment measures unless the oncogenic or highly pathogenic genes are eliminated before cloning.

In certain respects, the physical and biological containment requirements in the French guidelines differ from those in the United States. Although the French guidelines use four levels of physical containment as in the United States, they appear to be more flexible than the U.S. guidelines with respect to upgrading containment. In some cases, the French guidelines permit a laboratory's containment level to be upgraded without requiring construction of a new facility. Use of an approved safety cabinet will give the laboratory the next higher rating. If a safety cabinet is used to render a P3 laboratory equivalent to a P4 laboratory (the laboratory with the highest degree of containment), however, the National Control Commission must certify the facility. This upgrading system should expand the ranges of research that a French laboratory can do, as well as make research at higher containment levels less expensive. With respect to biological containment, the French guidelines use four levels, unlike the U.S. guidelines, which use two levels. Biological containment is based on the safety of the host-vector system. In effect, the French approach to biological containment appears quite similar to that of the United States, with the four levels of containment in France being finer gradations of the two levels used in the United States.

France allows biological agents containing rDNA to be imported and exported freely, although the French guidelines specify that certain measures must be met to safely transport and import rDNA materials. Large-scale research—i.e., experiments involving volumes of 10 liters or more—is not covered by the French guidelines for rDNA research, but Government oversight exists on a case-by-case basis.

SWITZERLAND

The Swiss have basically adopted the U.S. guidelines as their national rDNA research guidelines. Although the Swiss generally have amended their guidelines whenever the NIH Guidelines are amended, they are currently using a version based on the NIH Guidelines in effect in April 1982 (14).

There are other basic differences. The Swiss Government has no direct role in regulation of rDNA research; Swiss scientists instead have established a system of complete self-regulation. The Commission for Experimental Genetics (Kommission für Experimentelle Genetik) created by the Swiss Academy of Medical Sciences, is responsible for monitoring rDNA research. The guidelines that this commission has promulgated apply to all research involving rDNA in Switzerland, not only that funded by the Government. Moreover, the Swiss guidelines do not require special approval for work using cell culture volumes in excess of 10 liters.

The adminstrative structure for oversight in Switzerland is quite similar to that in the United States. The Commission for Experimental Genetics must approve certain experiments in advance, such as those involving the deliberate release into the environment of any organism containing rDNA. For two other classes of experiments, scientists must notify the commission but need not obtain approval. A final class of experiments are exempt from the guidelines. Principal investigators, safety officers, and institutional safety committees also bear oversight responsibility.

JAPAN

Japan's guidelines for rDNA research (11) are promulgated by the Ministry of Education (on recommendation by the Science Council). The guidelines apply only to publicly funded research, but private industry has followed them on a voluntary basis.

Each research institution is required under these guidelines to have laboratory supervisors, a safety committee, and a safety officer. The head of each research institution is also charged with specific duties

in supervising the rDNA work. The laboratory supervisor must submit plans of experiments and changes in plans to the head of the research institution for his or her approval. The head of the institution then consults with the safety committee—a body consisting of "members representing the relevant fields, and having high standards of both professional and technical knowledge and judgment"—to determine whether the plans comply with the guidelines, what training will be necessary, and other issues relevant to the safety of the research. The safety officer's role is to monitor the safety of ongoing work and to make appropriate reports to the safety committee.

The Japanese Government monitors rDNA research through two bodies: 1) the Council for Science and Technology, which advises the Prime Minister and which oversees work by private institutions; and 2) the Science Council, which advises the Ministry of Education and which supervises Government-funded university research. The Science Council and the Ministry of Education formerly had to approve university rDNA research; now it is only necessary that the university safety committee and the university president approve the experiment (7,9). Ministry authorization is still required, however, for experiments involving specified "especially dangerous" organisms and the release of such organisms into the environment.*

Certain experiments are effectively prohibited in Japan, because the Japanese guidelines for rDNA research specify no safety or containment rules for them. Effectively prohibited experiments include large-scale research (more than 20 liters of cell culture) and experiments in which recombinant organisms infect individual animals and plants, in which the source of the DNA is other than specified cells or host-vector systems. Such experiments can be done once containment standards are set, but setting such standards depends under the guidelines on confirmation of the safety of these experiments, which has not been completed for most types of this research. Large-scale research is possible if special permission is granted by the Ministry of Education; few companies have sought it successfully. Japanese companies using biotechnology are now lobbying heavily for relaxation of restrictions on large-scale research.

For permissible experiments, the Japanese rDNA research guidelines require physical and biological containment based on the perceived risk of each experiment. Under the guidelines, risk is assessed principally according to a phylogenic scale** but also according to the biological characteristics of the source of the DNA,* the purified or unpurified nature of the DNA,** the size of the clone number,*** and the scale of the cultivation.† Required physical containment measures resemble those under the NIH Guidelines and are categorized in a similar P_1 to P_4 scale. Similarly, the Japanese guidelines provide for two levels of biological containment.

Historically, the Japanese guidelines have been among the most restrictive in the world. Although Japan's guidelines have recently been relaxed considerably to bring them more into line with the guidelines in other countries, they are still the most restrictive of the ones surveyed in this appendix. Japanese companies applying biotechnology consider themselves handicapped in competition against their foreign counterparts for two principal reasons. First, hosts are limited in Japan, with a few exceptions, to *E. coli* and *B. subtilis*; other micro-organisms such as the actinomycetes, which is effective in producing antibiotics, therefore cannot be used. Second, work in Japan is limited to volumes of 20 liters or less, and successful commercial development requires larger fermenters (8). Japanese companies using biotechnology have mounted an intensive lobbying campaign to eliminate the 20-liter rule (10).

Environmental laws and regulations

UNITED STATES

The United States has no laws specifically directed toward biotechnology, but, as discussed in *Chapter 15: Health, Safety, and Environmental Regulation,* the Toxic Substance Control Act (15 U.S.C. §§2601-2629) and the Federal Insecticide, Fungicide, and Rodenticide Act (47 U.S.C. §136(a)-(y)) will play a major role in preventing any adverse environmental impacts from biotechnology products. In addition, there are several statutes dealing with pollution that would apply because they generally define pollutants or wastes so as to cover biological materials. They are:

- The Federal Water Pollution Control Act, as amended by the Clean Water Act of 1977 (33

*"Especially dangerous" experiments include the transplant of manipulated genes with toxicity into animal and plant cells. University presidents may still approve work with disease pathogens, including influenza and hepatitis viruses (7).

**DNA donor organisms closer phylogenically to humans are considered riskier.

*The relevant biological characteristics of the DNA are pathogenicity, toxin-producing ability, carcinogenicity, parasitic quality, drug resistance, likelihood of becoming an allergen, masked infective factors such as nucleic acids related to C-type virus, vulnerability to contamination by viruses, bacteria, or other parasites, ability to produce substances such hormones or metabolic intermediates affecting the metabolism of human beings, and possibility of causing ecological disturbances.

**Purified DNA, proved to carry only nonhazardous genes, is deemed safer than unpurified DNA.

***The fewer the number of clones, the safer the experiment is, on the reasoning that a lower number will reduce the probability that harmful genes will appear.

†Smaller-scale experiments are considered safer than large-scale ones.

U.S.C. §§1251-1376, *as amended by* Public Law No. 95-217, 91 Stat. 1566 (1977)).
- The Marine Protection, Research and Sanctuaries Act of 1972 (33 U.S.C. §§1401, 1402, 1411-1421, 1441-1445).
- The Clean Air Act (42 U.S.C. §§7401-7508, 7521-7574, 7601-7626).
- The Solid Waste Disposal Act, as amended by the Resource Conservation and Recovery Act of 1976 (42 U.S.C. §§6901-6987, *as amended by* Public Law No. 94-580, 90 Stat. 2795 (1976)).

Under the Federal Water Pollution Control Act, as amended, the Environmental Protection Agency has promulgated regulations on wastewater from the manufacture of pharmaceuticals by fermentation (4 C.F.R. Part 439 (1982)).

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.—Although the EEC has issued no directives or taken any other action specifically to regulate the environmental effects of biotechnology, several general directives concerning waste disposal and water pollution will be applicable to biotechnological products (30,31,33). The EEC's environmental regulations are general and flexible, giving maximum discretion and authority to the bureaucrats that implement them.

Companies using biotechnology will encounter environmental regulation in manufacturing biotechnological products in the EEC member states and in exporting products to those states. Under the premarketing notification requirement imposed by the Sixth Amendment to the EEC's dangerous substances directive (32),* a firm must test a new chemical before marketing, must provide the proper authorities in the member states where the product is to be marketed with the results of the "base test" (minimum testing requirements), and must conduct such further tests as those authorities may deem necessary before approval may be granted. Since many biotechnology products will likely qualify as "new chemicals," the Sixth Amendment's requirements would apply. Of course, a firm seeking to build a plant to manufacture biotechnology products in a member state would be required not only to secure "new chemical" approval, but also to comply with the more comprehensive system of environmental regulation in the member state.

Federal Republic of Germany.—The Federal Republic of Germany is a federal state, and under its Constitution, the 11 Länder (States) share power with the Federal Government. In controlling pollution, poisonous substances, and waste, the Federal Government and the Länder have concurrent jurisdiction, but the Länder may pass laws in these areas only if the Federal Government has not done so. In environmental protection, land use, and water law, the Federal Government may enact broad "framework" legislation, but the Länder must implement the general Federal laws by enacting detailed legislation adapted to the conditions of each State.

The Ministry of the Interior (Bundesministerium Des Innern) coordinates the environmental policies of the West German Federal Government, including environmental planning, waste and water management, and control of air pollution. The Federal Environmental Agency (Umweltbundesamt), which is more concerned with environmental protection, furthers Federal environmental policies by developing planning programs and performing research. Coordination of Federal environmental programs also is conducted by a Cabinet Committee for Environmental Questions (Arbeitsgemeinschaft für Umweltfragen E.V.).

The only environmental regulations directed specifically at biotechnology are contained in the Federal Republic of Germany's guidelines for rDNA research (39). The German guidelines impose requirements on disposal of waste from rDNA experiments, requirements that depend on the containment level of the work involved. In no case may biological agents containing rDNA be released into the environment. Experimental plants and animals containing rDNA must be kept under conditions of isolation. All rDNA material may be removed from the laboratory only in airtight packaging and must eventually be destroyed, usually by incineration. All wastes containing microorganisms or nucleic acids must be sterilized or denatured. Waste water from experiments at the L3 or L4 level must be decontaminated.

Apart from the rDNA research guidelines, it appears that the Federal Republic of Germany's legislation and implementing regulations do not specifically regulate environmental impacts from biotechnological products and processes. Instead, companies using biotechnology would appear to be subject, like other firms in West Germany, to a series of general environmental protection laws and regulations.

The most general of these laws is the Chemicals Act (40), which is designed to protect humans and the environment from all types of dangerous substances. This law set up compulsory testing of substances and compulsory classification, labeling, and packaging of dangerous substances and materials. It implements in the Federal Republic of Germany the Sixth Amendment to the EEC's environmental protection directive.

*The first directive in the field of dangerous substances was Council Directive of June 27, 1967 (29).

Other relevant statutes in the Federal Republic of Germany are the following: the Law for the Prevention of Harmful Effects on the Environment Caused by Air Pollution, Noise, Vibration, and Similar Phenomena (Federal Emission Control Law) (37), the Law on Disposal of Wastes (36). Act on Regulation of Matters Relating to Water (Federal Water Act) (35), and the Waste Water Charges Act (Waste Water Law) (38).

A Committee of the German Society for Chemical Engineering (Deutsche Gesellschaft für chemisches Apparatewesen E.V.) completed a study of the risks specifically associated with biotechnology and of the relevant statutory and regulatory provisions that could be used to control those risks (34). The study concluded that adequate legal authority exists in the Federal Republic of Germany for regulating the kinds of hazards most likely to arise in connection with biotechnology.

United Kingdom.—Responsibility for protection of the environment in the United Kingdom lies primarily with the Department of the Environment. In addition, a Royal Commission on Environmental Pollution was established in 1970 to advise the government on environmental issues. As in the United States, much environmental regulation in the United Kingdom is the responsibility of local governments.

Although the United Kingdom has an extensive statutory environmental protection scheme, there is no legislation or regulation specifically concerned with environmental impacts of biotechnological products and processes. Companies using biotechnology, therefore, would be subject to the general environmental protection laws and regulations.

The Control of Pollution Act of 1974 (53), provides in chapter 40 for licensing of sites for the disposal of "controlled waste," defined as household, industrial, and commercial waste, both on land and in water. The penalties for unlicensed disposal are fines and imprisonment. The law is to be phased in between July 1983 and July 1986. Waste products of biotechnological processes would appear to be covered by this law.

France.—The principal environmental protection agency in France is the Ministry of the Environment (Ministére de l'Environnement). Environmental protection legislation applies broadly to activities that degrade the environment in a variety of ways. The touchstone of most regulation is not the nature of a particular activity, but whether it produces environmentally adverse effects. To the extent that biotechnological products and processes produce such effects, they would be subject to these laws.

The most general environmental statute is the Law on Installations Classified for Purposes of Environmental Protection (44). This law covers all types of risk to humans and the environment resulting from the activities of various types of facilities, including but not limited to industrial and commercial establishments. These facilities are subject to requirements specific to the type of danger or inconvenience involved. This determination rests largely in the hands of local authorities, who have a continuing right of access to the regulated facilities. Failure to comply with the law may result in administrative and criminal penalties. No rules specifically aimed at biotechnology facilities have yet been adopted under the authority of this law.

The Chemicals Control Law of France (45), which predates the Sixth Amendment to the EEC's dangerous substances directive, would apply to chemical compounds produced by biotechnology. This law aims to protect human beings and the environment against risks arising from both naturally occurring and industrially produced chemicals. Any producer or importer seeking to import or manufacture commercially a chemical which has never been placed on the French market before must notify the relevant authority, provide certain information, and submit to whatever conditions may be imposed.*

Two other statutes would be particularly relevant to biotechnology. They are the Law on Waste Disposal and Recovery of Materials (43) and the Act on the Administration and Classification of Waters and the Control of Water Pollution (42).

SWITZERLAND

Although the Swiss rDNA research guidelines prohibit the release of biological agents containing rDNA into the environment, they do not mention effects on the environment from other forms of waste which may result from applications of biotechnology. These would presumably be regulated in Switzerland under Article 24 *septies* (seventh) of the Federal Constitution, which gives the Federal Government far-reaching powers to pass environmental laws.

Legislation under this article has been sparse, however, and there are apparently no confederal rules in Switzerland on air pollution, noise abatement, or waste disposal. Only in the area of water pollution has legislation been enacted. The Water Protection Act of October 8, 1971 (51), seeks to ensure the quality of the nation's water by means of sweeping protective measures which cover all natural, artificial, ground, and surface waters.

In addition, Article 6 of the Federal Act on Work in Industry, Trade, and Commerce (52) requires employers to protect the area surrounding their business enterprise from harm or discomfort by taking all measures shown necessary by experience and found to be technically feasible and appropriate.

*Decree No. 79-35 describes the technical dossier to be provided when providing notice concerning a new chemical substance (41).

JAPAN

Specific measures governing environmental effects of biotechnology applications have not been prepared by the Japanese Government. The regulations applicable to biotechnology are those applicable to all industry. The agencies with responsibility for environmental protection in Japan include the Environmental Protection Agency, the Ministry of International Trade and Industry (MITI), the Ministry of Health and Welfare, and the Ministry of Agriculture, Forestry, and Fishery. The Environmental Protection Agency has jurisdiction over basic policy, general coordination of governmental pollution control activity, budgetary policy, and research and investigation.

The Basic Law for Environmental Pollution Control (46) establishes fundamental national principles and policies and establishes the basic regulatory framework for environmental protection in Japan. The law applies to air, water, soil, and other pollution. It empowers the Central Government to promulgate and enforce environmental quality standards necessary to protect the public health and conserve natural resources. This and other environmental laws are supplemented by and implemented through Cabinet orders issued by the Prime Minister, and through ministerial orders and Environmental Protection Agency notifications. Administrative guidance is used to regulate pollution from specific industrial plants and industries. Local governments have responsibility with the Central Government in monitoring pollution and for regulation, and they may set more stringent standards than those set by the Central Government.

Japan's Basic Law for Environmental Pollution Control is supplemented by laws aimed at specific types of pollution. These include the Air Pollution Control Law (47), the Water Pollution Control Law (49) and the Waste Management Law (48).

Finally, the Chemical Substances Control Law (50) requires manufacturers to notify the Japanese Government and to test all new chemical substances to be produced in quantities exceeding 100 kilograms. Chemicals are tested for their biodegradability and bioaccumulation. Manufacturers and importers of chemical substances must notify MITI of their intent to use or market a new chemical. Japan's Environmental Protection Agency monitors the effect of chemicals in the air and water, and the Ministry of Health and Welfare administers laws on chemical products.

Regulation of worker health and safety

UNITED STATES

The Occupational Safety and Health Administration (OSHA), which is part of the U.S. Department of Labor, is the agency primarily responsible for worker safety and health. OSHA's authority derives from the Occupational Safety and Health Act of 1970 (29 U.S.C. §§651-678) which creates a broad mechanism for protecting workers from workplace hazards. Section 5(a)(1) of the act requires U.S. employers to furnish their employees with a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm." Section 5(a)(2) requires employers to comply with safety and health standards set by the U.S. Secretary of Labor. Under a recent U.S. Supreme Court decision (62), the Secretary of Labor can promulgate permanent standards for toxic substances or harmful physical agents only after a finding that the standard is "reasonably necessary to remedy a significant risk of material health impairment." Section 6(c) of the act permits the Secretary of Labor to promulgate emergency temporary standards after a finding that employees are "exposed to grave danger." The statute also creates the National Institute for Occupational Safety and Health to gather data, assess risks, and recommend safety and health standards to OSHA. Other sections grant OSHA authority to require record keeping and medical surveillance and to enforce the act and its regulations through civil and criminal penalties.

Given the language quoted above regarding risk and hazard, the applicability of the Occupational Safety and Health Act to biotechnology would be limited when risk is conjectural. However, the act would be applicable to large-scale processes using known human toxins, pathogens, or their DNA. It also would be applicable to physical hazards presented by the fermentation process, such as temperature, pressure, and toxic solvents. OSHA has not promulgated health and safety standards for bioprocesses and has made no statements on how it might apply the act to biotechnology.

OSHA arguably has authority to require a medical surveillance program, although this is not clear cut. Section 8(c)(1) of the Occupational Safety and Health Act requires employers to "make, keep and preserve" such records as the U.S. Secretary of Labor prescribes

by regulation as "necessary or appropriate for the enforcement of this act or for developing information regarding the causes and prevention of occupational accidents and illness." Further, section 8(c)(2) of the act authorizes the Secretary of Labor to require employers to "maintain accurate records of, and to make periodic reports on, work-related deaths, injuries and illnesses other than minor injuries . . . ." Since the purpose of a surveillance program would be to develop information on any occupational disease related to biotechnology, section 8(c)(1) of the Occupational Safety and Health Act would seem to apply. In addition, the information developed in such a program would also be the kind of information necessary for compliance with regulations promulgated under section 8(c)(2). Employers, on the other hand, might argue that both sections require an initial showing that biotechnology causes occupational disease.

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.—Although its powers in the area of worker health and safety regulation are limited and indirect, the EEC has attempted to ensure at least minimal protection for most industrial workers. In 1980, the EEC adopted a directive that required each member state to adopt a variety of measures to protect workers' health and safety (54).* The directive covers work that does or may involve a "chemical, physical or biological agent . . . likely to be harmful to health." The directive is quite general; the specific content and substance is left to the discretion of the member states.

The directive does not refer explicitly to rDNA work or other applications of biotechnology. Thus, the question of how worker health and safety laws will affect the biotechnology industry is left to the discretion of each member state.

Federal Republic of Germany.—The rDNA research guidelines of the Federal Republic of Germany (57) provide specifically for the health-monitoring and training of laboratory workers. Each worker at an rDNA laboratory that is above the lowest containment level must have a pre-employment examination by an authorized doctor. If the results of this examination reveal a susceptibility to hazards which may be involved in the contemplated research, the worker may not be employed. Appropriate immunizations are required for work with pathogenic micro-organisms. Blood serum from the worker must be taken at the first examination and at the end of employment and stored until at least 2 years after the end of participation in the research. All workers must receive instruction before the research begins and annually thereafter in the methods to be used, the conceivable hazards of the experiment, and the protective measures to be applied.

The Federal Republic of Germany's general worker health and safety regulations would also apply to commercial uses of biotechnology. At the Federal level, substantive workplace health and safety requirements are stated in the Act Respecting Plant Physicians, Safety Engineers, and Occupational Safety Specialists (55),* in the Ordinance Respecting Workplaces (56),** and in rules that are issued by the Dangerous Industrial Substances Committee (Ausschus für Gefährliche Arbeitsstoffe) of the Federal Ministry of Labor and Social Affairs (Bundesministerium für Arbeit und Sozialordnung) concerning the marketing and handling of dangerous substances (70).

Within this Federal framework, a significant regulatory role is played in the Federal Republic of Germany by accident insurance funds. These funds are authorized by statute to issue regulations setting standards for workplace health and safety (58). When approved by the Federal Minister of Labor and Social Affairs, the regulations become binding on covered employers. The funds, which are organized by indus-

*The required measures include the following:
1. limitations on the use of chemical, physical or biological agents in the workplace;
2. limitations on the number of workers exposed or likely to be exposed to such agents;
3. engineering controls;
4. establishment of exposure limit values for such agents and methods of assessing their level;
5. safe working procedures and methods;
6. collective protection measures;
7. individual protection measures, where exposure cannot reasonably be avoided by other means;
8. hygiene measures;
9. information for workers on potential risks associated with the exposures to such agents, technical preventive measures workers should take, and precautions to be taken by the employer and the workers;
10. use of warning and safety signs;
11. surveillance of workers' health;
12. maintenance of current records of exposure levels, workers exposed, and medical records;
13. emergency procedures; and
14. if necessary, general or limited bans on an agent from which protection cannot be adequately ensured.

*The Act Respecting Plant Physicians, Safety Engineers, and Occupational Safety Specialists requires each employer to appoint a plant physician and an occupational safety specialist. The appointed physician must conduct medical examinations of employees, advise the employer concerning health and safety precautions (including technical equipment and personal protective devices), supervise workplace safety, investigate and report to the employer on the causes of work-related illnesses, and instruct employees concerning the dangers to which they are exposed in the course of their work and the measures available to avert such dangers.

**Section 3(1)1 of the Ordinance Respecting Workplaces imposes a general obligation on employers to operate workplaces in accordance with both the law and the "generally recognized rules of safety engineering, occupational medicine and hygiene and any other scientifically established findings in the labor field." Its specific requirements, however, relate to physical design and construction.

try, are authorized not only to promulgate the applicable standards, but also to enforce them through inspections and fines. Because all employers must carry accident insurance, the funds have a large role in occupational safety and health.

United Kingdom.—Guidelines promulgated by GMAG contain specific requirements regarding the health and safety of laboratory workers who are involved in rDNA research (67,68,69) (see discussion of "Recombinant DNA Research Guidelines" above). Each laboratory must appoint a supervisory medical officer with experience in public health, infectious diseases, or occupational medicine, and conduct health reviews of all workers before they start work involving genetic manipulation. The reviews are designed to check workers for particular susceptibilities and to assist in determining whether any laboratory-contracted illnesses have developed. If a worker's medical history indicates that the worker's participation in genetic manipulation may be particularly hazardous, appropriate steps may be required to prevent his or her exposure to genetic manipulation work. The institution must also investigate any unexplained illiness, and if a laboratory-contracted infection is suspected, the institution must inform both the worker and the worker's physician as well as GMAG and other authorities.

Companies using biotechnology in the United Kingdom must also fulfill the obligations imposed on virtually all employers and manufacturers by the Health and Safety at Work Act of 1974 (66). In general, an employer must ensure so far as reasonably practicable that employees are not exposed to health and safety risks and to inform them of the risks that are created. Employees also have certain obligations under the act.

Health and safety regulations in the United Kingdom, under the Health and Safety at Work Act, are promulgated by the Secretary of State, on the advice of the Health and Safety Commission. The Health and Safety Commission also supervises efforts to improve worker health and safety, makes necessary investigations, and may approve codes of practice for particular industries.

There is no code of practice for biotechnology other than the GMAG guidelines for rDNA research. If a broader code were developed, it would be only advisory; violation of a code is not per se a violation of the Health and Safety Work Act but is only evidence tending to show a violation of the act. HSE (and local authorities) enforce the act through appointed inspectors, who may issue "notices" prohibiting certain activities as too risky or requiring remedial actions. Violators of the act are subject to civil and criminal penalties.

France.—The guidelines for rDNA research in France contain no provisions dealing expressly with the health or the health-monitoring of laboratory workers. The guidelines do require, however, that scientists and technicians be familiar with the physical and biological containment measures involved in rDNA research and be prepared to take emergency action in the event of an accident.

The formulation and implementation of general policy on the prevention of occupational hazards in France is the responsibility of the Central Council for the Prevention of Occupational Hazards (Conseil Central pour la Prevention des Risques Professionalle). So far, the council has not specifically addressed worker health problems arising from biotechnology.

Specific employee health and safety regulations are promulgated and enforced in France by the Minister of Labor, who is in charge of conditions in industrial and commercial establishments, and by the Minister of Agriculture, who is granted the same authority over agricultural facilities.

An occupational safety and health committee must be set up in any industrial establishment normally employing 50 or more workers (59,60). The committee advises management on safety procedures and periodically inspects the establishment to ensure that the safety laws and regulations are being applied. It also is supposed to take immediate action to avert imminent danger at the facility and to conduct an inquiry into the causes of any accident or serious occupational disease.

The manufacture of chemical substances potentially harmful to workers is also regulated by statute (61). Prior to the marketing of any substance or preparation that may involve a danger to workers, the manufacturer, importer, or seller must file with a Government-approved laboratory the information necessary to assess the risks of the manufacturing process. If the chemical substance has already been placed on the market, its manufacture, sale, transfer, or use may be restricted or prohibited in the interests of occupational health and safety.

SWITZERLAND

By following the U.S. guidelines for rDNA research, Switzerland applies to rDNA work the worker health and safety rules set out therein. Thus, each research institution in Switzerland must ensure that laboratory workers receive appropriate training, determine whether a health surveillance program is appropriate, and report to the Commission for Experimental Genetics any work-related accidents or illness. The re-

sponsibility for assessing the training provided to personnel and the adopting emergency plans for accidental spills and personnel contamination rests with the institution's biohazards committee. The biological safety officer must report work-related accidents or illnesses and assist in developing emergency plans. The group leader is obligated to train and supervise his or her staff.

Worker health and safety not specifically related to rDNA research is regulated in Switzerland on the cantonal rather than the confederal level. In one canton, Geneva, an advisory committee has been established to serve as a channel of communication between public authorities and business and to develop proposals on worker health and safety. The committee meets four times a year (63). The other cantons do not have such committees.

JAPAN

The basic law governing worker health and safety in Japan is the Industrial Safety and Health Law of 1972 (64).* This law imposes on employers health and safety obligations which are comprehensive in scope but very general in actual language. Among these obligations is the duty to take necessary measures to prevent health impairment caused by substances, agents, and conditions found in the workplace. The law vests broad discretion in the Japanese Ministry of Labor to determine when regulation is appropriate and what kinds of precautions an employer must take. Employers who manufacture, import, or use "chemical substances" may be subject to special requirements. Medical examinations must be conducted on all employees, but employers may also be required to provide special tests for employees engaged in harmful work. At the present time, no regulations have been addressed specifically to biotechnology.

The Industrial Safety and Health Law includes a stringent enforcement mechanism. Substantial criminal penalties and fines are imposed for violations. For the most serious violations, offending employers may also be ordered to close or alter their operations.

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*This discussion is based on a 1980 publication of the Japanese Government entitled *Labour Laws of Japan* (65), and does not reflect changes that may have been subsequently enacted.

**Note: S.Ct. = Supreme Court Reporter.

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Appendix G

Intellectual Property Law

Chapter 16: Intellectual Property Law discusses three areas of intellectual property law that are particularly relevant to the commercialization of biotechnology: patents, trade secrets, and plant breeders' rights. That chapter focuses initially on the United States and then discusses the laws of the other countries by comparing them to the U.S. laws. This appendix elaborates on the intellectual property laws of the five countries likely to be the major competitors of the United States in the commercialization of biotechnology—Japan, the Federal Republic of Germany, the United Kingdom, Switzerland, and France—and is the basis for the comparisons in chapter 16. The first section examines the laws of the four European countries, and the second section considers the intellectual property law of Japan.

Intellectual property laws of the Federal Republic of Germany, the United Kingdom, Switzerland, and France

The Federal Republic of Germany, the United Kingdom, Switzerland, and France, have created an intellectual property law similar to that of the United States. Important differences exist, however, especially on a country-by-country basis. Patent laws, laws of trade secrets, and plant breeders' rights in these countries are reviewed in the sections that follow.

PATENT LAW

Eleven European countries, including the Federal Republic of Germany, the United Kingdom, Switzerland, and France, have agreed to a treaty, the European Patent Convention (EPC), that creates a European patent system (8). These countries also have patent systems created by national laws.

European Patent Convention.—The EPC entered into force on October 7, 1977, and as of January 1, 1983, the treaty had been ratified by Belgium, the Federal Republic of Germany, France, the United Kingdom, Luxembourg, the Netherlands, Switzerland, Sweden, Italy, Austria, and Liechtenstein. The EPC establishes a legal system for granting European patents through a single supranational European Patent Office and a uniform procedural system with respect to patent applications. The single European patent application, if granted, becomes a bundle of individual European patents, one for each of the countries designated by the applicant.

The EPC system and the resulting patents exist in parallel with the patent systems of the member countries. The ultimate goal is for each of the member countries to adopt in its national law the same substantive law of patents set forth in the EPC; in the beginning, however, and perhaps always to a certain extent, differences in substantive law will exist between countries. Enforcement of European patents is handled by the same national authorities that are responsible for handling enforcement of national patents in the EPC member countries (EPC art. 64(3)).

Patentable Subject Matter. Under the EPC, patents can be granted for any invention susceptible of industrial application* that is new and involves an inventive step (EPC art. 52(1)). This broad definition is narrowed by specific exclusions. Discoveries, scientific theories, and naturally occurring products, for example, are not considered patentable inventions. Methods of treating humans or animals and related diagnostic methods are similarly excluded from patentability, although products so used are not. Finally, plant or animal varieties and essentially biological processes for the production of plants or animals are not patentable; however, their exclusion does not apply to microbiological processes or the products of such processes (EPC art. 53(a) and (b)). The question of whether a process is "essentially biological" depends on the extent to which there is technological intervention by humans in the process. Under the Guidelines for Examination of the European Patent Office, if such intervention plays a significant part in determining or controlling the result it is desired to achieve, the process would not be excluded (G.E. pt. C(IV)(3.4)).

Under EPC articles 52(1) and 53(b), as interpreted by the European Patent Office, microbiological inventions of the following kind would be patentable: 1) micro-organisms (including viruses and cell lines), 2) processes for making them, 3) processes using them, 4) products obtained from microbiological processes, and 5) DNA and RNA molecules or subcellular units (e.g., plasmids) (G.E. pt. C(IV)(3.5-3.6)). The European Patent Office also stated that the term "micro-organism" covers plasmids.

One major area that will require further clarification, however, is whether naturally occurring micro-organisms, subcellular units, or DNA and RNA molecules are patentable. Under the EPC, there appears to be no absolute bar, it will simply be a question of

*The term industrial application includes agricultural applications (EPC art. 57). This is actually the standard for utility under the EPC.

the degree to which such subject matter is naturally available and of the effort required to identify and/or isolate it (G.E. pt. C(IV)(2.1)).

Novelty. Under the EPC, an invention is new if it is not part of the state-of-the-art on the effective filing date of the patent application (EPC art. 54(1)). The EPC provides that the state-of-the-art comprises everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application (EPC art. 54(2)).* There are no restrictions as regards the geographical location where, or the language or manner in which, the relevant information is made available to the public.

This is known as an "absolute novelty standard" because certain public disclosures even by the inventor himself/herself before the filing can result in loss of patent rights. The absolute novelty standard is a major distinction of European patent law from that of the United States.

Standard of Invention. The EPC defines inventive step as follows (EPC art. 56):

> An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art.

This definition parallels the definition of nonobviousness under section 103 of the U.S. patent law (35 U.S.C. 103), except that §103 refers to a person of *ordinary* skill in the art and also to the differences between the invention and the prior art.

The European Patent Office's Guidelines for Examination indicate that the test of obviousness to be applied by the European patent examiners is consistent with the objective test under section 103 (G.E. pt. C(IV)(9.9)). In particular, the European Patent Office apparently will consider such factors as unexpected advantages, evidence of immediate commercial success, and evidence of long felt need (18,30).

Disclosure Requirements. The basic disclosure requirement under the EPC is as follows (EPC art. 83):

> The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

This enablement requirement has as its essential element the concept of the reproducibility or repeatability; i.e., the making of the invention must not be dependent on chance. For micro-organisms, enablement generally is satisfied by depositing a culture of the micro-organism in a depository to which the public has access and referencing the depository and file number in the patent application. However, a deposit need not be made if the micro-organism is already publicly available or can be described so as to be reproducible.

Deposit Requirements. If a deposit is required, it must be made with a recognized depository not later than the date the application is filed. The European Patent Office publishes a list of recognized depositories, and, since it adheres to the Budapest Treaty, the European Patent Office also recognizes deposits made pursuant to the treaty. Cultures must be maintained for at least 30 years.

Since all European patent applications are published approximately 18 months after their filing date (unless previously withdrawn) (EPC art. 93(1)), the deposited micro-organism can become publicly available before the patent has been issued. The EPC sets up certain safeguards on access to prevent abuse.*

Claims. Claims in an EPC application must define the subject matter for which protection is sought, be clear and concise, and be supported by the description (EPC art. 84; G.E. A(III)(4)-(6)).

Enforcement. Under the EPC, European patents are granted for a term of 20 years. Enforcement is handled by the national courts of the EPC member countries. The question of infringement is considered under national law principles, but taking account of treaty requirements regarding claim interpretation. European patents may be revoked by a national court on certain specified grounds (EPC arts. 138(1) and 139(2)).

Patent Laws of the Federal Republic of Germany, the United Kingdom, Switzerland, and France.—As described below, the patent laws in the Federal Republic of Germany, the United Kingdom, Switzerland, and France vary with respect to certain provisions regarding patentable subject matter, novelty, disclosure requirements, or enforcement.

Patentable Subject Matter. The provisions defining patentable subject matter in the patent law of the Federal Republic of Germany are virtually identical with the corresponding provisions of the EPC. Regarding biological inventions, the Federal Republic of Germany has been a pioneer in recognizing the patentability of micro-organisms per se. After deciding in 1969 that patents could be obtained for inventions in the field of biology (22), the German Federal Supreme Court specifically held in 1975 that micro-organisms per se constituted patentable subject matter (2). Therefore, in line with EPC law, the same categories of biologi-

*Implicit in the concept of the state-of-the-art is the concept that the public disclosure must be enabling.

*The safeguards are as follows: 1) the recipient may not pass the sample on to anyone else unless or until the application is abandoned or all European patents have expired; 2) the recipient can only use the micro-organism for experimental purposes until the application is abandoned or a patent issues; 3) the patentee can elect to permit samples to be given only to certain neutral experts (EPC Rule 28(3)-(4)).

cal inventions are patentable in principle according to West German law.*

In its Patent Act of 1977, the United Kingdom adopted the EPC definition of patentable subject matter. The British Patent Office has taken the position that all of the five general categories of biological subject matter listed above are patentable (27).

Section 1a of the Swiss Patent Law corresponds to EPC Article 53(b), stating that "micro-biological methods and products obtained thereby shall be patentable." There is no specific provision in the law which states that "discoveries" are not patentable subject matter, although prior case law recognizes such an exclusion (5).

Nevertheless, it appears that Swiss practice varies considerably from that under the EPC. According to the Swiss Patent Office, micro-organisms per se are not patentable, including human-made ones. The Patent Office has apparently not yet taken a position on the patentability of DNA and RNA molecules or subcellar units (7).

As to the remaining categories of subject matter involving micro-organisms, the Swiss law provides for patent protection in the same manner as the EPC. Furthermore, since microbiological processes are explicitly patentable, some protection is obtainable for micro-organisms per se under Swiss law, because section 8 of the Swiss Patent Act provides that the protection of a patent claiming a process shall extend also to the immediate products of the process.

The substantive law regarding patentable subject matter in France corresponds to the EPC, specifically in all respects which are relevant to micro-organisms. However, article 7 of the French patent law (1978) excludes patents on plant varieties to the extent to which such varieties are protectable under French plant protection legislation.

Utility. All of the EPC countries have adopted the EPC requirement for utility—that the invention be useful in industry (including agriculture) (24). However, Swiss law restricts the concept of industrial use by excluding private use and use for research (15).

Novelty. The Federal Republic of Germany, United Kingdom, and France have adopted the EPC absolute novelty standard in their latest national patent laws (24). Switzerland also has adopted the absolute novelty standard with one technical exception relating to prior filed Swiss or EPC applications (Swiss Patent Law, art. 7a).

Disclosure and Deposit Requirements. The statutory provision of West German law governing disclosure requirements (West German patent law sec. 35(2), 1981) is identical to article 83 of the EPC, i.e., enablement of a person skilled in the art. However, there are certain differences in practice regarding biological inventions. By court decision, a new micro-organism cannot be patented unless the application discloses a *reproducible* method of producing it. Thus, a deposit without an enabling written description is inadequate to support a claim to the micro-organism itself (3,26). This is in marked contrast to the law of the other countries. On the other hand, a deposit alone is sufficient to support a claim to a method of using a new micro-organism (32). A required deposit must be made no later than the filing date (or the priority date) (32). Although the applicant must furnish samples of the deposit to third parties after publication of the application, the applicant can require that the samples not be removed from the Federal Republic of Germany and not be passed on to others.

The British Patents Act, in section 14(3), has the same enablement standard as the EPC. In the case of an invention involving a micro-organism, the application as filed must contain the relevant information on the characteristics of the micro-organisms, to the extent known to the applicant. The required deposit must be made no later than the filing date or the priority date (British Patent Office Rule 17(1) (1978)). Samples will be publicly available when the application is published 18 months after the priority date. Those who request samples must undertake not to pass them on to others and to use them only for experimentation until the patent is granted or the application is abandoned (British Patent Office Rule 17(2) (1978)).

The Swiss Patent Act, in section 50 (1978), contains the same enablement standard as the EPC. The Patent Ordinance, section 26(6) (1977), also requires that the description explain how the invention may be used industrially. In the case where the micro-organism is not publicly available or cannot be described in an enabling manner, a deposit in a recognized depository is required. The application must identify the depository, the deposit number, and the date of the deposit (Swiss Guidelines for Examination, Z-14.3 and 14.4, May 12, 1980). In the case of a micro-organism that is available to the public, identification of a known source need not be disclosed in the application as originally filed. Such information (e.g., reference to a deposit that was publicly available on the application filing date) can be added to the application after the filing date (Swiss Guidelines for Examination, Z-13.2, May 12, 1980). Since Swiss applications are not published before the patent is granted, culture samples are not required to be furnished until the patent is granted. Then samples are released only to identified

*The German Federal Patent Court has also upheld a patent on a micro-organism obtained as a pure culture from an unpurified, naturally occurring state through a selective culture process (16).

parties, who undertake not to pass them on (Swiss Patent Ordinance, sec. 27(6)).

The French patent law, in article 14bis (1978), sets forth the same standard of enablement as the EPC. Publicly available micro-organisms need not be deposited. Required deposits must be made in a Government-authorized depository no later than the priority date. A regulation under the statute (Decree No. 79-822 on Sept. 19, 1979, amended by Decree No. 81-865 issued on Sept. 11, 1981) contains provisions regarding the content of a French patent application relating to a micro-organism that are consistent with EPC Rule 28. Thus, the application must contain (French patent law, art. 10):

- the available information as to the characteristics of the micro-organism, and
- an identification of the depository and deposit number.

Access to the deposit, which is granted at the time of publication, can be limited to recognized experts until the patent is granted or the application is abandoned (French patent law, art. 31).

Claim Practice. Claims acceptable under EPC practice should be acceptable in the four countries. Switzerland, however, will not accept claims to a micro-organism per se.

*Enforcement.** Subject to specific requirements contained in the EPC regarding claim interpretation, European patents as well as national patents are interpreted and considered with respect to the questions of both infringement and validity in accordance with national law in the EPC member countries.

In the Federal Republic of Germany, an infringer is broadly defined as any person who makes use of a patented invention. Protection for a patented process extends to the product directly obtained by that process. Provisional rights for reasonable compensation are given for applications which have been published but not yet granted.

Infringement was defined for the first time in the new British law, and a separate Patent Court was established for the purpose of trying patent infringement cases. Infringement includes the acts of making, using, importing, disposing of, or offering to dispose of an infringing product. Similar provisions are provided with regard to a process and with regard to a product obtained by a patented process. Provisional rights are given for published applications, and full recovery for damages from the date of publication may be obtained after grant. The 1977 act also provides that the scope of the patent may extend beyond the literal meaning of the words of the claims.

Swiss law defines infringement to include any unlawful utilization of the patent invention, including imitation. Patent protection for a process also extends to products which are directly made from the process. The patent rights begin at publication, but suit for damages may be initiated only after grant. Criminal sanctions may also be imposed as well as confiscation and destruction of the infringing goods.

Infringement in France is defined broadly to include the acts of manufacture, offer, commercial disposal, use, or import of the patented product. However, for actions other than manufacturing or importing, there is no liability unless the acts were committed with knowledge of infringement. Process patents extend coverage to products obtained directly by the process. Provisional rights for published applications are limited to reasonable compensation. Suit may be brought before grant but will probably be suspended until after grant.

In countries with national laws providing for provisional protection after preliminary publications—namely, the Federal Republic of Germany, the United Kingdom, and France—there should be no difference in treatment between published national applications and published European applications. In Britain and France, damages may be recovered for published national or European applications. Moreover, in France, damages are recoverable from the time of notification to the infringer of the patent application contents. Only reasonable compensation may be obtained in West Germany.

The EPC also provides for provisional protection after publication of a European patent application. Generally, the right is limited to recovery of damages after the patent issues.

In Switzerland, on the other hand, provisional protection is not provided. But, in ratifying the EPC, Switzerland has provided a provisional remedy for European patent applications.

Remedies for infringement include injunctions and monetary damages. In addition, as a general rule, the loser pays most or all of the costs of litigation of the winning party. Finally, in most cases, the infringing goods will be destroyed or handed over to the patentee.

Criminal sanctions exist in the national patent laws of the Federal Republic of Germany and Switzerland, but they are not of much practical importance.

LAW OF TRADE SECRETS

National laws that protect trade secrets, confidential information, and know-how (hereinafter sometimes referred to collectively as "proprietary information") are designed to prevent the misappropriation

*The discussion in this section is based substantially on ch. III in Schwaab and Thurman (24).

of a competitor's technical and commercial information. These laws coexist with the patent laws of the various countries and are a necessary adjunct to those laws in order to provide basic protection in many areas where the patent laws do not reach.

There are no treaties, such as the EPC for patents, dealing with the international protection of proprietary information. Thus, when a question involving trade secrets comes before the European Court of Justice, it will be decided generally in accordance with the national laws of the member states, much like U.S. Federal Courts are governed by State law in trade secret cases.

Federal Republic of Germany.—The West German law dealing with trade secrets has at least two components, "industrial secrets" and "commercial secrets." Although no distinction is made in enforcement of rights as to one type or the other, the fact that both are protected makes it clear that not only technical secrets are protected, but also secret commercial or business information.

With respect to the elements for establishing protectable industrial and commercial secrets, the German Supreme Court has stated on several occasions that such a secret may be any fact that is: 1) connected with a business, 2) known only to a small number of persons, 3) for which its possessor has a justifiable interest in keeping secret, and 4) for which its possessor has manifested an express or recognizable intent to keep secret (33).

The West German law is more liberal than the U.S. law as to the degree of public knowledge required to destroy a trade secret. In the Federal Republic of Germany, if information is discernible only with a great deal of work and expense, it is still protectable as an industrial or commercial secret. Thus, for example, even the purchase of a machine does not destroy the secret nature of its contents if the purchaser must dismantle, tear apart, and put in substantial time and effort to uncover its secrets (33). Further, knowledge by a small group of persons, particularly if they are not competitors, will not destroy the secret nature of an industrial or commercial secret.

As in the United States and the United Kingdom, neither novelty nor technical advance need be established in order for information to be classified as an industrial or commercial secret in West Germany.

One element of a trade secret is whether the information gives its possessor an advantage in competition which would be lost if it were disclosed to competitors. But at least one commentator has suggested that the industrial or commercial secret need not be actually industrially or commercially utilized at the time of its loss (4). Thus, it would appear that research data that would or potentially could give the holder a competitive advantage would satisfy the requirements for an industrial secret.

Substantial civil and criminal liabilities for violation of trade secret rights are written in statutory law. The most pertinent provisions are in the German Unfair Competition Law of 1909 (UWG, Gesetzgegen den unlauteren Wettbewerb). An employee who wrongfully communicates an industrial or commercial secret may be imprisoned for up to 3 years and fined. If the employee uses the secret abroad, or knows it is to be used abroad, the prison sentence is increased to up to 5 years. Civil penalties and a civil right of action for damages or an injunction are also available (6,20,33).

United Kingdom.—The British courts, much like their American counterparts, have refrained in most instances from adopting a hard and fast definition of the term "trade secret." One definition is as follows (31):

1. It consists of information;
2. The information must be secret either in an absolute or a relative sense;
3. The possessor must demonstrate that he has acted with an intention to treat the information as a secret;
4. The secret information must be capable of industrial or commercial application; and
5. The possessor must have an interest in the information worthy of legal protection, bearing in mind English principles of equity. This will generally be an economic interest.

The English (as well as the other Europeans) are rather parochial in their approach to the question of whether something is secret. They are concerned most with public knowledge in their own country. For example, knowledge by other people outside of the United Kingdom would not be as great a threat as knowledge of a few people inside of the United Kingdom (31).

One possible problem for biotechnology in Great Britain is the requirement that information must have some industrial or commercial use in order to qualify as a trade secret. Thus, research data or abstract ideas not capable of being used commercially in the near future may not be a trade secret (31). Such information may be protectable, however, as "confidential information" (23). While English legal scholars have debated the degree of secrecy necessary for information to be protected as confidential, it is clear that the degree necessary to protect such information pursuant to a confidentiality agreement is less than that required to establish a trade secret. The British "confidential information" approach might well be the way to avoid the problem raised by some U.S. cases which

have indicated that technical information will not be protected if it is not developed to the stage of practical application (9).

Enforcement of trade secret law in the United Kingdom is by way of civil actions for damages. Unlike other major industrialized countries, the United Kingdom has no specific statute making misappropriation of trade secrets a crime, and there has been no significant prosecution under more general theft or conspiracy statutes.

Switzerland.—Swiss law recognizes "industrial secrets" and "commercial secrets."* The elements of protectable industrial and commercial secrets are quite similar to those under West German law. Knowledge by a small number of people, or public availability, but only after substantial expense or effort, does not defeat the secrecy of the information (19,20). There must be an intention to maintain the secrecy of the information and an intent in maintaining its secret for the purpose of enhancing economic or competitive position (19). One additional element to the Swiss law, however, is that the secret must have a relationship to a particular business enterprise. Secrets held by professors, scientists, factory workers, and others not engaged in business do not qualify as industrial and commercial secrets, unless, of course, they own or participate in a business and the secret is possessed by the enterprise rather than themselves as individuals (19).

Switzerland's Unfair Competition Law of 1943 specifically prohibits the misappropriation of industrial or commercial secrets, and contains sections establishing both civil and criminal liability. One who is injured by an act of unfair competition may obtain injunctive relief and damages (19).

Switzerland has a wide variety of criminal statutes prohibiting misappropriation of industrial and commercial secrets and various other types of industrial espionage. The Unfair Competition Law provides that those guilty of the same acts of unfair competition discussed above shall be punished by a fine or imprisonment, on complaint of the aggrieved party (19).

Thus, Switzerland has a formidable array of civil and criminal liabilities to discourage industrial espionage and misappropriation of propriety information.

*The Swiss Supreme Court has defined "industrial secret" as (BGE 64 II 66) (19):

> All facts related to a manufacturing process or method and neither in the public domain nor generally available, in the secrecy of which the holder has a justified interest and which he actually wishes to be maintained secret, can be the subject matter of an idustrial secret.

and "commercial secret" as (BGE 74 IV 103) (19):

> The term "commercial trade secret" encompasses basically all facts of economic life in the maintenance of secrecy of which an interest worthy of protection exists.

France.—French law, like West German law, rather than following the single concept of "trade secret" found in the U.S. and English law, segregates the secrets into "manufacturing secrets" (secrèt de fabrique) and "commercial secrets" (secrèt de commerce) (10). A commercial secret is treated by the commentators similarly to a manufacturing secret, although there is no direct reference to commercial secret in the French Code (10). For information to be a manufacturing secret, it must be: 1) relatively secret, 2) of industrial application, 3) of commercial or market value, 4) a secret of the factory; and 5) the misappropriator must know it is a secret (10).

The difficulty for researchers is the requirement of industrial application. The majority view seems to be that to be a manufacturing secret, the secret information must either be suitable for immediate industrial application or have already been used industrially. For example, a process not yet applied industrially, but used only in research and experimentation cannot be a manufacturing secret. Mere unapplied, theoretical ideas of a technical or scientific nature do not qualify (10).

Misappropriation of manufacturing secrets by an employee is a criminal violation under article 418 of the French Penal Code, if the employee has the requisite criminal intent for doing the act for his or her own benefit (10). Disclosure to aliens or non-French residents is punishable by significantly higher fines and much longer prison terms.

PLANT BREEDERS' RIGHTS

The important provisions of the plant breeders' rights laws of the Federal Republic of Germany, the United Kingdom, Switzerland, and France are as follows.

Federal Republic of Germany.—Article 2(3) of the Federal Republic of Germany's Law on the Protection of Plant Varieties (text of May 20, 1968) covers both sexually and asexually reproduced varieties. The variety must be new, sufficiently homogeneous, and stable. Novelty exists when the variety is clearly distinguishable by at least one important morphological or physiological characteristic from any other variety, the existence of which is a matter of common knowledge at the time for which protection is applied. Common knowledge is defined in terms of absolute novelty in Germany, with commercialization of the variety in Germany prior to filing the application constituting a statutory bar (art. 2(3)). Homogeneous means plants of the variety must be identical in all their essential characteristics (art. 5). Stability is demonstrated when plants of the variety retain their essential characteristics true to the definition of the

variety after each successive reproduction or reproductive cycle (art. 6).

Article 36 provides that as a part of the examination procedure, the variety must be grown, either by the Federal Office of Plant Varieties or a delegated outside service. The holder of the protection right also is required to submit to the Federal Office of Plant Varieties, upon request, material for establishing the continued existence of that variety. If the holder is unable to do so, the protection right ceases (arts. 16 and 20).

The duration of protection or grant is for 20 years, except for certain varieties for which it is 25 years (art. 18). The law provides for criminal penalties comprising fine or imprisonment of a term of up to 1 year (arts. 48 and 49). The holder of the protection right may claim remuneration from any person who has propagated material without authorization in the interval between the publication of the application and the grant of title of protection (art. 47(4)).

United Kingdom.—The Plant Varieties and Seed Act of 1964 covering United Kingdom is the basis for adherence to the UPOV 1961 Convention, with ratification being effective September 17, 1965.* The act covers both sexually and asexually reproduced plant materials.

The new variety must be distinct, uniform, and stable. To meet the first requirement, it must be clearly distinguishable by one or more important morphological, physiological, or other characteristics from any other variety whose existence is a matter of common knowledge at the time of the application (pt. II, 1(1)). The variety must be sufficiently uniform or homogeneous (pt. II(4)). The variety must be stable in its essential characteristics—i.e., it must remain true to its description after repeated reproduction or propagation (pt. II(5)).

There is an absolute novelty requirement, that is, the variety may not have been offered for sale or sold in the United Kingdom prior to the filing of the application. Where such sales or offers for sales are made outside the United Kingdom, a grace period of 4 years is provided prior to the filing of the application (pt. II, (2)(1) and (2)).

The scope of protection afforded by the rights include the exclusive right to produce or propagate the variety for the purpose of selling the variety or parts or products of the variety (pt. II, 3(1) and (2)). The term of protection ranges from 15 to 25 years, depending on the type of plant.

A growing trial is required during the examination period, thus requiring the submission of plant material. Further, every holder of plant breeders' rights must ensure that, throughout the period for which the rights are exercisable, he or she is in a position to provide reproductive material that is capable of producing the variety, and the holder must provide such information and facilities as the plant variety rights office may request for the purpose of fulfilling the maintenance requirements. If plant material cannot be so provided, the protection rights shall be terminated (pt. I(6)).

The law provides for a Plant Variety Rights Tribunal having jurisdiction over cases brought under the act, with the tribunal being authorized to sit in any designated place in Great Britain to hear any proceedings.

Switzerland.—Switzerland ratified the 1978 UPOV Text on June 17, 1981. Under Swiss law, sexually and asexually reproduced varieties are covered. Protected varieties must be novel, stable, and sufficiently homogeneous. The variety is considered novel unless, at the time the application is filed, the variety has already been offered for sale or marketed in Switzerland or for more than 4 years outside of Switzerland. A "variety" refers to any cultivar, clone, line, stock, or hybrid and is considered new if it is clearly distinguished by one or more important features from any other variety whose existence is generally known at the time the application is filed.

Variety protection precludes another, without the consent of the holder, from producing propagation material of the protected variety with a view to marketing it, offering it for sale, or selling it in the course of business. Propagation material includes seeds, fruits, or vegetative material. Protection is for a term of 20 years following issue, but it can be extended in certain cases.

The applicant is required to deposit propagation material for purposes of conducting examination for verifying the stated characteristics of the plant. The title of protection can be annulled when the title holder cannot supply a propagation material capable of producing the new variety with its morphological and physiological characteristics as defined when the right was granted.

Action for variety infringement is brought in the canton of the defendant's place of residence in Switzerland. Intentional infringement can be punished by imprisonment for up to 1 year or by a fine.

France.—Although France was an early ratifier of the 1961 UPOV Convention Text, and a signatory to the 1978 Text, it has not yet ratified the latter. France continues to operate under the Law on the Protection of New Plant Varieties, Law No. 70-489 of June 11, 1970.

Both sexually and asexually produced plant materials of all species are covered, including bacteria, although

*For further information about UPOV, see *Chapter 16: Intellectual Property Law.*

the schemes are limited to specified varieties. For a variety to be "new," it must be distinct from similar known varieties, by reason of one characteristic that is important, specific, and subject to little fluctuation, or more than one characteristic where the combination thereof is such as to give it the quality of a new plant variety (ch. I, sec. 1). Further, the variety must not have been exploited in France, or appear in specified publications, before the filing of the application in France; if so, a valid certificate cannot be issued. The variety must be homogeneous in all of its characteristics, and must remain stable—i.e., it must remain identical with its original definition at the end of each propagating cycle (ch. 1, sec. 1). An application for each new variety fulfilling the above requirements must be given a denomination and a sample to be left in a collection (ch. II, sec. 2).

The plant variety certificate confers on the certificate owner the exclusive right to produce, import into France, sell, or offer for sale all or part of the plant (ch. II, sec. 3). The certificate is valid for 20 years from the date of issue, although this period shall be extended to 25 years if the constitution of the elements for production of the species requires a considerable time.

The breeder must at all times keep a vegetative collection of the plant variety (ch. I, sec. 9). If the owner is unable to furnish the administration at any time with the elements of reproduction or vegetative propagation so that the specified characteristics of the variety can be ascertained, the rights of the owner will be forfeited (ch. IV, sec. 22).

Chapter IV, section 23 relates to infringement, which is broadly defined. It provides that any violation of the rights of the owner of a new plant variety certificate shall constitute an infringement for which the offender shall be liable.

Intellectual property law of Japan

Having discussed the patent law, trade secret law, and plant breeders' rights in the European competitor countries, we turn now to Japan.

PATENT LAW

Patentable Subject Matter.—The Japanese Patent Act contains the following broad definition of patentable subject matter (art. 29(1), 1976):

> Any person who has made an invention which can be utilized in industry may obtain a patent . . . .

Until 1979, the Japanese Patent Office took the position that micro-organisms were unpatentable because they are not industrially applicable. After reversing that position, the Japanese Patent Office issued a set of Working Standards for micro-organism inventions in November 1979, and in August of 1980, it issued a Classification of Inventions Relating to Genetic Engineering (14).* According to these guidelines, recombination of the genes of higher animals is not permitted, so that inventions in that area are thought to not be patentable (14).

In the intervening years, the greatest obstacle to securing patent protection for microbiological inventions in Japan was the rDNA research safety guidelines published by the Science and Technology Council and the Ministry of Education. These guidelines originally permitted only *E. coli* bacteria to be genetically modified. In January 1980, yeast strains were also included. Since then, other micro-organisms have been included.** Any rDNA inventions that were not directed to subject matter approved by the safety guidelines were considered to fall into the category of inventions "likely to injure the public health" and thus were precluded from patenting under article 32(2) of the patent law (13).

Subject to the above considerations, therefore, the following five basic categories of biotechnological inventions appear to be patentable: 1) micro-organisms, 2) processes for producing micro-organisms, 3) processes using micro-organisms, 4) products obtained from microbiological processes, and, 5) DNA and RNA molecules or subcellular units.

Novelty.—Under article 29 of the Japanese Patent Act (1978), an invention is novel if it is not worked or publicly known in Japan, or it is not described in a publication anywhere prior to the application filing date (or priority date). A 6-month grace period is provided in article 30 (1978) for: 1) experimentation, publication, and papers presented before scientific organizations by the applicant, 2) unauthorized disclosure by a third party, and 3) displays at authorized exhibits.

Utility.—The standard of utility is one of industrial applicability, similar to the EPC. Processes in the field of medicine, diagnosis, therapy, and pharmacology in which the human body is an indispensible element are excluded from patentability by the Japanese Manual for Examination and by court decision, as not being usable in industry (11).

Standard of Invention.—Under article 29(2) of the Japanese Patent Act, a claimed invention is not patentable, even if novel, if it "could easily have been made, at the filing of the application, by a person with ordinary skill in the art to which the invention pertains." This standard is similar to the concept of obviousness under U.S. law, except that U.S. law focuses

*The guidelines also mention vectors, DNA molecules, and enzymes.

**See *Chapter 15: Health, Safety, and Environmental Regulation* for details.

on the difference between the claimed invention and the prior art.

Disclosure Requirements.—Disclosure requirements for inventions under article 37 of the Japanese Patent Act (1976) require that an application be accompanied by a specification setting forth a detailed explanation of the invention including the purpose, construction, and effect of the invention to the extent that any person having an ordinary knowledge in the technical field to which the invention belongs may easily make it. This is basically an enablement standard.

Deposit Requirements.—A micro-organism must be deposited *except* in the case where:

- it cannot be preserved in a depository for technical reasons or cannot be controlled under safe conditions; or
- it is readily available to those skilled in the art (e.g., a commercially available micro-organism or one constituting a stock culture listed in a catalog published by a reliable depository) (35).

The situation is unclear in the case of micro-organisms for which an enabling disclosure is presented in the patent application (35).

Japan is bound by the Budapest Treaty, and therefore, it must accept deposits made thereunder, without requiring deposit in Japan. For those deposits not made under the Budapest Treaty, the minimum required maintenance period for the culture deposit is the lifetime of the Japanese patent (28).

Generally, no sample of a deposited culture will be furnished to third parties (without consent of the depositor) until the patent application is accepted and published for opposition. After publication, access is granted on the condition that the party will not furnish the sample to others (28).

Claims Practice.—There are no formal limitations on the basic type, style, or category of claims (1).

Enforcement.—Infringement is defined in article 101 and 3(2) of the Japanese Patent Act (1978) to include the acts of making, using, selling, and importing the patented article and/or patented process, including importing an article produced by a patented process. There is a presumption that a claimed process for producing a *novel* product has been used to produce the product whenever found in Japan (art. 104, 1978).

It is the predominant view that claims in a Japanese patent define the outer boundary of the invention and that only in rare instances is it possible to establish infringement for anything outside of the literal language of the claims, i.e., there is no traditional doctrine of equivalents (29).

Article 65(3) of the Japanese Patent Act provides that after the first publication of a Japanese application, the applicant has a right to reasonable compensation. After acceptance and grant, the patentee has the right to injunctive relief as well as monetary damages and, in theory, criminal sanctions (29).

LAW OF TRADE SECRETS

There are no specific statutes assigning liability for misappropriation of trade secrets;* thus, one must rely on general principles of Japanese civil law (see 17). That is, an injured party may sue under general tort law principles.** Employees, however, are viewed as having an implied contractual obligation not to misappropriate or improperly disclose trade secrets of their employer.

The Japanese Penal Code does not contain a provision specifically punishing misappropriation of trade secrets, manufacturing secrets, or commercial secrets. Criminal liability can only attach through the general sections of the penal code dealing with larceny, embezzlement, receiving stolen property, fraud, etc. Misappropriation of trade secrets has been successfully criminally prosecuted under such general statutes in Japan (see 12).

Trade secret protection in Japan for any type of technology is seen as very unsatisfactory. Liability for misappropriation has been the exception rather than the rule. In fact, one commentator has described Japan as the world's leading country for industrial espionage (34).

PLANT BREEDERS' RIGHTS

A Seed and Seedling Law in Japan, enacted July 10, 1978, conforms to the provisions of the UPOV Treaty, which Japan has signed (21). The details of the Japanese legislation are similar in essential respects to the EPC countries discussed previously.

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*While the term "trade secret" is sometimes used in Japanese law, one is more likely to find the terms "industrial secret" and "commercial secret" utilized, in a manner similar to that of German law (34).

**The general tort principle is set out in art. 709 of the Japanese Civil Code as follows: "A person who, willfully or negligently, has injured the right of another is bound to compensate him for the damage which has arisen therefrom."

***Note: R.P.C. = Reports of Patent, Design, and Trade Mark Cases (Great Britain).

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Appendix H

Selected Aspects of U.S. University/ Industry Relationships in Biotechnology

University/industry relationships in biotechnology were the focus of the discussion in *Chapter 17: University/Industry Relationships*. Material on selected university/industry agreements is presented below. Also described are guidelines for university/industry research adopted by the National Association of Land Grant Colleges and the 1982 Pajaro Dunes Conference, selected statements on patent rights and commingling of research funds, and university policies on patents, consulting, and sponsored research in the United States.

Selected university/industry agreements in biotechnology

Selected university/industry arrangements in biotechnology are discussed below. The arrangements were selected for discussion because they represent different approaches to university/industry relationships, because they are relatively large agreements, and because some of them have raised issues central to university/industry agreements. The agreement between the Whitehead Institute and the Massachusetts Institute of Technology (MIT) is not strictly a university/industry agreement, but has been included because it raises issues in university/industry relationships and because it is a product of industrial interest in biotechnology research.

RESEARCH PARTNERSHIPS

Monsanto/Washington University.—Washington University and Monsanto (U.S.) have a 5-year renewable contract totaling $23.5 million. Under the contract, individual research projects in biotechnology will be carried out by cooperative arrangements involving Washington University faculty and Monsanto scientists. About 30 percent of the research will be fundamental research (terminology of the agreement) and 70 percent will be special research directly applicable to human disease. The contract between Washington University and Monsanto establishes an 8-person advisory committee made up of 4 members from each institution. This committee will solicit research proposals from the faculty of Washington University and from researchers at Monsanto, review and approve the proposals on the basis of individual merit, distribute appropriate funding, and act as a liaison between the university and Monsanto.

Monsanto's participation in the program will begin with a $3 million grant the first year (1982) and rise annually to accommodate expansion in the number and scope of research projects involved. Washington University faculty members will be at liberty to publish results of any research done under the Monsanto funding. Monsanto will exercise the right of prior review of draft materials, because they may contain potentially patentable technical developments. If they contain patentable developments, Monsanto can request a short delay of submission for publication or other public disclosure in order to begin the patent process. Monsanto will pay for and carry out the entire patent application process. If Monsanto does not elect to license a patent, the university is free to license the patent to others.

Washington University will retain patent rights, while Monsanto will have exclusive licensing rights. Royalties will go to Washington University for support of its education and research programs—not to individual researchers. The portion of royalty normally going to the individual will instead be channeled to his/her laboratory to support more research.

During the third year of the 5-year agreement, the entire program will be reviewed by a panel of distinguished scientists who are independent of both Monsanto and Washington University.

The schedule for funding in millions of dollars is as follows (11,13):

The schedule for funding in millions of dollars is as follows (11,13):

Contract year	*Exploratory projects*	*Specialty projects*	*Contract year total budget*
1982-83	$1.5	$1.5	$3.0
1983-84	1.6	2.2	3.8
1984-85	1.7	3.0	4.7
1985-86	1.8	3.8	5.6
1986-87	1.9	4.5	6.4
Total	$8.5	$15.0	$23.5

The process by which the agreement between Washington University and Monsanto came about had some major strengths. First, individuals from Monsanto and Washington University met continually over a period of 2½ years to discuss the project. Second, members of the university faculty and administrative staff and representatives of the company held a 3-day retreat to discuss the interactions and what form they should take. Furthermore, the Washington University/Monsanto agreement is unlike other agreements in that it is intended to be a cooperative research agree-

ment with industrial and university scientists working together on research projects. In other agreements, the explicit purpose has been to allow industry to gain a window on the technology and educate its personnel.

Hoechst/Massachusetts General Hospital.—A $70 million agreement between Massachusetts General Hospital, a teaching hospital associated with Harvard University, and the West German company Hoechst will create a department of molecular biology at Mass General and will provide support for the department for 10 years. The department of molecular biology will be headed by Dr. Howard Goodman and will eventually have a staff of about 100 persons. Hoechst will fund basic research in eukaryotic cell gene regulation, somatic cell genetics, microbial genetics, virology, immunology, and plant molecular biology.

The department faculty will be regular members of the staff of Mass General and will be nominated for membership on the faculty of the Harvard Medical School. Faculty duties will primarily consist of research for the department of molecular biology. Faculty may "also devote a reasonable amount of time to faculty duties other than research and to consulting for non-profit-making entities so long as such activities do not interfere materially with their research activities under the agreement."

Hoescht has the right to send up to 4 individuals to work and be trained in the department at any one time and to send up to 40 individuals over the life of the contract. The individuals that Hoechst sends, however, must have qualifications acceptable to the department.

The contract between Hoechst and Mass General states that the scientists in the department of molecular biology are free to collaborate with others but that "research collaborations funded in part by the Company and in part by others shall take into account the interest of the Company in obtaining exclusive, worldwide licenses." If Hoechst cannot obtain an exclusive license from such collaboration, it must be assured of a nonexclusive license.

All faculty in the department have the right to publish but must submit early drafts of all manuscripts from Hoechst-sponsored research not less than 30 days prior to the submission of the manuscript for publication.

Mass General will hold any patents that may arise out of the Hoechst-sponsored research. The hospital will grant Hoechst an exclusive worldwide license for the life of the patent. Hoechst will pay the hospital royalties at rates that give "due consideration" to the fact that Hoechst paid for the research (2,10).

The exclusive funding may preclude department scientists from seeking grants from the U.S. National Institutes of Health (NIH), thereby taking them out of the peer review process. The department will report to a scientific advisory committee of two members from Mass General, two from Hoechst, and two from elsewhere. The committee's review, however, may not be the equivalent of the critical peer review of proposals at NIH. The department will be physically separate from Mass General, and all equipment and physical plant will be paid for by Hoechst. Department scientists will generally be free to collaborate with others but will have to obtain written permission from Hoescht. Dr. Goodman hopes to collaborate with Dr. Philip Leder who has a 5-year $6 million research agreement with DuPont. Whether Hoechst will grant this request will probably depend on the nature of the collaboration.

Whitehead Institute/Massachusetts Institute of Technology.—Whitehead Institute, a biomedical research institute administratively separate from MIT, has been provided for by Edwin C. Whitehead, the President of Technicon Corporation. Whitehead has bequeathed about $20 million to build the structure, $5 million annually to operate it through the year 2003, and a gift of $100 million upon his death. Whitehead has also given $7.5 million to MIT plus support moneys estimated to be worth about $1 million a year for faculty, graduate students, and research assistants in MIT's biology department.

The Whitehead Institute is headed by a 14-member board of directors that includes 3 MIT directors, 3 of the Whitehead children, and David Baltimore, the director of Whitehead Institute who is serving a renewable 5-year term. Whitehead Institute faculty will have joint appointments with MIT but will be paid entirely from Whitehead Institute funds. Faculty appointments will be proposed by Whitehead Institute according to the research needs of the institute and in consultation with the appropriate MIT department. Appointees will follow the rules and regulations of MIT with regard to teaching, consulting, tenure, benefits, salaries, etc. It is expected that 10 to 15 appointments will be made during the first 7 or 8 years. Graduate students will also be supported.

Whitehead Institute will retain the patent rights on any inventions arising from the research. After deduction for expenses, the royalty will be shared according to the following formula: one-half to the inventor and one-half shared by Whitehead Institute and MIT. The term of the agreement is 10 years, with a 5-year renewal and 2 years written notice necessary for termination. If the agreement should be terminated, faculty will be given the choice of joining the MIT or Whitehead Institute faculty.

Prior to the signing of the agreement, the agreement was extensively discussed by MIT faculty and administrators. Some were concerned that an imbalance in

the MIT biology department might result from the addition of 15 new faculty members in molecular biology; other important specialties would have less representation. Since the members of the faculty of Whitehead Institute, though approved by MIT, would be chosen for their research contributions to Whitehead Institute rather than to MIT's educational or research needs, there was also concern over the possibility that the loyalty of the Whitehead Institute faculty would be divided. Other concerns centered on conflict of interests. Some faculty thought that the findings of Whitehead Institute could turn up in the investment portfolio of Whitehead Associates, Edwin H. Whitehead's venture capital firm. Furthermore, since David Baltimore has equity in the Collaborative Research Company, and several other proposed faculty of Whitehead Institute consult for the company, there were concerns that the link between Collaborative and Whitehead Associates might be too close. After extensive discussions, the MIT faculty decided that the positive aspects of the arrangement outweighed these concerns and voted overwhelmingly to approve the agreement. MIT's Board of Trustees would not have approved the arrangement without faculty support. Furthermore, a special committee will be appointed to monitor the arrangement so that any misunderstandings can be avoided (3).

PRIVATE CORPORATIONS

Engenics/Center for Biotechnology Research and Stanford University.—The for-profit company Engenics was established in September 1981, along with the nonprofit Center for Biotechnology Research (CBR). The purpose of CBR is to support basic and applied biotechnology research at universities, disseminate the results of such research to the public, and facilitate the conversion of knowledge into products and processes. The purpose of Engenics is to carry out research and process development and to establish new businesses. Although the two organizations are separate, they have the same six corporate sponsors and will work in close cooperation.

CBR is receiving $2.5 million from its six corporate sponsors over a period of 4 years. The six sponsors of CBR are Elf Technologies, Inc. (a U.S. venture capital subsidiary of Elf Aquitaine), General Foods, Koppers Co. Inc., Bendix Corp., Mead Corp., and McLaren Power and Paper Co. (a subsidiary of Noranda Mines). CBR holds about 30-percent of the equity in Engenics, equity that was issued to Engenics in exchange for options to licenses under university patents. The same six corporations that sponsored CBR paid $7.5 million for a total of about 30 percent of the equity in Engenics. The remaining 30 percent of the equity in Engenics is shared by the line officers and the consultants Channing Robertson (Chairman of the Chemical Engineering Department at Stanford), Abdul Matin (Professor at Stanford's Medical School), and Harvey W. Blanch (Professor of Chemical Engineering at the University of California, Berkeley).

CBR can use all capital appreciation or dividends from the equity in Engenics only for the support of university research. Any patents resulting from CBR-sponsored research will be held by the university at which the work was performed, with CBR, Engenics, and the six corporate sponsors receiving royalty-bearing licenses. Negotiations at the time of the patent will determine the terms of the license. Investigators performing CBR-sponsored research will retain the right to publish their findings.

CBR is currently funding three university research contracts. One is a 4-year $970,000 contract with Drs. Robertson and Matin, both of Stanford, as principal coinvestigators. The second contract is a 5-year $783,000 contract with Dr. Blanch, of the University of California, Berkeley, as the principal investigator. This contract is funded by both CBR and Engenics, because University of California policy stipulates that licensing agreements cannot be made with nonprofit organizations. The third contract is with Anthony Sinsky at MIT. No data on the amount of this contract are available. Dr. Sinsky is on the Scientific Advisory Board of Engenics (68).

Neogen/Michigan State University Foundation and Michigan State University.—Neogen was founded in July of 1981 by the Michigan State University (MSU) Foundation, an independent nonprofit fundraiser and disburser of donations and royalty income to MSU. Neogen, which was organized to seek venture capital for limited partnerships to develop and market innovations arising out of research at MSU, was formed for several reasons: MSU wished to retain faculty members who are getting lucrative offers from other small companies; MSU would like to allow faculty to develop their entrepreneurial talents and remain at the university; and a company such as Neogen can help diversify Michigan's economy. The company was organized with full knowledge of the board of trustees, the administration, and the faculty of MSU.

Neogen limited partnership purchases are being managed by an investment firm in Detroit. The MSU Foundation, which purchased $100,000 of stock when the company was founded, will soon purchase another $130,000 of stock, and Doan Resources is buying $250,000 in stock.

One project (a parasite diagnosis project) is ready to begin (funded at $455,000) and two projects are awaiting funding. Neogen will be able to buy title to any resulting patents from MSU for the parasite diagnosis project. The money will be paid through the MSU Foundation to Neogen.

Patents will usually be applied for by MSU. The patents will be assigned by MSU to the MSU Foundation for subsequent sale to Neogen in exchange for stock. Inventors will receive a 15-percent royalty or can exchange this for a 1-to 2-percent stock option in Neogen.

Because Neogen is tied to the MSU Foundation, MSU receives moneys from successful commercialization of products or processes and the individuals are rewarded commensurate with their efforts. The basic research takes place on the campus of MSU, but commercialization will be moved off-campus to a nearby research park in order to avoid conflicts of interest.

The MSU faculty and administration were aware of and/or participated in the founding of the company, and there is a scientific advisory board that reviews the projects, thus preserving the principle of peer view.

Guidelines for industrial sponsorship of university research in biotechnology

NATIONAL ASSOCIATION OF STATE UNIVERSITY AND LAND GRANT COLLEGES, DIVISION OF AGRICULTURE

A document titled "Genetic Engineering Policy for the State Agricultural Experiment Stations" was adopted by the Experiment Station Committee on Policy (ESCOP) in November 1981 at a meeting held in conjunction with the fall meeting of the National Association of State University and Land Grant Colleges (NASULGC). ESCOP, headed by Dean Clarke of Texas, was brought together after Clarke and several other members observed that several State Agricultural Experiment Stations (SAES) were being simultaneously approached by industry to do genetic research. Since there were no policy guidelines for the new field of biotechnology, SAES often found themselves in a weak position during contract negotiations. Thus, ESCOP was formed to draw up guidelines.

Because the field of "genetic engineering" is changing rapidly, the November 1981 ESCOP policy document is regarded by ESCOP as an interim document subject to annual revision, if necessary. In addition, Clarke is collecting copies of legal documents from SAES institutions and will develop an aggregate summary of appropriate components of general agreements to be made available to all members of NASULGC's Division of Agriculture. Work is now underway to draw up guidelines for NASULGC's Division of Agriculture. The committee that is drawing up these guidelines is headed by Dean F. A. Wood of the University of Florida.

The ESCOP document of November 1981 is summarized below because it addresses issues that are common to most industry/university relationships in biotechnology. As noted in that document, the SAES have five general concerns (5):

1. As publicly supported institutions, the SAES will need to assure that industrial relationships generate an end result in the interest of the general public. This end result should reward the industrial investor but avoid placing such an investor in an unwarranted position of financial advantage through privileged use of information or technology partly derived from research using public funds; nor should a curtailment of new information to the public occur.
2. The SAES are greatly concerned about the curtailment of communication on early research results and about the constraints on sharing of germplasm emerging due to concerns . . . for protecting potentially patentable research results. . . .
3. There is general concern in the academic community about the drain of scientific manpower from the universities to industry. . . .
4. There is concern that individual scientists may place themselves in the positions of compromise or conflict of interest as they establish personal relationships with industry as contractors, consultants or institutional officers.
5. There is concern on the part of both scientists and the SAES that through industrial sponsorship of research, there may be introduced an undesirable level of direction of effort by industry.

The guidelines set forth in the ESCOP document are subsumed under the three major issue areas outlined below (5):

A. Institutional relationships

1) Maintain SAES management control of research:

Consensus: SAES should retain the ability to manage research programs, and control the direction of new investigations, regardless of the source of support, including situations in which one or several firms may sponsor research at several institutions.

2) Strong basic research and graduate education capability:

Consensus: SAES should maintain and expand the basic research capability in genetic engineering and related areas within the domain of publicly supported institutions.

3) Faculty-industry relationships:

Consensus: Scientists should maintain close communication with institutional administrators in development of relationships and commitments with the commercial sector. Institutional guidelines

should be developed which assist the scientists in avoiding institutional or personal conflicts of interest.

B. Technical relationships

4) Publication and communication:

Consensus: The ability to publish and exchange information is essential and must be secured in agreements. In some instances, publications or information exchange may need to be temporarily delayed to allow time for an institution or sponsor to assure adequate patent protection. The final decision to defer or modify a publication should reside with the public institution.

5) Trade secrets and confidential information:

Consensus: Protection of "trade secrets" or "confidential information" for more than a very limited period should be avoided by public institutions. Advance review by a private sponsor, to avoid premature release of information, may be advisable but should not become a mechanism to "shelve" useful information or unpatentable technology.

6) Patent rights and premature disclosure:

Consensus: SAES should retain the right to participate in the decisions related to the disposition of intellectual and real property and patent rights resulting from research. Retained ownership of patents by the SAES is preferred. In any agreement, the SAES should retain the right to use discoveries and inventions from SAES research to extend and enhance public research and education. The need of private sponsors to obtain a return on investment must be recognized, and agreements may provide for special licenses for patents originating from sponsored research.

7) Biosafety of recombinant DNA:

Consensus: SAES must retain responsibility for review and decisions in the release or distribution of laboratory research products, although some research may be supported by outside sponsors.

C. Fiscal and management relationships

8) Grants and income earnings:

Consensus: Extending knowledge and developing new technology while serving the public interest should be the prime motivations in agreements between SAES and the private sector. Royalty income from discoveries originating under such agreements should be recognized as a secondary consideration.

9) Licensing responsibilities and performance expectations:

Consensus: SAES should assure that "due diligence" clauses are included in contracts to assure that new technology is not shelved and the public interest is served while private investment in commercialization is respected. Assignments of rights or licensing of patents for commercial use should be considered separately from contractual definition of research to be conducted. Initial or developmental processes and pervasive technology ultimately leading to improved biological materials generally should not be assigned for sole use by a sponsoring firm.

10) Tax code implications:

Consensus: When sponsored research is motivated by certain interpretations of Tax Code Section 1235, exclusive licensing or co-ownership of patent rights is a preferred alternative for the institution, since the institution maintains a vested interest and some ownership of patent rights involving the scientist, the institution, and the firm may require unique documentation. Careful attention to these rights and relinquishments is suggested.

PAJARO DUNES CONFERENCE, MARCH 1982

The March 1982 Pajaro Dunes Conference on university/industry relationships in biotechnology, which was financed by the Henry J. Kaiser Family Foundation, was organized principally by Donald Kennedy, the President of Stanford, and included the Presidents of Harvard, Derek Bok; California Institute of Technology, Paul Gray; and the University of California, David Saxon. Also invited were an administrator and two faculty from each university. Leading industrialists were also invited, among them representatives from Beckman Instruments, Inc.; Syntex Corp.; Cetus Corp.; Cabot Corp.; Applied Biosystems, Inc.; Damon Corp.; Gillette Corp.; Eli Lilly and Co.; E. I. du Pont de Nemours; and Genentech Corp. A statement drafting guidelines and principles emerged from the conference, although Kennedy and others stressed its role as a draft of the process of policy formation rather than a statement of policy.

The premise of the Pajaro Dunes Conference was that collaboration between universities and industry will benefit all parties, including the general public, if the university's ideals are not distorted. The general consensus was as follows (9):

> . . . research agreements and other arrangements with industry (must) be so constructed as not to promote a secrecy that will harm the progress of science; impair the educational experience of students and postdoctoral fellows; diminish the role of the university as a credible and impartial resource; interfere with the choice by faculty members of the scientific questions they pursue, or divert the energies of faculty members and the resources of the university from primary educational and research missions.

The consensus of the Pajaro Dunes Conference with respect to specific issues is discussed further below.

Disclosure of Research Agreements.—On this topic, the following views were expressed (9):

> In order to satisfy the faculty and general public that the role of the university is being maintained, contracts should be made public. This could involve publication of relevant provisions of research contracts with industry or, alternatively, examination by a facul-

ty committee or some other competent body of all research contracts to assure that terms are consistent with university values.*

Patents and Licenses.—The consensus on patents and licenses was as follows (9):

> The traditions of open research and prompt transmission of research results should be maintained. However, it is appropriate for the institution to file for patent coverage; actions which might require brief delays in publication or other public disclosure. Receipt of proprietary information may occasionally be desirable to facilitate research. These situations must be handled on a case-by-case basis so as not to violate the educational process or the traditions of openness.

There was a disagreement on the issue of whether exclusive rights should be given, although the document does appear to favor the granting of exclusive licenses (9):

> Some people fear that allowing a single firm the sole right to develop a patent will necessarily remove competition, slow the development of the patent, or even prevent development altogther. This fear is exaggerated. . . . Thus, universities should be able to negotiate exclusive licenses provided that exclusivity seems important to allow prompt, vigorous development of the patent to occur.

In license negotiations, the consensus was that the university should insist on a requirement of due diligence on the part of the licensee in developing and using the patent.

The situation is more difficult when a sponsor requests the right to exclusive licenses on all discoveries made as a result of the research funded by the company (9):

> Some of us believe that such exclusive rights are an appropriate quid pro quo for the funds provided for research. Others believe that the university should be willing to agree to provide instead nonexclusive royalty-free licenses to the sponsor, but should not give up its right to examine the appropriateness of exclusivity for each invention on a case-by-case basis.

Conflict of Interest.—Discussion focused on two aspects of the problem. The first was the propriety of a university's taking an equity position in a company in which one of its faculty is a major stockholder or officer. Most were against such investments (9):

> It is not advisable for universities to make such investments unless . . . there are sufficient safeguards to avoid adverse effects on the morale of the institution . . . .

The second and really complex issue, conflict of interests, was avoided by participants entirely. Issues related to university/industry relationships are not new, and the Pajaro Dunes Conference participants were all experienced with and knowledgeable about these relationships. Rather than producing some definite guidelines regarding the structuring of such relationships, however, Pajaro Dunes Conference participants provided only general principles underlying general university policies.

*Harvard has elected to keep its contracts confidential and Stanford is following an informal policy of full disclosure (1).

Selected statements on patent rights and commingling of research funds

Since one of the purposes of the 1980 U.S. patent law (Public Law 96-517) is to foster cooperative research arrangements among government, universities, and industry, one question that immediately arises is how the establishment of patent rights is affected by potential commingling of funds. Circular A-124 issued by the U.S. Office of Management and Budget (OMB) sets out some guidance on this (4):

> Notwithstanding the right of research organizations to accept supplemental funding from other sources for the purpose of expediting or more comprehensively accomplishing the research objectives of the government sponsored project, it is clear that the Act would remain applicable to any invention "conceived or first actually reduced to practice in performance" of the project. Separate accounting for the two funds used to support the project in this case is not a determining factor.
>
> To the extent that a non-government sponsor establishes a project which, although closely related, falls outside the planned and committed activities of a government funded project and does not diminish or distract from the performance of such activities, inventions made in performance of the non-government sponsored project would not be subject to the conditions of the Act. An example of such related but separate projects would be a government sponsored project having research objectives to expand scientific understanding in a field with a closely related industry sponsored project having as its objectives the application of such new knowledge to develop usable new technology. The time relationship in conducting the two projects and the use of new fundamental knowledge from one in the performance of the other are not important determinants, since most inventions rest on a knowledge base built up by numerous independent research efforts extending over many years. Should such an invention be claimed by the performing organization to be the product of non-government sponsored research and be challenged by the sponsoring agency as being reportable to the government as a "subject invention," the challenge is appealable . . . .
>
> An invention which is made outside of the research activities of a government funded project but which in its making otherwise benefits from such project without adding to its cost is not viewed as a "subject invention," since it cannot be shown to have been "con-

ceived or first actually reduced to practice" in performance of the project. An obvious example of this is a situation where an instrument purchased with government funds is later used, without interference with or cost to the government funded project, in making an invention all expenses of which involve only non-government funds.

Members of the Advisory Committee to the Director of NIH asked Mr. Dietrich of OMB for some guidance on problems posed by commingled funds. Dietrich noted that application of OMB and the Department of Health and Human Services cost-accounting and auditing principles can resolve some of the issues. He stated that one good way to distinguish between commingled funds is to determine whether a project was supported through direct costs (in which case the patent regulations would likely apply) or by indirect costs (in which case the regulations would likely not apply). He then provided an assessment of some specific cases (12).

- In a situation where privately supported work is done in a building previously constructed with Government funds, the Government obtains no patent rights in inventions developed through those private funds.
- Similarly, in a situation where privately supported work is done using equipment previously purchased with Government funds, the Government obtains no patent rights in inventions developed through those private funds; however, it does if the equipment is currently operated under Government support.
- If a single individual spends one-half time on a project supported with Government funds and one-half time on a privately supported project, the Government obtains patent rights only if the privately supported project is directly dependent on ideas or materials generated in the publicly supported project.
- Similarly, if a scientist spends 10 years on a publicly supported project and then 10 years on a privately supported project, the Government obtains no patent rights to the invention developed under private support unless it is clear the idea was conceived with public funds.
- In the case of a team working on a single project with both public and private support, the Government would obtain patent rights.
- For inventions resulting from normal intellectual intercourse in which two individuals, one privately and one publicly supported, exchange information, the Government would obtain no patent rights unless there is intent to commit fraud (e.g., the scientist on public funds provides information to the scientist in the private sector to increase the marketability of an invention and then shares in the profits).

Selected university policies

UNIVERSITY PATENT POLICIES

To analyze the patent policies of universities in the United States, OTA reviewed documents on the patent policies of the following 32 universities:

1. Alabama/Birmingham, University of
2. Arizona, University of
3. Boston University
4. California Insitute of Technology
5. California, University of
6. Case Western Reserve University
7. Colorado, University of
8. Connecticut, University of
9. Cornell University
10. Georgia, University of
11. Indiana University
12. Iowa, University of
13. Johns Hopkins University
14. Maryland, University of
15. Massachusetts Institute of Technology
16. Miami, University of
17. Michigan, University of
18. Minnesota, University of
19. Northwestern University
20. Ohio State University
21. Pennsylvania, University of
22. Purdue University
23. Rochester, University of
24. Rockefeller University
25. Rutgers University
26. Southern California, University of
27. Stanford University
28. Vanderbilt University
29. Virginia, University of
30. Washington University
31. Washington, University of
32. Wisconsin, U. of

In general, the patent policies of the 32 universities OTA sampled define the obligations and rights of the university and the university researchers who produce inventions that have commercial potential. They also recognize the rights of outside sponsors. Typically, university patent policy documents state that the relationships defined between the university and inventor are subject to the obligations that the inventor has made in return for outside support from either private or government sources. In some cases, an industrial sponsor may have retained the right to the invention (because most universities grant only nonexclusive licenses if they own the patent, subject to a short exclusive licensing period to help commercialize the invention) and also may have defined how royalties are to be shared. Thus, for example, the Stanford patent policy document notes:

> In practice, the great majority of inventions arise from externally funded research covered by agreements containing patent provisions. Some agreements permit the University to retain title and grant license rights to the sponsor; some provide for the reverse or defer allocation of rights.

The crucial issue, therefore, seems *not* to be the patent agreements between universities and their researchers (i.e., what is covered in the documents OTA reviewed), but the terms of contracts from external sponsors to individual researchers.

Most university patent policies cover anybody working with university facilities, although individual universities vary in the degree of specific identification of personnel types. Most of them also cover students, although MIT excepts students from the provision and Johns Hopkins invites students to "take advantage of the mechanisms set forth herein." University employees who produce inventions on their own time and without substantial use of university resources own their inventions, but all 32 universities invite them to use the university's commercialization mechanism.

All 32 universities require researchers to report inventions with potential commercialization promptly so that the university can assess their potential and file for a patent. Some universities (e.g., University of Pennsylvania) also require delay in publication of the findings to allow for filing of a patent. Since publications prior to patenting can make an invention nonpatentable, the practice of requiring a delay in publication is probably common even at universities whose documents do not explicitly mention it.

University administrative mechanisms have been set up to evaluate inventions, to settle disputes, and to attempt commercialization. Many universities use the services of commercialization firms such as Research Corporation of New York and Battelle Development Laboratories. Other universities have their own commercialization ventures (e.g., the Wisconsin Alumni Research Fund at the University of Wisconsin).

The sharing of royalties varies with each university. Almost all the universities use the U.S. Government's stipulation that no more than 15 percent of gross royalty income is to go to the inventor, but they usually set this as the minimum share (i.e., many give the inventor a bigger share if the stipulations of outside sources do not apply). Private universities have a greater propensity than public universities to give ownership of the invention to the inventor, while the university is given a license. This may not be a substantive difference, as the other provisions in university policies (commercialization, royalty sharing, etc.) do not seem to be related to whether the inventor rather than the university owns the invention. On the question of ownership, universities having the right to take ownership have the *option* to do so. Conversely, the inventor can petition to have the invention assigned to him/her if the university does not diligently pursue its commercial applications.

Royalties, after deduction for expenses and the inventor's share, may be assigned to a number of university activities. Some universities place the remaining royalty income in their general operating funds; often, however, royalties are assigned to "research" or to "research and training" either through stipulation or through a separate fund set up for that purpose (e.g., Cal Tech's California Institute Research Foundation). Some universities also allocate a share to the inventor's department, division, and/or area of activitiy (e.g., the University of Colorado allocates a 25-percent share each to the discoverer, to an account for support of the discoverer's research, to the discoverer's department or primary administrative unit, and to the university).

The crucial issue is the commercialization stipulations that are attached to funds provided by outside sponsors, public and private. The patent policies discussed here are subject to these external conditions, and, as the Stanford document states, external sponsorship of university research is more the rule than the exception.

UNIVERSITY POLICIES ON CONSULTING

The policies on consulting of five major U.S. universities (Harvard, MIT, Johns Hopkins, Stanford, and the University of California) are summarized in table H-1 below.

UNIVERSITY POLICIES ON SPONSORED RESEARCH

The policies on sponsored research of three major U.S. universities (Harvard, MIT, and Johns Hopkins) are summarized in table H-2 below.

Table H-1.—Summary of Selected University Policies on Consulting

Harvard University	Harvard Medical School	Massachusetts Institute of Technology	Johns Hopkins University	Johns Hopkins Medical School	Stanford	University of California (all campuses)
Conflict of interest:						
• Time for outside involvement regulated • Primary commitment to the university required • Disclosure of potential conflict required	• Time for outside involvement regulated • Primary commitment to the university required • Disclosure of potential conflict required	• Outside activities may not conflict with their obligations to the institute • For all those in decisionmaking roles required annual acknowledgement in writing of the policy • Required disclosure of all outside activities, including financial interests, to institute officers • Requirement: To seek advice of department head if a potential conflict exists	• No formal policy	• Time for outside involvement regulated • Primary commitment to the university required • Financial gain regulated	• Overriding professional allegiance to the university • Disclosure of potential conflict situations urged • Prewritten clause to be inserted into all agreements stating that university conditions of employment prevail before all other agreements	• Primary responsibilities to university stressed • Outlines specific examples of conflict-of-interest situations
Time regulation:						
• 20%	• 2x salary	• 1 day/week • No dollar amount	• 20%	• 20%	• 13 days per academic quarter (13-week quarter)	• No limit on consulting days unless time conflicts with primary responsibility to the university
Disclosure:						
• Not required, unless potential conflict exists	• Required annually—reported to the dean's office	• Faculty are required to keep their department heads continuously informed on all outside activities	• Not required	• Monthly reporting	• Disclosure of names of companies you request of dean, provost, etc.	• California Political Reform Act of 1982, requires disclosure of faculty member financial interest in industrial sponsor of his/her research • Annual reports of consulting activities to be supplied to heads of units

Table H-1.—Summary of Selected University Policies on Consulting (Continued)

Harvard University	Harvard Medical School	Massachusetts Institute of Technology	Johns Hopkins University	Johns Hopkins Medical School	Stanford	University of California (all campuses)
Policy enforcement:						
• Essentially self-enforced	• Essentially self-enforced	• Department heads are required to register once yearly faculty members outside commitments in terms of: — number of days spent — nature of the relationship — any significant financial interest the faculty member may have in the company	• Self-enforced	• By department director and dean	• Essentially self-enforced	• By department dean, variable enforcement among campuses and departments
• Minimally by department chairman	• By dean					
	• By department					

SOURCE: Management Analysis Center, Inc., "Study of University/Industry Relationships in Biotechnology," contract report prepared for the Office of Technology Assessment, U.S. Congress, January 1983; and P.R. Lee, W. Levinson, L.H. Butler, et al., "Industrial-Academic Relationships in Biotechnology at Stanford University, University of California, Berkeley, and University of California, San Francisco," contract report prepared for the Office of Technology Assessment, U.S. Congress, July 1982.

Table H-2.—Summary of Selected University Policies on Sponsored Research

Harvard University (includes Medical School and Mass. General Hospital)	Massachusetts Institute of Technology	Johns Hopkins University (includes Medical School)
Patent rights:		
• Retained by the university	• Retained by the university	• Retained by the university
License:		
• Generally nonexclusive encouraged	• Generally nonexclusive encouraged	• Generally nonexclusive encouraged
Publication rights:		
• Guaranteed • Sponsor preview	• Guaranteed • Sponsor preview deferrals up to 30 days	• Guaranteed • Sponsor preview deferrals up to 120 days
Confidentiality:		
• No confidentiality of results	• No confidentiality of results	• No confidentiality of results
Choice of research topics:		
• Selected by researcher • Reviewed by department chairman	• Selected by researcher • Reviewed by department head	• Selected by researcher • Reviewed by committees (by Biosafety Committee at the Medical School)
Policy enforcement:		
• Review by the department chairman. Approval by the Committee on Patents and Copyright required	• A three-stage approval process is utilized. The stages are: — review by department head — review by the Office of Sponsored Programs — review by dean or provost	• Review by the dean and Office for Sponsored Research (Office of Research Administration at the Medical School)
• Required disclosure to dean of faculty of all personal and remunerative commitments to potential industrial sponsor		
Policy development:		
• Currently underway at all faculties	• Centrally developed policies already in existence	• Being developed by divisions under the direction of central administration
• Decentralized development, moving toward greater centralization		

SOURCE: Management Analysis Center, Inc., "Study of University/Industry Relationships in Biotechnology," contract report prepared for the Office of Technology Assessment, U.S. Congress, January 1983.

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Appendix I

List of Acronyms and Glossary of Terms

List of acronyms

AAU —American Association of Universities
AcNPV —*Autographa californica* nuclear polyhedrosis virus
ACS —American Cancer Society
AHF —antihemophilic factor
AIDS —acquired immune deficiency syndrome
ANDA —Abbreviated New Drug Application
ANVAR —L'Agence Nationale de la Valorisation de la Recherche; National Agency for the Funding of Research (France)
ARES —Applied Research Systems (Netherlands)
ARS —Agricultural Research Service (U.S.)
AT&T —American Telephone & Telegraph Co. (U.S.)
BCr —Brazilian cruzeiros
BGA —Bundesgesundheitsamt: Federal Health Office (F.R.G.)
BISCT —Biotechnology Institute and Studies Centre Trust (U.K.)
BMFT —Bundesministerium für Forschung und Technologie; Federal Ministry of Science and Technology (F.R.G.)
BRL —Bethesda Research Laboratories (U.S.)
BTG —British Technology Group (U.K. Department of Industry)
CAMR —Center for Applied Microbiology and Research (U.K.)
CCL —Commodity Control List (U.S.)
CDC —Centers for Disease Control (U.S.)
C.F.R. —Code of Federal Regulations (U.S.)
CNPq —Conselho Nacional de Desenvolvimento Cientifico e Tecnologico; National Research Council, now known as the Council for Development of Science and Technology (Brazil)
CNRS —Centre National de la Recherche Scientifique; National Center for Scientific Research (France)
CoCom —Coordinating Committee for Multi-Lateral Export Controls
CODIS —Comité d'Orientation des Industries Stratégiques; Committee for the Organization of Strategic Industries (France)
COGENE —Committee on Genetic Experimentation (international)
CRGO —Competitive Research Grants Organization (U.S.)
CSIRO —Commonwealth Science and Research Organisation (Australia)
CSRS —Cooperative State Research Service (U.S.)
DARPA —Defense Advanced Research Projects Agency (U.S. Department of Defense)
DECHEMA —Deutsche Gesellschaft für Chemisches Apparatewesen; German Society for Chemical Engineering (F.R.G.)
DESAT —Defense Business Advanced Technology program (U.S. Department of Defense)
DFG —Deutsche Forschungsgemeinschaft; German Research Society (F.R.G.)
DHHS —Department of Health and Human Services (U.S.)
DM —Deutsche mark
DNA —deoxyribonucleic acid
DOD —Department of Defense (U.S.)
DOE —Department of Energy (U.S.)
DSM —Deutsche Sammlung von Mikroorganismen; German Collection of Micro-Organisms (F.R.G.)
EAA —Export Administration Act of 1979 (U.S.)
ECUT —Energy Conversion and Utilization Technologies program (U.S.)
EEC —European Economic Community
EMBL —European Molecular Biology Laboratory
EPA —Environmental Protection Agency (U.S.)
EPC —European Patent Convention
EPO —European Patent Office (supranational)
ETH —Eidgenössiche Technische Hochschule; Federal Institute of Technology (Switzerland)
FDA —Food and Drug Administration (U.S.)
FFDCA —Federal Food, Drug and Cosmetic Act (U.S.)
FIFRA —Federal Insecticide, Fungicide, and Rodenticide Act U.S.)
FINEP —Financiadora de Projetos National Funding Agency for Studies and Projects (Brazil)
FMD —foot-and-mouth disease
FRI —Fermentation Research Institute (Japan)
F.R.G. —Federal Republic of Germany
FTC —Federal Trade Commission (U.S.)
GAO —General Accounting Office (U.S.)
GBF —Gesellschaft für Biotechnologische Forschung; Society for Biotechnological Research (F.R.G.)
GE —General Electric Corp. (U.S.)
G.E. —Guidelines for Examination
GENBANK —Genetic Sequence Data Bank (U.S.)
GG —gamma globulin

GH —growth hormone
GMAG —Genetic Manipulation Advisory Group (U.K.)
GRAS —generally recognized as safe by qualified experts
GWB —Gesetz gegen Wettbewerbsbeschrankungen; Act Against Restraints of Competition (F.R.G.)
HBsAg —hepatitis B surface antigen
hCG —human chorionic gonadotropin
HFCS —high fructose corn syrup
hGH —human growth hormone
hI —human insulin
HPLC —high-performance liquid chromatography
H.R. —House of Representatives (U.S. Congress)
HSA —human serum albumin
HSE —Health and Safety Executive (U.K.)
HSV —herpes simplex virus
HSV2 —herpes simplex virus type 2
IBC —Institutional Biosafety Committee
IBM —International Business Machines Corp. (U.S.)
ICI —Imperial Chemical Industries (U.K.)
Ifn —interferon
IMC —International Minerals & Chemicals Corp. (U.K.)
IND —Notice of Claimed Investigational Exemption for a New Drug
Ingene —International Genetic Engineering, Inc. (U.S.)
INSERM —Institut National de la Santé et de la Recherche Médicale; National Institute of Health and Medical Research (France)
IOCM —Interkantonale Kontrollstelle für Heilmittel: Intercantonal Office for the Control of Medicaments (Switzerland)
IRS —Internal Revenue Service (U.S.)
ITC —International Trade Commission (U.S.)
JAFCO —Japan Associated Finance Corporation
JDB —Japan Development Bank
JETRO —Japan External Trade Organization
JFTC —Japanese Fair Trade Commission (Japan)
LSI —Large-Scale Integration
MAbs —monoclonal antibodies
MAFF —Ministry of Agriculture, Forestry, and Fisheries (Japan)
MCC —Microelectronics Computer Corp. (U.S.)
MCTL —Militarily Critical Technologies List (U.S. Department of Defense)
MEOR —microbial enhanced oil recovery
MGH —Massachusetts General Hospital
MGI —Molecular Genetics, Inc. (U.S.)
MIT —Massachusetts Institute of Technology
MITI —Ministry of International Trade and Industry (Japan)
MOF —Ministry of Finance (Japan)
MRC —Medical Research Council (U.K.)
mRNA —messenger RNA
MS —multiple sclerosis
MSG —monosodium glutamate
MSH —melanoycte-stimulating hormone
MSI —Medium-Scale Integration
NAS —National Academy of Sciences (U.S.)
NASA —National Aeronautics and Space Administration (U.S.)
NBFs —new biotechnology firms
NCDRH —National Center for Devices and Radiologic Health (U.S.)
NCI —National Cancer Institute (U.S.)
NDA —New Drug Application
NIBSC —National Institute of Biological Standards and Controls (U.K.)
NIH —National Institutes of Health (U.S.)
NIOSH —National Institute for Occupational Safety and Health (U.S.)
NLG —Netherlands guilder
NRC —National Research Council (Canada)
NSF —National Science Foundation (U.S.)
NYU —New York University
OECD —Organisation for Economic Co-Operation and Development
OMB —Office of Management and Budget (U.S.)
OSHA —Occupational Safety and Health Administration (U.S.)
OSRD —Office of Scientific Research and Development (U.S.)
OSTP —Office of Science and Technology Policy (Executive Office of the President, U.S.)
OTA —Office of Technology Assessment (U.S.)
PAL —phenylalanine ammonia lyase
PEPCase —phosphoenol pyruvate carboxylase
PHB —polyhydroxybutyrate
PMA —Pharmaceutical Manufacturers Association (U.S.)
PTO —Patent and Trademark Office (U.S.)
PVPA —Plant Variety Protection Act of 1970 (U.S.)
RAC —Recombinant DNA Advisory Committee (U.S.)
R&D —research and development
rDNA —recombinant DNA
Ri —root-inducing
RuBPCase —ribulose bisphosphate carboxylase
SAES —State Agricultural Experiment Stations (U.S.)
SBA —Small Business Administration (U.S.)

SBF	—Stiftelsen Bioteknisk Forksning; Biotechnology Research Foundation (Sweden)
SBIC	—Small Business Investment Corporation
SBIR	—Small Business Innovation Research
SCP	—single-cell protein
SERC	—Science and Economic Research Council (U.K.)
SFr	—Swiss francs
SNDA	—Supplemental New Drug Application
SOCal	—Standard Oil of California
SRBCs	—sheep red blood cells
STA	—Science and Technology Agency (Japan)
STU	—Stryelsen for Teknisk Utveckling; National Swedish Board for Technical Development
TDC	—Technical Development Corporation (U.K.)
T-DNA	—transferred-DNA
THMs	—trihalomethanes
Ti	—tumor-inducing
tPA	—tissue plasminogen activator
TRP	—tangible research property
TSCA	—Toxic Substance Control Act (U.S.)
UCLA	—University of California, Los Angeles
UCRDO	—University Connected Research and Development Organization (Israel)
UCSD	—University of California, San Diego
UCSF	—University of California, San Francisco
U.K.	—United Kingdom
UPOV	—International Convention for the Protection of New Varieties and Plants
U.S.C.	—United States Code
USDA	—U.S. Department of Agriculture
USM	—Unlisted Securities Market (U.K.)
UWG	—Gesetz gegen den unlauteren Wettbewerb; Unfair Competition Law of 1909 (F.R.G.)
VLSI	—Very-Large Scale Integration
VOCs	—volatile organic compounds
VST Act	—Virus, Serum, Toxin Act of 1913 (U.S.)
WARF	—Wisconsin Alumni Research Fund
WFG	—Deutsche Wagnisfinanzierungs-Gesellschaft; Risk Financing Society (F.R.G.)
WHO	—World Health Organization

Glossary of terms

Accession: In biotechnology, the addition of germplasm deposits to existing germplasm storage banks.

Acclimatization: The biological process whereby an organism adapts to a new environment. Describes process of developing micro-organisms that degrade toxic wastes in the environment.

Active immunity: Disease resistance in a person or animal due to antibody production after exposure to a microbial antigen following disease, inapparent infection, or inoculation. Active immunity is usually long-lasting. (Compare *passive immunity.*)

Adsorption: The taking up of molecules of gases, dissolved substances, or liquids by the surfaces of solids or liquids with which they are in contact.

Aerobic: Living or acting only in the presence of oxygen.

Affinity chromatography: The use of compounds, such as antibodies, bound to an immobile matrix to "capture" other compounds as a highly specific means of separation and purification.

Amino acids: The building blocks of proteins. There are 20 common amino acids.

Amino acid sequence: The linear order of amino acids in a protein.

Anaerobic: Living or acting in the absence of oxygen.

Antibiotic: A specific type of chemical substance that is administered to fight infections, usually bacterial infections, in humans or animals. Many antibiotics are produced by using micro-organisms; others are produced synthetically.

Antibody: A protein (immunoglobulin) produced by humans or higher animals in response to exposure to a specific antigen and characterized by specific reactivity with its complementary antigen. (See also *monoclonal antibodies.*)

Antidumping laws: Laws that prevent a country from exporting goods to another country and selling those goods below cost or more cheaply than in the home market. Antidumping duties may be imposed by a country to offset damages sustained from dumping. In the United States, the antidumping law most relevant to biotechnology is Section 337 of the Tariff Act of 1930 (19 U.S.C. 1337).

Antigen: A substance, usually a protein or carbohydrate which, when introduced in the body of a human or higher animal, stimulates the production of an antibody that will react specifically with it.

Antihemophilic factor (AHF): The fraction of whole blood that contains blood clotting agents. AHF is used to treat hemophilia, a set of hereditary disorders that prevent blood clotting.

Antimicrobial agent: See *antibiotic.*

Antiserum: Blood serum containing antibodies from animals that have been inoculated with an antigen. When administered to other animals or humans, antiserum produces passive immunity.

Applied research: Research to gain knowledge or understanding necessary for determining the means by which a recognized and specific need may be met (National Science Foundation definition). (See also *generic applied research.*)

Aromatic compound: A compound containing a benzene ring. Many specialty and commodity chemicals are aromatic compounds.

Ascites: Liquid accumulations in the peritoneal cavity. Used as a method for producing monoclonal antibodies.

Assay: A technique that measures a biological response.

Attenuated vaccine: Whole, pathogenic organisms that are treated with chemical, radioactive, or other means to render them incapable of producing infection. Attenuated vaccines are injected into the body, which then produces protective antibodies against the pathogen to protect against disease.

Autotrophic: Capable of self-nourishment (opposed to heterotrophic).

Bacillus subtilis (B. subtilis): An aerobic bacterium used as a host in rDNA experiments.

Bacteria: Any of a large group of microscopic organisms having round, rodlike, spiral, or filamentous unicellular or noncellular bodies that are often aggregated into colonies, are enclosed by a cell wall or membrane, and lack fully differentiated nuclei. Bacteria may exist as free-living organisms in soil, water, organic matter, or as parasites in the live bodies of plants and animals.

Bacteriophage (or phage)/bacterial virus: A virus that multiplies in bacteria. Bacteriophage lambda is commonly used as a vector in rDNA experiments.

Basic research: Research to gain fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind (National Science Foundation definition).

Batch processing: A method of bioprocessing in which a bioreactor is loaded with raw materials and micro-organisms, and the process is run to completion, at which time products are removed. (Compare *continuous processing*.)

Betaendorphin: A neuro-active polypeptide with analgesic properties similar to opiate compounds such as morphine.

Biocatalyst: An enzyme that plays a fundamental role in living organisms or industrially by activating or accelerating a process.

Biochemical: Characterized by, produced by, or involving chemical reactions in living organisms; a product produced by chemical reactions in living organisms.

Biochip: An electronic device that uses biological molecules as the framework for molecules that act as semiconductors and functions as an integrated circuit.

Bioconversion: A chemical conversion using a biocatalyst.

Biodegradation: The breakdown of substances by

Biological oxygen demand (BOD): The oxygen used in meeting the metabolic needs of aerobic organisms in water containing organic compounds.

Biological response modifer: Generic term for hormones, neuroactive compounds, and immunoactive compounds that act at the cellular level; many are possible targets for production with biotechnology.

Biological warfare agents: Biological products or processes that are determined to be useful in military applications and whose export is restricted for national security reasons.

Biologics: Vaccines, therapeutic serums, toxoids, antitoxins, and analogous biological products used to induce immunity to infectious diseases or harmful substances of biological origin.

Biomass: All organic matter that grows by the photosynthetic conversion of solar energy.

Biooxidation: Oxidation (the loss of electrons) catalyzed by a biocatalyst.

Biopolymers: Naturally occurring macromolecules that include proteins, nucleic acids, and polysaccharides.

Bioprocess: Any process that uses complete living cells or their components (e.g., enzymes, chloroplasts) to effect desired physical or chemical changes.

Bioreactor: Vessel in which a bioprocess takes place.

Biosensor: An electronic device that uses biological molecules to detect specific compounds.

Biosurfactant: A compound produced by living organisms that helps solubilize compounds such as organic molecules (e.g., oil and tar) by reducing surface tension between the compound and liquid.

Biosynthesis: Production, by synthesis or degradation, of a chemical compound by a living organism.

Biotechnology: Commercial techniques that use living organisms, or substances from those organisms, to make or modify a product, and including techniques used for the improvement of the characteristics of economically important plants and animals and for the development of micro-organisms to act on the environment. In this report, biotechnology is used to mean "new" biotechnology, which only includes the use of *novel* biological techniques—specifically, recombinant DNA techniques, cell fusion techniques, especially for the production of monoclonal antibodies, and new bioprocesses for commercial production.

Callus: An undifferentiated cluster of plant cells that is a first step in regeneration of plants from tissue culture.

Capacitor: A device that consists of two conductors insulated from each other by a dielectric. A capaci-

current, and introduces alternating current into a circuit.

Carboxylation: The addition of an organic acid group (COOH) to a molecule.

Catalysis: A modification, especially an increase, in the rate of a chemical reaction induced by a material (e.g., enzyme) that is chemically unchanged at the end of the reaction.

Catalyst: A substance that induces catalysis; an agent that enables a chemical reaction to proceed under milder conditions (e.g., at a lower temperature) than otherwise possible. Biological catalysts are enzymes; some nonbiological catalysts include metallic complexes.

Cell: The smallest structural unit of living matter capable of functioning independently; a microscopic mass of protoplasm surrounded by a semipermeable membrane, usually including one or more nuclei and various nonliving products, capable alone, or interacting with other cells, of performing all the fundamental functions of life.

Cell culture: The in vitro growth of cells isolated from multicellular organisms. These cells are usually of one type.

Cell differentiation: The process whereby descendants of a common parental cell achieve and maintain specialization of structure and function.

Cell fusion: Formation of a single hybrid cell with nuclei and cytoplasm from different cells.

Cell line: Cells that acquire the ability to multiply indefinitely in vitro.

Cellulase: The enzyme that digests cellulose to sugars.

Cellulose: A polymer of six-carbon sugars found in all plant matter; the most abundant biological compound on earth.

Centrifuge: A machine for whirling fluids rapidly to separate substances of different densities by centrifugal force; also, to whirl in a centrifuge.

***Chakrabarty* decision:** *Diamond* v. *Chakrabarty*, U.S. Department of Commerce, PTA, sec. 2105, 1980; landmark case in which U.S. Supreme Court majority held that the inventor of a new microorganism, whose invention otherwise met the legal requirements for obtaining a patent, could not be denied a patent solely because the invention was alive.

Chemostat selection: Screening process used to identify micro-organisms with desired properties, such as micro-organisms that degrade toxic chemicals. (See also *acclimatization*.)

Chloroplasts: Cellular organelles where photosynthesis occurs.

Chromatography: A process of separating gases, liquids, or solids in a mixture or solution by adsorption as the mixture or solution flows over the absorbent medium, often in a column. The substances are separated because of their differing chemical interaction with the absorbent medium.

Chromosomes: The rodlike structures of a cell's nucleus that store and transmit genetic information; the physical structure that contain genes. Chromosomes are composed mostly of DNA and protein and contain most of the cell's DNA. Each species has a characteristic number of chromosomes.

Clinical trial: One of the final stages in the collection of data for drug approval where the drug is tested in humans.

Clone: A group of genetically identical cells or organisms produced asexually from a common ancestor.

Cloning: The amplification of segments of DNA, usually genes.

Coding sequence: The region of a gene (DNA) that encodes the amino acid sequence of a protein.

Cofactors: Additional molecules needed for enzymatic function.

Colibacillosis: A bacterial disease that causes diarrhea, dehydration, and death in calves and piglets.

Commodity chemicals: Chemicals produced in large volumes that sell for less than $1 per pound (50¢ per kg). (Compare *specialty chemicals*.)

Commodity controls list (CCL): Large roster of items that have been identified under the Export Administration Act by the U.S. Department of Commerce to require a "validated license" before they can be exported to certain countries.

Complementary DNA (cDNA): DNA that is complementary to messenger RNA; used for cloning or as a probe in DNA hybridization studies.

Compulsory licensing: Laws that require the licensing of patents, presumably to ensure early application of a technology and to diffuse control over a technology.

Continuous processing: Method of bioprocessing in which raw materials are supplied and products are removed continuously, at volumetrically equal rates. (Compare *batch processing*.)

Corn wet milling: The processing of corn, including hydrolysis of starch, to yield products used for food and chemicals.

Cosmid: A DNA cloning vector consisting of plasmid and phage sequences.

Countervailing duties: Duties charged to importers when their product is determined to cause or threaten material injury to domestic industries producing similar products.

Corporate venture capital: Capital provided by

major corporations exclusively for high-risk investments.

Culture deposits: See *accession*.

Culture medium: Any nutrient system for the artificial cultivation of bacteria or other cells; usually a complex mixture of organic and inorganic materials.

Cytoplasm: The "liquid" portion of a cell outside and surrounding the nucleus.

Cytotoxic: Damaging to cells.

Debt financing: The use of outside or borrowed capital to finance business activities.

Deoxyribonucleic acid (DNA): A linear polymer, made up of deoxyribonucleotide repeating units, that is the carrier of genetic information; present in chromosomes and chromosomal material of cell organelles such as mitochondria and chloroplasts, and also present in some viruses. The genetic material found in all living organisms. Every inherited characteristic has its origin somewhere in the code of each individual's DNA.

Deposit requirements: Patent requirements for inventors to turn over at the time of patent application a sample of the invention which is maintained throughout the life of the patent.

Diagnostic products: Products that recognize molecules associated with disease or other biologic conditions and are used to diagnose these conditions.

Dicots (dicotyledons): Plants with two first embryonic leaves and nonparallel veined mature leaves. Examples are soybean and most flowering plants.

Disclosure requirements: A patent requirement for adequate public disclosure of an invention that enables other people to build and use the invention without "undue" experimentation.

DNA: Deoxyribonucleic acid.

DNA base pair: A pair of DNA nucleotide bases. Nucleotide bases pair across the double helix in a very specific way: adenine can only pair with thymine; cytosine can only pair with guanine.

DNA probe: A sequence of DNA that is used to detect the presence of a particular nucleotide sequence.

DNA sequence: The order of nucleotide bases in the DNA helix; the DNA sequence is essential to the storage of genetic information.

DNA synthesis: The synthesis of DNA in the laboratory by the sequential addition of nucleotide bases.

Downstream processing: After bioconversion, the purification and separation of the product.

Drug: Any chemical compound that may be administered to humans or animals as an aid in the treatment of disease.

Elution: The removal of adsorbed material from an adsorbent, such as the removal of a product from an enzyme bound on a column.

Emulsification: The process of making lipids soluble in water.

Enablement requirement: A patent requirement for adequate public disclosure of an invention, enabling others in the relevant field of technology to build and use the invention.

Endorphins: Opiate-like, naturally occurring peptides with a variety of analgesic effects throughout the endocrine and nervous systems.

Enkephalins: Small, opiate-like peptides with analgesic effects in the brain.

Enzyme: Any of a group of catalytic proteins that are produced by living cells and that mediate and promote the chemical processes of life without themselves being altered or destroyed.

Equity capital: Capital proceeds arising from the sale of company stock.

Equity investment: An investment made in a company in exchange for a part ownership in that company.

***Escherichia coli* (*E. coli*):** A species of bacteria that inhabits the intestinal tract of most vertebrates. Some strains are pathogenic to humans and animals. Many nonpathogenic strains are used experimentally as hosts for rDNA.

Eukaryote: A cell or organism with membrane-bound, structurally discrete nuclei and well-developed cell organelles. Eukaryotes include all organisms except viruses, bacteria, and blue-green algae. (Compare *prokaryote*.)

Export controls: Laws that restrict technology transfer and trade for reasons of national security, foreign policy, or economic policy.

Fatty acids: Organic acids with long carbon chains. Fatty acids are abundant in cell membranes and are widely used as industrial emulsifiers.

Feedstocks: Raw materials used for the production of chemicals.

Fermentation: An anaerobic bioprocess. Fermentation is used in various industrial processes for the manufacture of products such as alcohols, acids, and cheese by the action of yeasts, molds, and bacteria.

Fibrinolytic agents: Blood-borne compounds that activate fibrin in order to dissolve blood clots.

Flocculating agent: A reagent added to a dispersion of solids in a liquid to bring together the fine particles into larger masses.

Food additive (or food ingredient): A substance that becomes a component of food or affects the characteristics of food and, as such, is regulated by the U.S. Food and Drug Administration.

Foot-and-mouth disease: A highly contagious virus disease of cattle, pigs, sheep, and goats that is characterized by fever, salivation, and formation of vesicles in the mouth, pharynx and on the feet and is transmissable to humans.

Fractionation (of blood): Separation of blood by centrifugation, resulting in components sold as plasma, serum albumin, antihemophilic factor, and other products.

Free-living organism: An organism that does not depend on other organisms for survival.

Fungus: Any of a major group of saprophytic and parasitic plants that lack chlorophyll, including molds, rusts, mildews, smuts, and mushrooms.

Gamma globulin (GG): A protein component of blood that contains antibodies and confers passive immunity.

Gene: The basic unit of heredity; an ordered sequence of nucleotide bases, comprising a segment of DNA. A gene contains the sequence of DNA that encodes one polypeptide chain (via RNA).

Gene amplification: In biotechnology, an increase in gene number for a certain protein so that the protein is produced at elevated levels.

Gene expression: The mechanism whereby the genetic directions in any particular cell are decoded and processed into the final functioning product, usually a protein. See also *transcription* and *translation*.

Generic applied research: Research along the continuum between the two poles of basic and applied. This research may be characterized as follows: 1) it is not committed to open-ended expansion of knowledge as university basic research typically is but is less specific (more widely applicable or "generic") than the typical industrial product or process development effort; 2) it has more well-defined objectives than basic research but is long term relative to product and process development; and 3) it is high risk, in the sense that the stated objectives may fail and the resources committed may be lost for practical purposes.

Gene transfer: The use of genetic or physical manipulation to introduce foreign genes into host cells to achieve desired characteristics in progeny.

Genome: The genetic endowment of an organism or individual.

Genus: A taxonomic category that includes groups of closely related species.

Germ cell: The male and female reproductive cells; egg and sperm.

Germplasm: The total genetic variability available to a species.

Glycoproteins: Proteins with attached sugar groups.

Glucose: A 6-carbon sugar molecule used as a basic energy source by the cells of most organisms.

Glycosylation: The attachment of sugar groups to a molecule, such as a protein.

Government procurement: The acquisition by a government of goods or services. Government procurement may stimulate development of technology.

Growth hormone (GH): A group of peptides involved in regulating growth in higher animals.

Helminth: Parasitic worm.

Herbicide: An agent (e.g., a chemical) used to destroy or inhibit plant growth; specifically, a selective weed killer that is not injurious to crop plants.

High performance liquid chromatography (HPLC): A recently developed type of chromatography that is potentially important in downstream processing.

Hormone: A chemical messenger found in the circulation of higher organisms that transmits regulatory messages to cells.

Host: A cell whose metabolism is used for growth and reproduction of a virus, plasmid, or other form of foreign DNA.

Host-vector system: Compatible combinations of host (e.g., bacterium) and vector (e.g., plasmid) that allow stable introduction of foreign DNA into cells.

Human chorionic gonadotropin (HCG): A hormone produced by human placenta, indicating pregnancy; widespread target of MAb developers to diagnose pregnancy at an early stage.

Human insulin (hI): Hormone that stimulates cell growth via glucose uptake by cells. Insulin deficiency leads to diabetes.

Human serum albumin (HSA): Abundant protein in human blood; as a product, used in highest quantities in medicine, primarily in burn, trauma, and shock patients.

Hybrid: The offspring genetically dissimilar parents (e.g., a new variety of plant or animal that results from cross-breeding two different existing varieties, a cell derived from two different cultured cell lines that have fused).

Hybridization: The act or process of producing hybrids.

Hybridoma: Product of fusion between myeloma cell (which divides continuously in culture and is "immortal") and lymphocyte (antibody-producing cell); the resulting cell grows in culture and produces monoclonal antibodies.

Hybridoma technology: See *monoclonal antibody technology*.

Hydrolysis: Chemical reaction involving addition of water to break bonds.

Hydroxylation: Chemical reaction involving addition of hydroxyl (-OH) group to chemical compound.

Immobilized enzyme or cell techniques: Techniques used for the fixation of enzymes or cells onto solid supports. Immobilized cells and enzymes are used in continuous bioprocessing.

Immune response: The reaction of an organism to invasion by a foreign substance. Immune responses are often complex, and may involve the production of antibodies from special cells (lymphocytes), as well as the removal of the foreign substance by other cells.

Immunoassay: The use of antibodies to identify and quantify substances. The binding of antibodies to antigen, the substance being measured, is often followed by tracers such as radioisotopes.

Immunogenic: Capable of causing an immune response. (See also *antigen*.)

Immunotoxin: A molecule attached to an antibody capable of killing cells that display the antigen to which the antibody binds.

Interferons (Ifns): A class of glycoproteins (proteins with sugar groups attached at specific locations) important in immune function and thought to inhibit viral infections.

In vitro: Literally, in glass; pertaining to a biological reaction taking place in an artificial apparatus; sometimes used to include the growth of cells from multicellular organisms under cell culture conditions. In vitro diagnostic products are products used to diagnose disease outside of the body after a sample has been taken from the body.

In vivo: Literally, in life; pertaining to a biological reaction taking place in a living cell or organism. In vivo products are products used within the body.

Joint venture: Form of association of separate business entities which falls short of a formal merger but unites certain agreed on resources of each entity for a limited purpose; in practice most joint ventures are partnerships.

Leaching: The removal of a soluble compound such as an ore from a solid mixture by washing or percolating.

Lignin: A major component of wood.

Lignocellulose: The composition of woody biomass, including lignin and cellulose.

Lignolytic: Pertaining to the breakdown of lignin.

Linker: A small fragment of synthetic DNA that has a restriction site useful for gene cloning, which is used for joining DNA strands together.

Lipids: A large, varied class of water-insoluble organic molecules; includes steroids, fatty acids, prostaglandins, terpenes, and waxes.

Liposome transfer: The process of enclosing biological compounds inside a lipid membrane and allowing the complex to be taken up by a cell.

Lymphocytes: Specialized white blood cells involved in the immune response; B lymphocytes produce antibodies.

Lymphokines: Proteins that mediate interactions among lymphocytes and are vital to proper immune function.

Medical device: An instrument or apparatus (including an in vitro reagent such as MAbs) intended for use in the diagnosis or treatment of a disease or other condition and which does not achieve its intended purpose through chemical action within or on the body.

Messenger RNA (mRNA): RNA that serves as the template for protein synthesis; it carries the transcribed genetic code from the DNA to the protein synthesizing complex to direct protein synthesis.

Metabolism: The physical and chemical processes by which foodstuffs are synthesized into complex elements, complex substances are transformed into simple ones, and energy is made available for use by an organism.

Metabolite: A product of metabolism.

Metallothioneins: Proteins, found in higher organisms, that have a high affinity for heavy metals.

Methanogens: Bacteria that produce methane as a metabolic product.

Micro-organisms: Microscopic living entities; microorganisms can be viruses, prokaryotes (e.g., bacteria), or eukaryotes (e.g., fungi).

Microencapsulation: The process of surrounding cells with a permeable membrane.

Mixed culture: Culture containing two or more types of micro-organisms.

Molecule: A group of atoms held together by chemical forces; the smallest unit of matter which can exist by itself and retain its chemical identity.

Monoclonal antibodies (MAbs): Homogeneous antibodies derived from a single clone of cells; MAbs recognize only one chemical structure. MAbs are useful in a variety of industrial and medical capacities since they are easily produced in large quantities and have remarkable specificity.

Monoclonal antibody technology: The use of hybridomas that produce monoclonal antibodies for a variety of purposes. Hybridomas are maintained

in cell culture or, on a larger scale, as tumors (ascites) in mice.

Monocots (monocotyledons): Plants with single first embryonic leaves, parallel-veined leaves, and simple stems and roots. Examples are cereal grains such as corn, wheat, rye, barley, and rice.

Multigenic: A trait specified by several genes.

Mutagenesis: The induction of mutation in the genetic material of an organism; researchers may use physical or chemical means to cause mutations that improve the production of capabilities of organsims.

Mutagen: An agent that causes mutation.

Mutant: An organism with one or more DNA mutations, making its genetic function or structure different from that of a corresponding wild-type organism.

Mutation: A permanent change in a DNA sequence.

Myeloma: Antibody-producing tumor cells.

Myeloma cell line: Myeloma cells established in culture.

Neurotransmitters: Small molecules found at nerve junctions that transmit signals across those junctions.

New biotechnology firm (NBF): A company formed after 1976 whose sole function is research, development, and production using biotechnological means.

NIH Guidelines: Guidelines established by U.S. National Institutes of Health to regulate the safety of NIH-funded research involving recombinant DNA.

Nitrate: A compound characterized by a NO_3-group. Sodium nitrate and potassium nitrate are used as fertilizers.

Nitrogen fixation: The conversion of atmospheric nitrogen gas to a chemically combined form, ammonia (NH_3) which is essential to growth. Only a limited number of micro-organisms can fix nitrogen.

Nodule: The anatomical part of a plant root in which nitrogen-fixing bacteria are maintained in a symbiotic relationship with the plant.

Nodulins: Proteins, possibly enzymes, present in nodules; function unknown.

Nontariff trade barrier: A government regulation, other than a tariff (see below), that directly alters the volume or composition of international trade. Examples include quotas (restrictions on the quantity of goods imported), orderly marketing agreements (by which exporters agree to restrict the volume of goods exported), exchange controls (which constrain the value of foreign exchange spent rather than the number of units purchased), government preferences in purchases, and standards and certification systems.

Nucleic acids: Macromolecules composed of sequences of nucleotide bases. There are two kinds of nucleic acids: DNA, which contains the sugar deoxyribose, and RNA, which contains the sugar ribose.

Nucleotide base: A structural unit of nucleic acid. The bases present in DNA are adenine, cytosine, guanine, and thymine. In RNA, uracil substitutes for thymine.

Nucleus: A relatively large spherical body inside a cell that contains the chromosomes.

Oligonucleotides: Short segments of DNA or RNA.

Organelle: A specialized part of a cell that conducts certain functions. Examples are nuclei, chloroplasts, and mitochrondria, which contain most of the genetic material, conduct photosynthesis, and provide energy, respectively.

Organic compounds: Molecules that contain carbon.

Organic micropollutant: Low molecular weight organic compounds considered hazardous to humans or the environment.

Passive immunity: Disease resistance in a person or animal due to the injection of antibodies from another person or animal. Passive immunity is usually short-lasting. (Compare *active immunity*.)

Patent: A limited property right granted to inventors by government allowing the inventor of a new invention the right to exclude all others from making, using, or selling the invention unless specifically approved by the inventor, for a specified time period in return for full disclosure by the inventor about the invention.

Pathogen: A disease-producing agent, usually restricted to a living agent such as a bacterium or virus.

Peptide: A linear polymer of amino acids. A polymer of numerous amino acids is called a *polypeptide*. Polypeptides may be grouped by function, such as "neuroactive" polypeptides.

pH: A measure of the acidity or basicity of a solution on a scale of 0 (acidic) to 14 (basic). For example, lemon juice has a pH of 2.2 (acidic), water has a pH of 7.0 (neutral), and a solution of baking soda has a pH of 8.5 (basic).

Pharmceuticals: Products intended for use in humans, as well as in vitro applications to humans, including drugs, vaccines, diagnostics, and biological response modifiers.

Photorespiration: Reaction in plants that competes with the photosynthetic process. Instead of fixing CO_2, RuBPCase can utilize oxygen, which results in a net loss of fixed CO_2.

Photosynthesis: The reaction carried out by plants where carbon dioxide from the atmosphere is fixed into sugars in in the presence of sunlight; the transformation of solar energy into biological energy.

Plant Patent Act of 1930 (35 U.S.C. §5161-164): Confers exclusive license on developer of new and distinct asexually produced varieties other than tuber-propagated plants for 17 years.

Plant Variety Protection Act of 1970 (7 U.S.C. §2321): Provides patent-like protection to new plants reproduced sexually.

Plasma: The liquid (noncellular) fraction of blood. In vertebrates, it contains many important proteins (e.g., fibrinogen, responsible for clotting).

Plasmid: An extrachromosomal, self-replicating, circular segment of DNA; plasmids (and some viruses) are used as "vectors" for cloning DNA in bacterial "host" cells.

Polymer: A linear or branched molecule of repeating subunits.

Polypeptide: A long peptide, which consists of amino acids.

Polysaccharide: A polymer of sugars.

Prior art: Publicly known technology; patent requirements include the demonstration of the novelty of an invention, as distinguished from prior art.

Probe: See *DNA probe.*

Proinsulin: A precursor protein of insulin.

Prokaryote: A cell or organism lacking membrane-bound, structurally discreet nuclei and organelles. Prokaryotes include bacteria and the blue-green algae. (Compare *eukaryote.*)

Promoter: A DNA sequence in front of a gene that controls the initiation of "transcription" (see below).

Prophylaxis: Prevention of disease.

Protease: Protein digesting enzyme.

Protein: A polypeptide consisting of amino acids. In their biologically active states, proteins function as catalysts in metabolism and, to some extent, as structural elements of cells and tissues.

Protoplast fusion: The joining of two cells in the laboratory to achieve desired results, such as increased viability of antibiotic-producing cells.

Protozoa: Diverse phylum of eukaryotic microorganisms; structure varies from simple single cells to colonial forms; nutrition may be phagotropic or autotrophic; some protozoa are pathogenic.

Pyrogenicity: The tendency for some bacterial cells or parts of cells to cause inflammatory reactions in the body, which may detract from their usefulness as pharmaceutical products.

Public offering: The Securities and Exchange Commission approved sale of company stock to the public.

R&D limited partnership: A risk capital source and tax sheltered mechanism for funding the R&D of new products. It raises the potential rate of return to investors without adding extra cost to the corporation.

Reagent: A substance that takes part in a chemical reaction.

Recombinant DNA (rDNA): The hybrid DNA produced by joining pieces of DNA from different organisms together in vitro.

Recombinant DNA technology: The use of recombinant DNA for a specific purpose, such as the formation of a product or the study of a gene.

Recombination: Formation of a new association of genes or DNA sequences from different parental origins.

Regeneration: The laboratory process of growing a whole plant from a single cell or small clump of cells.

Regulatory sequence: A DNA sequence involved in regulating the expression of a gene.

Replication: The synthesis of new DNA from existing DNA and the formation of new cells by cell division.

Resistance gene: Gene that provides resistance to an environmental stress such as an antibiotic or other chemical compound.

Resistor: A device designed to limit electron flow in an electric circuit by a definite amount, resulting in a limited current or a voltage drop.

Restriction enzymes: Bacterial enzymes that cut DNA at specific DNA sequences.

Ri-plasmid: Plasmid from *Agrobacterium rhizogenes* used as plant vector.

RNA: Ribonucleic acid. (See also *messenger RNA.*)

RuBPCase (ribulose bisphosphate carboxylase): An enzyme that catalyzes the critical step of the photosynthetic CO_2 cycle.

Saccharification: The degradation of polysaccharides to sugars.

Scale-up: The transition of a process from an experimental scale to an industrial scale.

Selection: A laboratory process by which cells or organisms are chosen for specific characteristics.

Semiconductor: A material such as silicon or germanium with electrical conductivities intermediate between good conductors such as copper wire and insulators such as glass.

Semiconductor device: An electronic device that uses a semiconductor to limit or direct the flow of electrons. Examples are transistors, diodes, and integrated circuits.

Semiconductor industry: Companies that manufacture semiconductor devices. As used in this report, the description of the semiconductor in-

dustry is that deriving from the period between 1947 (discovery of the transistor) to the early 1960's.

Single cell protein: Cells, or protein extracts, of micro-organisms grown in large quantities for use as human or animal protein supplements.

Slimes: Aggregations of microbial cells that pose environmental and industrial problems; may be amenable to biologic control.

Sludge: Precipitated solid matter produced by water and sewage treatment or industrial problems; may be amenable to biologic control.

Small Business Investment Corporations (SBICs): Private companies licensed by the Small Business Association (SBA) and owned by stockholders who have made investments in exchange for equity. SBICs are required by SBA to invest or loan money exclusively to U.S. small businesses.

Somaclonal variation: Genetic variation produced from the culture of plant cells from a pure breeding strain; the source of the variation is not known.

Specialty chemicals: Chemicals, usually produced in small volumes, that sell for more than $1 per pound (50¢ per kg). (Compare *commodity chemicals.*)

Species: A taxonomic subdivision of a genus. A group of closely related, morphologically similar individuals which actually or potentially interbreed.

Spectrometer: An instrument used for analyzing the structure of compounds on the basis of their light-absorbing properties.

Starch: A polymer of glucose molecules used by some organisms as a means of energy storage; starch is broken down by enzymes (amylases) to yield glucose, which can be used as a feedstock for chemical or energy production.

Startup financing: Financing usually supplied by venture capitalist to fund the early R&D, production, sale of a new company's products.

Steroid: A group of organic compounds, some of which act as hormones to stimulate cell growth in higher animals and humans.

Storage protein genes: Genes coding for the major proteins found in plant seeds.

Strain: A group of organisms of the same species having distinctive characteristics but not usually considered a separate breed or variety. A genetically homogenous population of organisms at a subspecies level that can be differentiated by a biochemical, pathogenic, or other taxonomic feature.

Subsidy: A government intervention in the form of either grants, loans, or tax preferences that are directed to a particular domestic industry.

Substrate: A substance acted upon, for example, by an enzyme.

Subunit vaccine: A vaccine that contains only portions of a surface molecule of a pathogen. Subunit vaccines can be prepared by using rDNA technology to produce all or part of the surface protein molecule or by artificial (chemical) synthesis of short peptides.

Symbiont: An organism living in symbiosis, usually the smaller member of a symbiotic pair of dissimilar size.

Symbiosis: The living together of two dissimilar organisms in mutually beneficial relationships.

Tariff: Charges levied on importers of a particular good by a government in return for granting access to the government's domestic markets, which may occur at the expense of domestic industry; sometimes high tariffs are used to discourage importation and protect domestic industry.

T-DNA: Transfer DNA; that part of Ri or Ti plasmids that is transferred to the plant chromosome.

Technology transfer: The movement of technical information and/or materials, used for producing a product or process, from one sector to another; most often refers to flow of information between public and private sectors or between countries.

Therapeutics: Pharmaceutical products used in the treatment of disease.

Thermophilic: Heat loving. Usually refers to micro-organisms that are capable of surviving at elevated temperatures; this capability may make them more compatible with industrial biotechnology schemes.

Thrombolytic enzymes: Enzymes such as streptokinase and urokinase that initiate the dissolution of blood clots.

Thrombosis: Blockage of blood vessels.

Ti plasmid: Plasmid from *Agrobacterium tumefaciens* used as a plant vector.

Totipotency: The capacity of a higher organism cell to differentiate into an entire organism. A totipotent cell contains all the genetic information necessary for complete development.

Toxicity: The ability of a substance to produce a harmful effect on an organism by physical contact, ingestion, or inhalation.

Toxin: A substance, produced in some cases by disease-causing micro-organisms, which is toxic to other living organisms.

Toxoid: Detoxified toxin, but with antigenic properties intact.

Trade secret: An invention used continuously by its holder in his or her business to maintain a competitive edge over other competitors who do not know or use it. Trade secrets are often used instead of patents to protect production information.

Transcription: The synthesis of messenger RNA on

a DNA template; the resulting RNA sequence is complementary to the DNA sequence. This is the first step in gene expression. (See also *translation*.)

Transformation: The introduction of new genetic information into a cell using naked DNA.

Transistor: An active component of an electrical circuit consisting of semiconductor material to which at least three electrical contacts are made so that it acts as an amplifier, detector, or switch.

Translation: The process in which the genetic code contained in the nucleotide base sequence of messenger RNA directs the synthesis of a specific order of amino acids to produce a protein. This is the second step in gene expression. (See also *transcription*.)

Transposable element: Segment of DNA which moves from one location to another among or within chromosomes in possibly a predetermined fashion, causing genetic change; may be useful as a vector for manipulating DNA.

Trihalomethanes (THMs): Organic micropollutants and potential carcinogens, consisting of three halide elements attached to a single carbon atom; their destruction during water purification may be done biologically.

Turbid: Thick or opaque with matter in suspension.

Vaccine: A suspension of attenuated or killed bacteria or viruses, or portions thereof, injected to produce active immunity. (See also *subunit vaccine*.)

Vector: DNA molecule used to introduce foreign DNA into host cells. Vectors include plasmids, bacteriophages (virus), and other forms of DNA. A vector must be capable of replicating autonomously and must have cloning sites for the introduction of foreign DNA.

Venture capital (venture capital funds): Money that is invested in companies with which a high level of risk is associated.

Virus: Any of a large group of submicroscopic agents infecting plants, animals, and bacteria and unable to reproduce outside the tissues of the host. A fully formed virus consists of nucleic acid (DNA or RNA) surrounded by a protein or protein and lipid coat.

Viscosity: A measure of a liquid's resistance to flow.

Volatile organic compounds (VOCs): Group of toxic compounds found in ground water and that pose environmental hazards; their destruction during water purification may be done biologically.

Wild-type: The most frequently encountered phenotype in natural breeding populations.

Yeast: A fungus of the family Saccharomycetacea that is used especially in the making of alcoholic liquors and as leavening in baking. Yeast are also commonly used in bioprocesses.

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Appendix J

Currency Conversion Factors

The following is a list of conversion factors for currencies from the countries studied in the report. All figures are averages from calendar year 1982 and were provided by the International Monetary Fund.

1 dollar = 249.05 Japanese yen (¥)

1 dollar = 179.51 Brazilian cruzeiros (BCr)

1 dollar = 24.267 Israeli shekels (IS)

1 dollar = 6.5724 French francs (F)

1 dollar = 6.2826 Swedish kroner (Skr)

1 dollar = 2.67021 Netherlands guilder (NLG)

1 dollar = 2.4266 German marks (DM)

1 dollar = 2.0303 Swiss francs (SwF)

1 dollar = 1.23370 Canadian dollars ($C)

1 dollar = 0.98586 Australian dollars ($A)

1 dollar = 0.5713 British Pounds (£)

Appendix K

Other Contractors, Contributors, and Acknowledgments

Other contractors

Robert Barker
Cornell University
Ithaca, N.Y.

Keith Gibson
Medical Research Council
London, England

Loren Graham
Washington, D.C.

Kozo Yamamura
University of Washington
Seattle, Wash.

Contributors

James E. Bailey
California Institute of Technology

Harvey Blanch
University of California

Hugh Bollinger
NPI

Charles Cooney
Massachusetts Institute of Technology

Morris Danzig
CPC International

Wensley Haydon-Baillie
Porton/LH International

Ed Lipinsky
Battelle Columbus Laboratories

Hunt McCauley
Big Timber, Mont.

Roger Morris
University of Minnesota

Patrick O'Connor
Genetic Sciences International

Robert Rabson
U.S. Department of Energy

Mark Radcliffe
Brobeck, Phleger & Harrison

John W. Schlicher
Townsend and Townsend

John Weil
(formerly of) Bendix Corp.

Acknowledgments

Lynne Alexander
Office of Technology Assessment

William Amon, Jr.
Cetus Corp.

Mary Anderson
Office of Technology Assessment

Roger Andewelt
U.S. Department of Justice

Paul Baumann
University of California

William R. Beisel
U.S. Army Medical Research Institute
for Infectious Diseases

Frederick Betz
U.S. Environmental Protection Agency

Judy Blakemore
Cetus Corp.

Detlef Boldt
Embassy of the Federal Republic of Germany

Lawrence J. Brady
U.S. Department of Commerce

Corale Brierley
Advanced Mineral Technologies, Inc.

Mark F. Cantley
Commission of the European Communities

Ronald Cape
Cetus Corp.

Peter Carlson
Crop Genetics International N.V.

Earl Cilly
Stanford University

Mary Clutter
U.S. National Science Foundation

Stanley Cohen
Stanford University

Eileen Collins
U.S. National Science Foundation

Brian Cunningham
Genentech, Inc.

Linda Curran
Battelle Columbus Laboratories

Michael Curran
Micro Industries

Eugene P. Damm, Jr.
International Business Machines Corp.

Lee Davenport
Greenwich, Conn.

William Davies
(formerly at) Armos Corp.

John Dearden
Johns Hopkins University

Arnold Demain
Massachusetts Institute of Technology

Roger G. Ditzel
University of California

Donald K. Dougall
University of Tennessee

Sidney Draggan
U.S. National Science Foudnation

George H. Dummer
Massachusetts Institute of Technology

Diana Dutton
Stanford University

James J. Eberhardt
U.S. Department of Energy

Gerry J. Elman
Elman, Shaiman and Moskowitz

Frederic Eustis
Biogen, Inc.

L. Peter Farkas
Craig and Burns

Norman Fast
Capital Publishing Corp.

Alan Fechter
U.S. National Science Foundation

Andrew J. Ferrara
Collaborative Research, Inc.

Philip Filner
ARCO Plant Cell Research Institute

William Finnerty
University of Georgia

James E. Flinn
Battelle Columbus Laboratories

Gene Fox
ARCO Plant Cell Research Institute

Orrie M. Friedman
Collaborative Research, Inc.

James Glavin
Genetic Systems Corp.

Norm Goldfarb
Calgene, Inc.

June Goodfield
East Sussex, England

Michael Gough
Office of Technology Assessment

Tom Graham
Kilpatrick & Cody

James D. Grant
CPC International

Harold P. Green
George Washington University

Lorance Greenlee
Agrigenetics Corp.

Joe Griffin
Wald, Harkrader, and Ross

Charles Groginski
Vega Biochemicals

Ben Hall
University of Washington School of Medicine

Albert P. Halluin
Cetus Corp.

Gerald Hickman
Collaborative Research, Inc.

Richard Hill
U.S. Environmental Protection Agency

Steven Hochhauser
Redwood City, Calif.

Anne Hollander
U.S. Environmental Protection Agency

John Holt
Eli Lilly & Co.

Jack Houck
Endorphin, Inc.

John Jennings
Pharmaceutical Manufacturers Association

Elmima Johnson
U.S. National Science Foundation

David Kabikoff
Hybritech, Inc.

Paul Kesselring
Swiss Federal Institute of Reactor Research

George H. Kidd
(formerly of) International Plant Research Institute

Wayne Kindsvogel
Zymos Corp.

Jay Kingham
Pharmaceutical Manufacturers Association

Jay Kraemer
Fried, Frank, Harris, Shriver, & Kampelman

Sheldon Krimsky
Tufts University

Lawrence P. Kunstadt
Novatech Resource Corp.

Stephen E. Lawton
Pierson, Ball, and Dowd

Jeff Lepon
Kornmeier, McCarthy, Lepon & Harris

Morris Levin
U.S. Environmental Protection Agency

Warren Levinson
Massachusetts General Hospital

Herman Lewis
U.S. National Science Foundation

Malcolm D. Lilly
University College, London

Charles R. Lipsey
Finnegan, Henderson, Farabow, Garrett and Dunner

Max Lyon
Genetic Systems Corp.

Hugh Macki
Cruachem, Inc.

Bruce F. Mackler
Meyer, Faller, and Weisman

William E. Marshall
General Foods Corp.

James McAlear
Gentronix International, Inc.

James McCullough
U.S. Congressional Research Service

Donald E. McElmury
CPC International

Thomas O. McGarity
University of Texas at Austin

Bruce Merchant
U.S. Food and Drug Administration

Larry Miike
Office of Technology Assessment

Teri Miles
Office of Technology Assessment

Elizabeth Milewski
U.S. National Institutes of Health

Henry Miller
U.S. Food and Drug Administration

Charles Muscoplat
Molecular Genetics, Inc.

Kay Noel
Cetus Corp.

John R. Norell
Phillips Petroleum Co.

Michael G. Norton
British Embassy

Thomas C. O'Brien
(formerly of) U.S. National Bureau of Standards

David V. O'Donnell
Commonwealth of Virginia

Sandra Panem
Brookings Institution

Richard Pearson
University of Sussex

Joseph Perpich
(formerly of) Genex Corp.

George Pierce
Battelle Columbus Laboratories

Jean-Claude Pinon
Embassy of France

Harvey S. Price
Industrial Biotechnology Association

Frank Pugliese
U.S. Food and Drug Administration

William H. Rastetter
Genentech, Inc.

Neils Reimers
Stanford University

David Rosenbloom
Boston, Mass.

Roy Rothwell
University of Sussex

Robert Ryan
U.S. Office of Naval Research

Louis G. Santucci
Pharmaceutical Manufacturers Association

Ken Sargeant
Commission of the European Communities

Holly Schauer
U.S. Department of Agriculture

Stanley Schlosser
U.S. Patent and Trademark Office

Charles D. Scott
Oak Ridge National Laboratory

David Seligman
Hoffmann-La Roche, Inc.

Al Shapero
Ohio State University

Stuart Shemtob
U.S. Department of Justice

Gerald D. Shockman
Temple University

Alexander W. Sierck
Beveridge and Diamond

David Silberman
Agrigenetics Corp.

Allen Singer
National Academy of Sciences

Ira Skurnick
U.S. Defense Advanced Research Projects Agency

Hedy Sladovich
(formerly of) E. F. Hutton

Ed Soule
Weyerhauser Co.

Gary Steele
Genentech, Inc.

R. W. Stieber
Merck & Co., Inc.

Eliezer Tal
Inter-American Development Bank

Masami Tanaka
Ministry of International Trade and Industry (Japan)

Fred Tarpley
Georgia Institute of Technology

Ron Taylor
Hybritech, Inc.

Albert H. Teich
American Association for the Advancement of Science

Elizabeth Terry
U.S. Central Intelligence Agency

Eleanor Thomas
U.S. National Science Foundation

Susan Thompson
U.S. Food and Drug Administration

Sue Tolin
U.S. Department of Agriculture

Ezra Vogel
Harvard University

Don Wallace
Georgetown University Law Center

William J. Walsh, III
U.S. Department of State

Amy Walton
U.S. National Science Foundation

Daniel Wang
Massachusetts Institute of Technology

Robert Warren
U.S. Naval Air System Command

Rick Weber
U.S. National Institute of Mental Health

William A. Weigand
(formerly of) U.S. National Science Foundation

Barry Weiner
Enzo Biochem

Bruno O. Weinschel
Weinschel Engineering

Philip J. Whitcome
Amgen

Bill Williams
ARCO Plant Cell Research Institute

John Wilson
(formerly of) Bendix Research

Phyllis Windle
Office of Technology Assessment

Zachary Wochok
Monsanto Co.

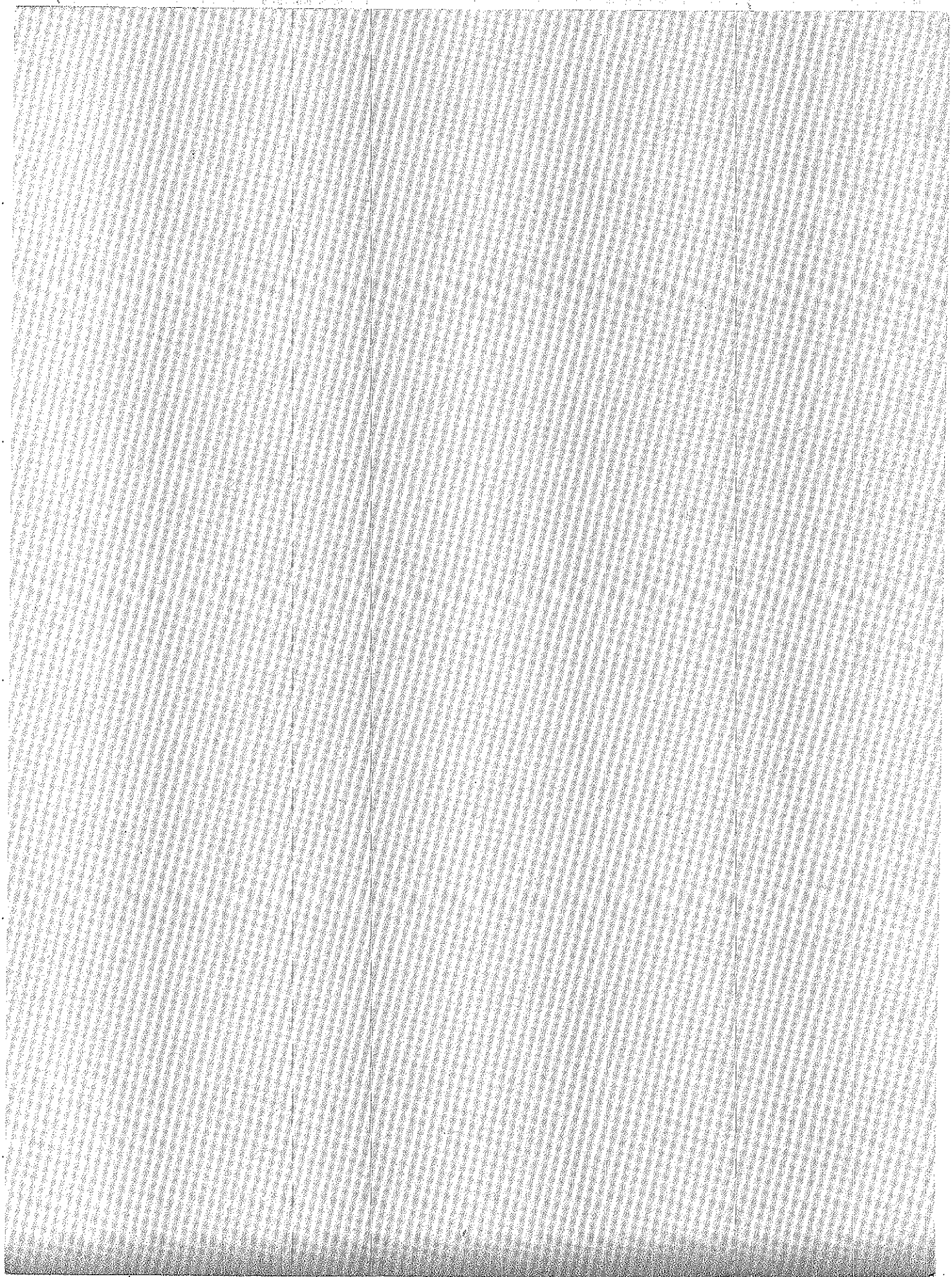
James Womack
Massachusetts Institute of Technology

Jim Young
Zoecon

Oskar Zaborsky
(formerly of) U.S. National Science Foundation

Michael E. Zacharia
U.S. Department of Commerce

Index



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