reaching the issue of patents on life forms of any kind, let alone higher form.[164]

The patentability of synthetic but naturally occurring plasmids was, in effect, considered in this treatise's discussion of "duplicated products of nature." The claim could be limited by the word "synthetic." The CCPA held in the *Wakefield* case that a claim to a synthetic rubber did not encompass purified natural rubber, which was prior art.[165]

A claim to a "hybrid" plasmid—plasmid whose genetic material comes from organisms which naturally exchange genetic material—might be attacked if it could be shown that a similar hybrid had arisen naturally prior to the "invention" of the plasmid by the claimant. In the tetracycline case, a critical question was whether tetracycline had been inadvertently produced in the prior art fermentation broth.[166]

This question as to the patentability of a hybrid plasmid is part of a larger question as to the legal effect of what is sometimes termed an "accidental anticipation." *Tilghman v. Proctor* held that the formation of fatty acid in prior art processes, "accidentally and unwittingly produced, whilst the operators were in pursuit of other and different results, without exciting attention and without even being known what was done or how it had been done, it would be absurd to say that this was an anticipation of Tilghman's discovery.[167] This statement of the law was refined by Learned Hand in *H.K. Regar & Sons v. Scott & Williams,* where he limited it to circumstances

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[164] Genentech S.Ct.Br. 15-16 and n.26 at 17. *Cf.* T. D. Kiley, Learning to Live with the Living Invention, 7 APLA Q.J. 220, 221-222, 230 (1979). On the other hand, Jackson states that "[I]f one talks about patenting a microorganism, one is talking about patenting a specific set of genes. . . . In terms of their functional potential, it is going to be very difficult to define when a DNA molecule, an inanimate object, stops and a microorganism, an animate object, starts." Jackson, Patenting of Genes: What Will the Ground Rules Be?, in ASM, Patentability of Microorganisms: Issues and Questions 23, 24 (1981). According to the UC Brief, prosecution of applications with claims directed to plasmids was suspended while Chakrabarty was *sub judice.*

[165] In re Wakefield, 164 U.S.P.Q. 636 (CCPA 1970).

[166] In re Steenbock, 82 F.2d 912 (CCPA 1936) (generic claim allowable if presented earlier).

[167] 102 U.S. 707, 711 (1881).

under which there was no "assurance that the result can be reached another time."[168] The Hand test would not exclude claims to rare mutants even if their prior natural occurrence were later established, since there would be no assurance that the roulette wheel of Fate would again reproduce that particular genetic sequence during this era of eternity.

It may be that a known microorganism may have a biological activity which is only belatedly revealed. Can a known organism with an unrecognized advantage, be claimed per se? It has been held that the discovery that if an electric light bulb is frosted on the inside in a particular manner, the glass is strengthened, would not warrant the allowance of a claim to the manufacture where bulbs so frosted on the outside surface were known, even if their advantage were not recognized in the art.[169] The same holding could be applied to patents on life forms.[170]

Recently, Upjohn obtained a patent with a "plasmid" claim:

> Essentially pure plasmid pUC6 which is characterized by a molecular weight of approximately 6.0 megadaltons, and a restriction endonuclease cleavage map as shown in the drawing.[171]

Let us assume that as a result of a series of cleavage and ligation operations, the applicant has assembled a gene sequence that does not exist in nature, and that he wishes, for the moment, merely to address a claim to that specific sequence. The claim must in some manner characterize and recite the sequence claimed.

One method is to actually recite the sequence, using, for convenience, the conventional alphabetic symbols for the nucleotides to express the detailed molecular structure which constitutes the claimed sequence.

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[168] 63 F.2d 229, 231, 17 U.S.P.Q. 81 (2d Cir. 1933). *See also* International Nickel Co. v. Ford Motor Co., 166 F. Supp. 551, 560-561, 119 U.S.P.Q. 72 (S.D.N.Y. 1958).

[169] General Electric Co. v. Jewel Incandescent Lamp Co., 326 U.S. 242, 67 U.S.P.Q. 155 (1945).

[170] *But see* In re Kratz, 29 U.S.P.Q. 71, 76 (CCPA 1979).

[171] Manis, U.S. Patent No. 4,273,875 [1981].

The other claim approaches require that an organism containing the desired sequence be on deposit in a culture collection. If the sequence claimed is an entire plasmid, the claim may refer to the reference number of the plasmid. The claim would be supported by a description of the manner in which that plasmid was constructed or obtained, together with a genotypic and phenotypic description of the plasmid.

If the claimed sequence is only a portion of a plasmid or chromosome (*e.g.*, a promoter sequence), it might be identified by reference to the replication time of the sequence. For example, the structural gene *his* might be identified as the forty-four to forty-five minute fragment of the chromosome of *E. Coli* K-12. This is, unfortunately, a very coarse method of identifying the relevant sequence, since the replication times cannot now be determined with accuracy. The total replication time for the chromosome of *E. Coli* K-12 is "100 + 2 minutes," so an error of a few seconds is equivalent to hundreds of base pairs. This method of identification is also applicable only to plasmid or genomes for which a detailed linkage map is available.

Alternatively, the sequence may be identified as a fragment with a particular molecular weight (and, if needed for identification, GC content) obtained from a source plasmid or chromosome by use of a particular restriction enzyme.

An interesting question is whether a claim to a sequence so claimed is, in essence, a "product-by-process" claim, and thus would not be infringed by one who obtained the same DNA sequence by cleavage of a different plasmid from a different organism. The reference in the claim to the use of a particular restriction enzyme to obtain the fragment is thereby viewed as a "process" limitation.

Others might view the claim as being, in essence, a "fingerprint" claim, since it recites the physical and chemical properties of the chemical moiety claimed. The reference to the use of the restriction enzyme is thereby viewed as a partial characterization of the structure of the molecule, since the enzyme leaves a signature in the form of characteristic termini. The more details are recited in the claim about the physical, chemical, and biological properties of the molecule, the more attractive the latter view becomes.

If the restrictive interpretation of the scope of protection afforded "product-by-process" claims is justified only by the argument that a competitor has no way of knowing from the patent whether a product produced by a different process is the same as the product, then it can be contended that this justification is inapplicable to these genetic molecule claims. If a competitor used a different process, the resulting DNA molecule may easily be hybridized with the molecular fragment obtained by the process recited in a claim in order to determine whether they are identical.

However, if there is, as A. W. Deller suggests, a different justification—that the inventor who has discovered a new substance but who has not benefited the art to the same extent as one who did both[172]—then it would be more difficult for the claimant to argue that the product of a different process is covered by his "restriction fragment" claim.

The narrowest genome claim is one which is directed to the base pair sequence itself. Even a slight change in the sequence would prevent the assertion of "literal infringement," forcing the patentee to rely upon the uncertain "doctrine of equivalents." Moreover, in order to advance such a claim, the applicant must painstakingly determine the sequence, an expensive and time consuming process which, at this time, is limited as a practical matter to relatively short sequences. "Sequence" claims may, nevertheless, be easier to obtain because of their narrow breadth, and they may be "enabled," in this author's opinion, merely by stating the sequence, rather than by deposit of the host organism.

A somewhat broader claim would be "A DNA sequence coding for the expression of amino acid sequence X." This claim is literally broader than a claim to the DNA base pair sequence itself, since the genetic code is "degenerate." The amino acid serine, for example, is coded for by the DNA codons [AGA], [AGG], [AGT], [AGC], [TCA], and [TCG] (*i.e.*, the mRNA codons [UCU], [UCC], [UCA], [UCG], [AGU], and [AGC]). A sequence which contained the DNA codon AGA in third position would not literally infringe one claimed to have codon AGG in that position, though both would code for se-

[172] Deller, 3 *Patent Claims* §532 at 330 (2d ed. 1971).

rine. The claim language recited above is thus of greater literal scope than one addressed to the DNA or mRNA sequence itself.

It should be noted that it may still be desirable to present a claim to the DNA or mRNA sequence itself. J. D. Watson suggests that the binding efficiencies of these codons with the various tRNA anticodons vary, and that "the rate of synthesis of a given protein will be controlled in part by which codons construct its particular amino acid sequence."

A truism of chemical patent practice is that claims may be addressed to classes of chemical compounds. In organic chemistry, one may frequently discern predictable relationships between structure and activity. Because of the ease with which multitudinous derivatives may be prepared from most compounds, it is not possible for the chemist to identify all of the possible derivatives which have the desired activity.[173] A "generic" claim is permitted when the chemist is familiar with sufficient examples of a class to be able to predict with reasonable confidence that the other members of the class will have the desired activity.

Part of the problem in determining the proper scope of genome claims is the sometimes strained analogy between DNA molecules and other chemical compounds. While it is true that DNA molecules are high molecular weight polymers, and are thus protectible as "compositions of matter," they are polymers whose detailed structure (the base pair sequence) radically affects their biological activity. Thus, while in most polymers, the length of the chain can be varied without grossly affecting its properties, and while in many compounds hydrocarbon chains can be varied in length without great effect, the DNA polymeric molecule has a very narrow range of homology of structure. It is thus difficult to characterize any approach to claiming gene sequences broadly as ideal.

One approach, pioneered by the Manis patent (U.S. 4,273,-

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[173] "In the field of carbon compounds, it is often, if not generally, true that so many slight variations in the way of substituting one element or radical for another are possible, that it becomes impracticable to test all possible resulting members." Ex parte Lulek, 25 U.S.P.Q. 370 (POBA 1934).

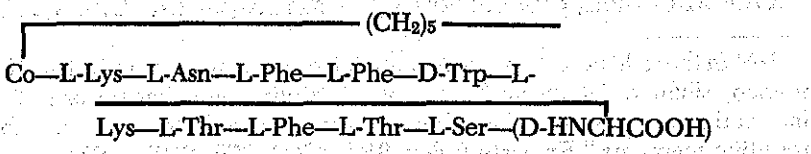
875), is to claim a plasmid broadly in terms of its molecular weight and restriction site map.

The various Type II restriction endonucleases have characteristic recognition and cleavage sites. For example, PST I (from *providencia Stuartii*) recognizes the sequence CTGCAG and cleaves the molecule between the fifth and sixth nucleotide in that sequence. One such site is known in the virus OX 174. It is possible to broadly limit a genome claim, as was done in the Manis patent, by limiting it to genomes having the specified restriction site map. This is a particularly desirable claim approach when the utility of the genome is as a vector for the introduction of exogenous DNA into a host organism, rather than for its own structural genes. If the former use is dominant, then the restriction site map defines its utility. A question yet to be determined is whether it is desirable to place (1) all restriction sites on the claim map, (2) only the unique restriction sites, or (3) only unusual restriction sites.

Similarly, a plasmid useful mainly as a vector may have a claim reciting the limitation that it bear specific "marker" genes.

It is a common chemical patent practice, where one part of a chemical compound is responsible for its utility for its intended purpose, to claim a broad class of compounds containing that moiety by diagramming its structure, with arbitrarily defined radicals attached to it. "R" is commonly used as a symbol for an organic group; and "M" for a metal or inorganic radical, though these symbols (or others) may be defined in any way desired. Subscripted symbols, such as "R1," "R2" and "R3" are employed where it is necessary to indicate that three different radicals of similar type may be present. An exemplary claim, to a class of polypeptide derivatives, appears below:[174]

1. A compound of the formula:



[174] U.S. Patent No. 4,261,885.

and pharmaceutically acceptable acid addition salts thereof.[174]

It should therefore be possible to protect critical sequences of nucleotide base pairs within a larger DNA molecule, such as a very efficient promoter sequence, or a recognition/cleavage site for a particular restriction endonuclease, by a claim to the entire molecule which identifies the critical sequence and broadly recites the remainder of the molecule. The Manis patent, presenting a claim to a plasmid with a particular restriction map, falls in this category, since the identification of the locations of the various cleavage points is tantamount to stating that a particular sequence of base pairs may be found at those locations, while the Manis claim does not state the nature of the intervening nucleotides.

Under some circumstances, it may be desirable to limit the claim to a particular genome obtained from a particular organism. This is similar in purpose to a product-by-process claim. The genome claimed in one for which molecular weight, GC content, and restriction site information is available, but which has not been fully characterized. The "source organism" limitation then further specifies the genome desired.

When the genome considered is one containing a structural gene, it may be desirable to limit the claim to a genome coding for the desired product. If the product is one which is known to be coded for by prior art genomes, but which is produced by prior art organisms in significantly lower yields, it may be desirable to limit the claim by a statement of the product yield from a unit number of transformed organisms. If the significance of the gene carried is related to its inducibility or repressibility, a claim might be advanced whose limitations express the bounds of induction or repression.

Another type of claim would be one limited to all sequences at least H percent homologous with a reference sequence, as measured by hybridizing the DNA of the test organism with that of the reference organism. (If 100 percent homology is required, we have, in essence, a "sequence" claim.) This claim, besides being broader than the "sequence" claim, is advanta-

[174] U.S. Patent No. 4,261,885.

geous in that it permits an objective determination of infringement.

A possible problem with this approach is the arbitrariness of the choice of "H," the required level of homology. In "composition of matter" cases, where the combination of ingredients is old, but the proportions are novel, patentability is usually predicated on the proportions being "critical," *i.e.*, "producing a difference in kind rather than in degree." It would certainly not be difficult for a molecular biologist to find in known organisms DNA sequences almost H percent homologous with the reference sequence. The choice of "H" might be predicated on a study of the effect of altering the sequence. If, statistically speaking, there is a sharp change in the probability that a randomly altered reference sequence will continue to code for the desired product, or act in the desired manner (*e.g.*, as ribosomal binding site) at a particular level of homology, then this level would be an appropriate choice for "H." If it should prove impossible or impractical to select an "H" level in this manner, there is still little cause for despair. The analogy between a "homology" sequence claim and a "new proportions" claim is, after all, far from perfect.

There is some tension between two tenets of patent law: that, where a new chemical substance possesses utility for one disclosed use, it may be patented for *all uses;* and that claims must not be drawn so as to read upon subsequent *independent* patentable inventions or discoveries of others. "Homologous" sequence claims may be in the middle of this tug-of-war. Suppose that a biologist comes up with sequence *A*, coding for protein *X*. His claim covers all sequences 90 percent homologous with sequence *A*, and is supported by numerous examples of similar sequences coding for proteins whose activity is similar to that of protein *X*. Another mutates sequence *A* into sequence *B*, 98 percent homologous with sequence *B*, and coding for the similar protein *Y*. Protein *Y* has the same kind of biological activity as protein *X*, but is far more potent. Does the use of sequence *B* infringe the claim to sequence *A*? While the usual rule in patent law is that one may have a patentable invention (*e.g.*, a new, nonanalogous method of using an old chemical compound) which cannot be practiced without infringing a pioneer patent, this author suspects that the unusual

biological activity of the protein coded for by sequence *B* would be deemed to fall outside the bounds of the first biologist's discovery, despite the fact that it is akin to that of protein *X*, and that sequence *B* would be deemed not to infringe the claim covering sequence *A* even though sequence *B* was likewise within its literal scope.

It is possible to limit the "homologous sequence" claim by expressly requiring that the sequence perform a desired function, *e.g.*, that it code for a desired protein, or repress a "downstream" structural gene in the presence of a specified repressor molecule. The author finds this claim format attractive, for much the same reason that he appreciated a similar approach, suggested by Woodruff, to claiming microorganisms and fermentation processes. If necessary to distinguish over the prior art, it may be required that the sequence perform the indicated function with a desired level of efficiency, *e.g.*, product yield per transformed organism.

While this author has not seen any published claims in which a particular level of homology is recited, many published European applications claim DNA sequences selected from the group consisting of particular DNA inserts and "DNA sequences which hybridize to any of the foregoing inserts."

Such claims are sometimes accompanied by a recitation to the effect that any DNA sequence derived from that sequence by single or multiple mutations, including replacements, insertions, deletions and transpositions, are included in the scope of the claim. Needless to say, any sequence can be transformed into any other sequence by a finite number of insertions and deletions. Thus, for such a claim to make sense, the word "derived" must be interpreted to mean that the infringer began with the recited sequence and then mutated it in some manner. Another question raised by such a claim is whether the term "mutation" is meant to imply the use of a particular process of obtaining the final sequence. Would the use of a restriction enzyme to remove a snippet of DNA from a nonessential region be considered a "mutation?"

Generalized sequence claims sometimes include a recitation that the sequence must code for a polypeptide having a particular activity. For example, one might claim "a DNA sequence coding for a polypeptide having substantially the same

biological or immunological activity as polypeptide *P.*" One application I have come across cautiously recited, "or a metabolite which may be modified in vivo or in vitro to obtain the desired metabolite."

Thus, claims to DNA sequences may recite structure and/or activity, broadly or specifically, in order to provide appropriate protection for a recombinant DNA invention.

[13] Generic Claiming

According to Robinson, "(S)everal distinct inventions often occupy toward some other invention the relation to species to a genus."[175] In U.S. patent practice, it is customary to address a broad claim to the generic invention and narrow claims to each of the species, by way of definiteness in depth against accusations of patent invalidity.

The Patent Office will reject generic claims as "unduly broad" when they are directed to inventions in arts, such as chemistry, where the results are unpredictable, and where the applicant supports his generic claim with but a single experimental example. This is because the applicant normally cannot predict that the other members of the genus will behave the same way.[176] In such disciplines, "(a)n inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.[177]

A single example is sufficient when the chemical equivalency of the class is clear[178] or when the claimant is the first to discover any representative of a well-defined natural class.[179] Several examples may be needed if the members of the class differ radically from each other. Thus in *Walker* a claim calling for "a polycyclic aromatic" compound could not be supported

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[175] 2 *Robinson on Patents* §535 at 151 (1890).

[176] MPEP 706.03(f).

[177] 3M v. Carborundum, 155 F.2d 746 (3rd Cir. 1946).

[178] Ex parte Chipman, 1929 CD 65.

[179] Gasselli Chemical Co. v. National Aniline & Chemical Co., 26 F.2d 305, 308 (2d Cir. 1928).

by the single example of naphthalene.[180] In *Cavallito,* the CCPA held that nineteen examples could support a claim embracing many thousands of compounds if the compounds were closely related, and if the examples were a well-distributed sampling of the areas covered by the claim.[181]

Because of the unpredictability of living processes, it is inevitable that generic microbiological claims will cover inoperative members of the class. This is not fatal to the claim if "a *majority* of the members" of the class are operative,[182] if a reasonable number of the members of the class are tested,[183] if the inoperative members are of little importance,[184] or if a person skilled in the art can recognize which species are operative and which are not.[185]

In *Ex parte Benedict,* the Board reversed the Examiner's "undue breadth" rejection of a microbiological process" claim:

> 6. A process of producing polymyxin comprising cultivating Bacillus polymyxa in an aqueous medium comprising a

(Text continued on page 4-89)

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[180] In re Walker, 70 F.2d 1008 (CCPA 1934).

[181] Application of Cavallito, 282 F.2d 363 (CCPA 1960).

[182] Compare Ex parte Geer, 3 U.S.P.Q. 131 (POBA 1929) with American Chemical Paint Co. v. Firestone Steel Products Co., 117 F.2d 927 (6th Cir. 1941).

[183] Fullerton Walnut Grower's Ass'n v. Anderson-Barngrover Mfg. Co., 166 Fed. 443 (9th Cir. 1908).

[184] Compare Fullerton, *supra,* with General Electric v. Paramet Chemical Corp., 26 U.S.P.Q. 71, 89 (E.D.N.Y. 1935).

[185] In re Sarett, 327 F.2d 1005 (CCPA 1964); Ex parte Phair, 7 U.S.P.Q. 33 (POBA 1930); Ex parte Clark, 174 U.S.P.Q. 40 (POBA 1971); International Nickel v. United States, 175 U.S.P.Q. 209 (Ct. Cl. 1972).

proteinaceous material and in the presence of not more than 4 percent of an assimilable carbon source, continuing said cultivation until substantially maximum yield of polymyxin is produced in the medium, substantially immediately thereafter separating the cells from the liquor and isolating the antibiotic from the cell-free liquor, said separation and isolation being carried out after not more than five days of fermentation.[186]

The Examiner's position was that applicant did not identify which strains produced which antibiotics of the "polymyxin" family, and that applicant had only established the value of strain NRRL B-698.

The Board held that the Examiner had not met the burden of supporting the allegation that the claim covered any strains "inoperative" under "proper cultural conditions."

It is interesting that the Board placed this burden on the Examiner, rather than requiring the applicant to demonstrate the predictability of the class.

Suppose that a claim was presented which covered all strains of an entire genus? How many operative examples would then be needed to support the claim?

The answer to the question depends on the degree to which taxonomically similar organisms are a class comparable to a class of structurally similar chemical compounds. It is difficult to escape the conclusion that traditional genera and species are far more diverse in the behavior of their members than are the members of a chemical class. The taxonomic divisions are frequently revised, and therefore are perhaps comparable to the "artificial" groups of compounds known as Markush groups. More examples are therefore necessary than would otherwise be the case.[187] Indeed, it may be that the activity of living organisms is so unpredictable that generic claims should be the exception, rather than the rule.

Subgeneric claims, to so-called "Markush groups," have frequently appeared in microbiological process patent applications. Markush group format product claims will probably be allowed as well. Patel's U.S. Patent 4,225,034 contains a lengthy subgeneric culture claim:

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[186] 111 U.S.P.Q. 354 (POBA 1956).

[187] Ex parte Klager, 1961 CD 91.

1. Isolated and biologically pure microbial cultures of CL compound utilizing microorganisms, said cultures being selected from the group consisting of those having the following identifying characteristics:

Methylosinus trichosporium	(CRL 15 PM1)	NRRL B-11,202
Methylosinus sporum	(CRL 16 PM2)	NRRL B-11,203
Methylocystis parvus	(CRL 18 PM4)	NRRL B-11,204
Methylomonas methanica	(CRL M4P)	NRRL B-11,205
Methylomonas methanica	(CRL 21 PM7)	NRRL B-11,206
Methylomonas albus	(CRL M8Y)	NRRL B-11,207
Methylomonas streptobacterium	(CRL 17 PM3)	NRRL B-11,208
Methylomonas agile	(CRL 22 PM9)	NRRL B-11,209
Methylomonas rubrum	(CRL M6P)	NRRL B-11,210
Methylomonas rubrum	(CRL 20 PM6)	NRRL B-11,211
Methylomonas rosaceus	(CRL M10P)	NRRL B-11,212
Methylomonas rosaceus	(CRL M7P)	NRRL B-11,213
Methylobacter chroococcum	(CRL M6)	NRRL B-11,214
Methylobacter chroococcum	(CRL 23 PM8)	NRRL B-11,215
Methylobacter bovis	(CRL M1Y)	NRRL B-11,216
Methylobacter bovis	(CRL 19 PM5)	NRRL B-11,217
Methylobacter vinelandii	(CRL M5Y)	NRRL B-11,218
Methylococcus capsulatus	(CRL M1)	NRRL B-11,219
Methylococcus minimus	(CRL 24 PM12)	NRRL B-11,220
Methylococcus capsulatus	(CRL 25 PM13)	NRRL B-11,221
Methylobacterium organophilum	(CRL 26 R6)	NRRL B-11,222
Pichia sp.	(CRL-72)	NRRL Y-11,328
Torulopsis sp.	(A1)	NRRL Y-11,419
Kloeckera sp.	(A2)	NRRL Y-11,420

and mutants thereof, said cultures capable of reproducing themselves and capable of producing secondary alcohol dehydrogenase or monooxygenase enzyme activity in isolatable amounts when cultured under aerobic conditions in a liquid growth medium comprising assimilable sources or nitrogen and essential mineral salts in the presence of methane or a methy radical donating compound as the major carbon and energy source.

The "overclaiming" problem is not a creation of U.S. patent law alone. A Canadian lawyer wrote

Careful thought should be given in drafting a patent specification as to how, for the purposes of the patent, the reader is to determine whether a particular microorganism is a member of any species or genus referred to in the claims. There is the danger that if one commits oneself to a particular taxonomic system, or to a series of criteria which are currently in vogue, in an effort to be reasonably precise as to what microorganisms are contemplated, such precision may be embarassing if useless microorganisms prove to be included. The problems of describing living things, and predicting their properties, are such that

the patent laws should perhaps be liberalized. This has been done, for example, in relation to plants in the U.S. Patent Act which does not require a description of how the plant may be obtained, nor a claim establishing verbally the limits of the monopoly, but requires only as complete a description of the plant as is reasonably possible. However, there is probably no infringement of a U.S. plant patent unless there has been unlicensed reproduction of plant stock obtained directly or indirectly from the patentee, and this U.S. legislation is not necessarily the ideal model.[188]

It is worth observing that references to broad and narrow claims as "genus" and "species" claims, while customary in the patent profession, is confusing when applied to microbiological claims. A "species" claim may cover only a single strain, while a "genus" claim may cover all of the effective strains of a biological species. This sort of semantic confusion reached apogee with the coinage of the term "sub-subgenus" in *In re Kaufmann.*[189]

In re Kaufmann is also interesting for its holding, which was that applicant's German application did not provide support for his claim to a fermentation method employing penicillin acylase-producing strains of species of the genus *Proteus.* The German application was supported by a single example of a 6-APA production method, one utilizing a *coli*-strain, though it referred generally to the utility of gram-negative bacteria, including "Coli, Proteus, Aerobacter aerogenes, Salmonella, and Shigella species." No species of the genus Proteus were "exemplified" or "mentioned," nor was any note taken of the importance of determining the penicillin-acylase producing ability of the strains.

In *Ex parte Jackson* (1982),[189.1] a nine member special panel of the Patent and Trademark Office Board of Appeals held, 6–3, that the following claim was properly rejected under the first paragraph of 35 U.S.C. §112 as being based on an insuffi-

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[188] W. L. Hayhurst, *Litigation Concerning Industrial Microorganisms in the English-Speaking Countries,* Genetics of Industrial Microorganisms, 377, 393-394 (1970).

[189] 451 F.2d 1096 (CCPA 1971).

[189.1] 217 USPQ 804 (Bd. App. 1982).

cient disclosure with respect to the broad recitation of a bacterial species:

> 2. A process for producing the antibiotic Ax-127B-1 which comprises culturing a microorganism belonging to the species Micromonospora pilospora having the ability to produce antibiotic Ax-127B-1 in a nutrient medium including a carbon and nitrogen source and accumulating the antibiotic in said medium.

The Board admitted that examiners differed in their attitude toward claims of this type, some rejecting them, others allowing them. It was for this reason that the case was heard by an expanded panel.

The majority was of the opinion that the use in the process of strains of the stated species, other than those deposited by the applicant, was not enabled, in that the mere written disclosure of the general metabolic characteristics of the species was insufficient to teach those skilled in the art how to find the undeposited strains without undue experimentation. Here, they relied heavily on an analogy to the CCPA's decision in the *Argoudelis* case: "Discovery of a fourth strain in nature would be just as non-enabled by the description of the three deposited strains in the present specification as was the discovery in nature of the single strain at issue in Argoudelis."

Taken out of context, this language might be read to restrict applicant's to claims limited to use of the deposited strains. However, the examiner's rejection of claim 3 was reversed by the Board:

> 3. A process according to claim 2 wherein said microorganism is selected from the group consisting of Micromonospora pilospora NRRL 11415, Micromonospora pilospora NRRL 11416, and Micromonospora pilospora NRRL 11417, and mutations thereof.

The last three words of claim 3 are quite significant. As noted by the Board, it was well known in the art "that spontaneous mutation is a common occurrence and that mutations can be intentionally produced by a variety of known procedures." Thus, mutants of the deposited species could in fact be

obtained without undue experimentation. The difficulty was in finding strains of the same species by the independent screening of soil and water samples.

> [T]he court in Argoudelis clearly indicated that the problems of enablement of processes carried out by microorganisms were uniquely different from those involved in the field of chemistry generally. . . . The experimentation involved in the ordinary chemical case, . . . , usually arise in testing to establish whether a particular species within the generic claim language will be operable in the claimed process. . . . [C]ases of the type before us are distinguished by the fact that the experimentation is associated with obtaining the species from nature before it can be tested.

It is curious indeed to hear that there is no problem in obtaining a desired chemical species; this would certainly have surprised the Swedish Academy of Sciences, which honored Robert B. Woodward in 1965 with the Nobel Prize for his syntheses of quinine, cholesterol, cortisone, strychnine and other compounds. Indeed, several judges have regarded both chemistry and biology to be uncertain arts, as compared to electronics and mechanics.

This author believes that, to the extent that the Board in *Jackson* would exclude generic claims for all inventions within the biological arts, it goes too far. Predictability must be assessed on a case-by-case basis. This point is well addressed by Examiner in Chief Katz in his concurring opinion:

> Some bacterial processes are so basic and pervasive, such as the fermentation of sugar to alcohol, the action of yeast on starch or the fixation of nitrogen, that the skilled person would have no difficulty in reaching the conclusion that all members of the species, even undiscovered members, would have the described basic property of the strains being worked on. . . . [H]ere we are dealing with an esoteric function of novel bacteria used to manufacture a novel antibiotic. . . . Each case must be examined to determine the type of organism, the metabolic reactions involved, and the evidence developed as to the universality of properties of the claimed organisms.
>
> In the situation before us, I remain unconvinced that the de-

scribed processes are so conventional and predictable that one would reasonably expect that all members of the species, though not yet discovered, would form the named antibiotic.

A key question which is never squarely addressed by the Board is *WHAT* is required to be "enabled:" a method of making an organism, or a method of making an antibiotic? The claim, of course, is to the latter, so it follows that the specification need merely enable the practice of the invention so claimed. It indeed teaches three methods of making the desired antibiotic, each employing a different strain. It also teaches that *IF* an organism having the morphological and general metabolic characteristics of Micromonospora pilospora should come into one's hand, it would be desirable to test it to see whether it could be made to produce the antibiotic Ax-127B-1.

A chemical claim may recite the use of a broad class of organic compounds without teaching how to make every single chemical species in that class, and without guaranteeing that every possible species thus covered, if obtained, is operable. There does not seem to be any justification for a different approach to biological patent subject matter.

An interesting argument is raised by Dana Schmidt of Eastman Kodak.[189.2]

> At the time of filing, there existed only these three strains in the species. There was no other way one skilled could easily create or find another member. Therefore, it is clear that the inventors taught how to use the generic class as it existed at the time of the filing of the application. The fact that additional members of the generic class might be discovered only in the future is irrelevant.

This argument creates a certain amount of philosophical tension. The coverage of additional members of the class discovered only in the future is certainly relevant to their discoverer who would, if Schmidt's reasoning is accepted, find his

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189.2 Schmidt, Comment, "Microorganisms Are Entitled to Generic Claims as Much as Anything Else," 2 Biotechnology Law Report 126 (Aug.-Sept. 1983 (BLR169)), at 128.

invention dominated by an earlier, broader patent. Mr. Schmidt suggests that a generic claim should be rejected if (1) the other members of the class could not readily be made, and (2) "there is reason to believe that the claimed class will substantially exceed, in a reasonable time (17 years?), the few species actually described by Applicant." Frankly, I consider this "line of demarcation" to be unworkable. I cannot see how one could rationally reach a belief as to the number of additional strains of Micromonospora pilospora would be isolated or developed during the next seventeen years, or even the next year.

An apter criticism of the Board's decision is that it runs counter to precedent. I am not referring merely to the fact that, as the Board admitted, some examiners "appear to routinely allow claims similar in scope to appealed claim 2." Rather, in *Feldman v. Aunstrup*,[189.3] the interference count was to a "process for the preparation of a milk-coagulating enzyme which comprises cultivating a milk-coagulating enzyme producing strain of Mucor miehei Cooney et Emerson or a natural or artificial variant or mutant thereof. . . ." (The interference count was identical to *Aunstrup's* claim 9.) The CCPA affirmed the BPI's decision awarding priority to *Aunstrup*, despite *Feldman's* argument that Aunstrup's deposit of a single culture in a foreign depository during the pendency of the U.S. application was nonenabling. Clearly, the CCPA's "adequate disclosure" holding in Feldman is inconsistent with the Board's position, since the Aunstrup claim is not limited to mutants of the deposited strain.

The Board in *Jackson* also ignored its own leading case, *Ex parte Benedict*. The claim in Benedict was to "a process of producing polymyxin comprising cultivating Bacillus polymyxa in an aqueous medium. . . ." The examiner there argued that "claim 6 does not identify the strain of the microorganism or the antibiotic produced therefrom in such a manner as to determine the scope of the claim. . . . [A]ppellants show using only strain NRRL B-698 of Bacillus polymyxa in their specific examples. . . . [G]eneric claims are not supported by a single species in the disclosure. . . ." *Benedict* held, however, that

189.3 517 F.2d 1351 (CCPA 1975).

appellants "were in possession of the generic concept of producing a polymyxin by cultivating a strain of Bacillus polymyxa in the manner recited."

The majority in *Jackson* would distinguish *Benedict* "summarily" on the ground that "the microorganism species claimed was not new but was in fact well known as was the class of antibiotics produced by the various strains of that species." But why should it matter whether the species is new or old? Even if twenty species of Bacillus polymyxa were readily available from culture depositories that would not enable another to find a twenty-first species other than by mutation of the twenty preceding it.

My view of *Benedict* differs sharply from that of the Board in *Jackson*. In *Benedict*, the Board reasoned as follows: "Since we find no valid reason from the record in this case to believe that strains other than B. polymyxa NRRL B-698 would not respond to treatment in a similar manner, we are of the opinion that the single species of the examples is sufficient to support the generic concept. . . . Although the assertions made by the examiner have indicated a doubt as to the operativeness of one or more species other than Bacillus polymyxa NRRL B-698 in the process; we are not convinced that the examiner has supported the allegation. . . . On the contrary, it appears from the informative art cited by the examiner that the different strains . . . ." known do produce antibiotics of the polymyxin family. It was, in other words, a case in which the burden of going forward with evidence on the issue of overbreadth rested on the examiner and the examiner failed to bring forward enough evidence to warrant shifting that burden to the applicant.

Ex parte Jackson may be an example of a case with an unusually poorly defined species. Footnote 3 states that "[A]lthough we do not decide this case on this narrow issue, we should note that the number of metabolic properties disclosed by appellants appears to be significantly smaller than the discussion of numerical taxonomy in the textbooks cited above would suggest are appropriate." More bluntly, it appeared that the claim language was tautological; any strain of the genus Micromonspora which happens to produce the antibiotic Ax-127B-1 is, by definition, a "Micromonspora pilospora." So, while the Board

says that it did not decide the case on this "narrow issue," it surely had an adverse influence on the Board's impression of the case.

What is the significance of *Ex parte Jackson* for patent prosecution? First, attorneys would be well advised to include a "deposited strain and mutants thereof" claim in their application, even if they plan to buck *Jackson* and seek a broader claim. Second, if a generic claim is advanced, and rejected under *Jackson,* the attorney should be prepared to support a "predictability" argument along the lines suggested by the concurring opinion (and should keep in mind that affidavits are a fertile source of grist for the "fraudulent procurement" mill should the patent ever be litigated). Finally, there is a silver lining in even the *Jackson* cloud: prior art references to novel microorganisms would seem to be nonenabling if they do not provide a deposit number, and a deposit of one strain would not render obvious, it would seem, strains of the same species not derived from it by mutation.

In *Jackson,* the novel microorganisms were obtained by mutation-and-selection. Since this was considered an unpredictable process, only the deposited strains and mutants thereof were considered "enabled." In *Ex parte Forman,* [189.4] the Board concluded that the Examiner correctly refused to allow generic claims on novel microorganisms obtained by hyperconjugation of *Salmonella typhi* and *Shigella sonnei.* The Board observed that: (1) one year was required to construct the claimed strains; (2) there were no "known clues to assist one of ordinary skill in predicting which of the myriad strains that are presumably produced would be useful"; (3) there was no "single detailed example which could be followed by another worker in another lab to obtain a single specific microorganism (vaccine) within appellants' claims without recourse to the deposited strains"; and (4) the art of hyperconjugation appeared to be "relatively underdeveloped."

While the absence of a working example did not itself deprive the specification of enablement for the generic claims sought, it was a relevant factor. It is unclear whether Forman could have established that "one of ordinary skill in this art has

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[189.4] 230 U.S.P.Q. 546 (P.T.O. Bd. Pat. App. Interf. 1986).

actually been able to produce additional species representative of any of the claims broader than those allowed"; a possibly pertinent Declaration was ignored as having been untimely filed.

[14] Further Pitfalls in Claim Drafting

In *Ranks Hovis McDougall, Ltd.*,[190] the Australian Commissioner of Patents suggested that a claim to "*Fusarium graminearum* Schwabe deposited with the commonwealth Mycological Institute and assigned the number I.M.I. 145425 and variants and mutants thereof" was "ambiguous."

> Ignoring for the moment the reference to variants and mutants, it may mean:
>
> (a) The specimen deposited with the Commonwealth Mycological Institute; or
>
> (b) The strain of Fusarium graminearum Schwabe, a sample of which is deposited with the Commonwealth Mycological Institute.
>
> Although grammatical considerations may point to the former meaning, a consideration of the whole specification suggests the latter meaning is intended. The matter should be clarified but I think I may safely proceed on the basis of the latter meaning.

§ 4.03 Nonobviousness, Infringement, and Taxonomically Similar Organisms

In determining whether a claim is patentable, the courts will consider

(1) The scope and content of the prior art;
(2) Differences between the prior art and the claims at issue; and

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[190] In re Ranks Hovis McDougall, Ltd., 8IIC 453, 458 (1977) (Austral. Comm'r Patents, October 21, 1976).

(3) The level of ordinary skill in the pertinent art.

In determining whether a claim is infringed, the courts will determine:

(1) Whether the "accused matter falls clearly within the claim";
(2) Whether the subject matter performs the same or a similar function in the same or a similar way to obtain the same or a similar result; and
(3) Whether the claims were narrowed by amendments in the Patent Office.

(*Text continued on page 4-93*)

The "equivalency" of the patented organism to other organisms, whether they be the organism employed by a supposed infringer or "prior art" organisms cited by the latter to invalidate the patent, is a critical factual question in any biological patent litigation.

The term "equivalency" is most often used by patent attorneys when discussing the second of the infringement issues referred to above, a statement of the so-called "doctrine of equivalents." Some courts have interpreted this doctrine as merely a requirement that the language of claims be "generously construed," but others have undermined the dogma that the claim is the measure of the right.[191] In *Graver Tank and Mfg. Co. v. Linde Air Products Co.*, a manganese silicate flux was deemed "equivalent" to an "alkaline earth metal silicate" flux even though manganese is not an alkaline earth, given evidence of the recognized interchangeability of manganese and magnesium compounds in welding compositions.[192]

Closely related to the concept of "equivalency" is the concept of "anticipation"; an ancient maxim is "that which anticipates, if earlier, infringes, if later."[193]

Application of the doctrine of equivalents to biological inventions is difficult, since even those skilled in the art are in dispute as to which organisms may be considered "similar" for taxonomic purposes.

Concern as to the doctrine of equivalency is apparent in the specification of Michel, U.S. Patent No. 4,247,542, A-40104 *Antibiotics and Process for the Production Thereof* (1981):

> As is the case with other organisms, the characteristics of the A-40104-producing culture, Clitopilus pseudopinsicus NRRL 11179, are subject to variation. For example, artificial variants and mutants of the NRRL 11179 strain may be obtained by

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[191] *Compare* Doble Eng'g Co. v. Leeds & Northrup Co., 134 F.2d 78 (1st Cir. 1943) *with* Claude Neon Lights, Inc. v. E. Machlett & Sons, 36 F.2d 574 (2d Cir. 1929).

[192] Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605 (1950).

[193] Imperial Stone Cutters, Inc. v. Schwartz, 370 F.2d 425, 429 (8th Cir. 1966).

treatment with various known mutagens such as ultraviolet rays, X-rays, high-frequency waves, radioactive rays and chemicals. All natural and artificial variants and mutants which have essentially the same identifying characteristics as Clitopilus pseudo-pinsitus NRRL 11179 and produce the A-40104 antibiotics may be used in this invention.

While no case has discussed the equivalency of two microorganisms in an infringement context, *Ex parte McCoy* is of interest. McCoy's claim to a process for the production of n-butyl alcohol and acetone by the action of *Clostridium saccharoacetobutylicum* was rejected in the light of a prior art reference disclosing a similar process employing *Clostridium saccharo butyl-acetomicum.* Applicant urged three distinct differences between the organisms—ethyl alcohol production, action on whole strain, and optimum temperatures. The Board held that a "doubt" had been established as to "the identity of the two groups of bacteria" and reversed the Examiner's "anticipation" rejection.[194]

A number of factors are likely to be considered by the courts when they address the issue of whether strain *A* is equivalent to strain *B*: (1) the formal taxonomic (genus-species) classifications of the strains; (2) the general phenetic or genetic similarity of the strain; (3) the phylogenetic (evolutionary) relationship between the strains (*e.g.*, was strain *A* a natural or artificial mutant of strain *B*); and (4) their economically significant metabolic activities (*e.g.*, is strain *A* a much better producer of substance *X* than strain *B*).

As in the field of chemical product patents, the first lawmakers in the virgin territories of microorganism patents will need to balance the need to encourage pioneer work with poorly understood organisms with the need to encourage others to engage in secondary research. In *Brenner v. Manson*, the Supreme Court referred to the possible "blocking effect" of pioneer patents.[195] The "utility" requirement and the "overclaiming" doctrine are among the means by which this balancing of interests is achieved.

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[194] 36 U.S.P.Q. 511 (POBA 1938).

[195] 383 U.S. 519, 534 (1966).

Stoy poses this issue in a series of rhetorical questions:

> The problem of mutants can be, however, viewed also from the other side: If an artificially induced mutant has definitely better properties than the originally described strain, where is the border line between the merits of the two breeders? Is the first inventor entitled to obtain rights involving also the not yet discovered new strains, the cultivation of which would perhaps require more effort than the finding of the strain? First discovery may be rather a lucky hit; but it is only the first step. On the one hand, the first inventor has to bear the burden of innumerable tests, the danger of the first clinical tests, the considerable effort connected with installing a large-scale production and bringing the product to the market. The further breeder may utilize the experience of the first one and profit by it. On the other hand, however, is the technical and scientific progress, caused by patents, not based on this very idea of utilizing the experience of previous workers for making new improvements in the art.[196]

Taxonomy is the art of bringing philosophical order out of biological diversity. Classical taxonomy, founded on the work of Aristotle and Linnaeus, groups organisms into kingdoms, divisions, phyla, classes, orders, families, genera, species, and subspecies on the basis of traits believed to be stable, representative, evolutionarily significant, and readily and objectively observable.

According to L. G. Silvestri and D. Gottlieb, "the absence of a solid scientific foundation of classification is the main cause of the difficulties facing us now as we attempt to solve the practical problem of protecting microbiological processes legally."[197]

It is easy for attorneys to accord more significance to microbial species than they deserve. As Locke said in 1689, "The boundaries of the species, whereby men sort them, are made

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[196] A. Stoy, Legal Protection of Industrial Microorganisms in European Socialist Countries, Genetics of Industrial Microorganisms, 397, 399 (1970).

[197] L. G. Silvestri & D. Gottlieb, Taxonomy and Legal Aspects of Industrially Important Microorganisms, in 1 Global Impacts Applied Microbiol. 109 (1964).

by men."[198] The biological and evolutionary concept of the species is that of a group of organisms reproductively isolated from all other organisms.[199] This conceptualization falters in organisms whose primary mode of reproduction is uniparental in nature.

"The species, in the case of a sexual group, is an actuality as well as a human concept; in an agamic complex it ceases to be an actuality."[200] Sexual reproduction is a relatively rare event in the life of most bacteria, prompting Cowan to remark, "the microbial species does not exist."[201] The microbial species concept as pronounced by Buchanan was the result of a "marriage of convenience" only: "A bacterial species [is] the type culture together with such other cultures or strains of bacteria as are accepted by bacteriologists as sufficiently closely related.[202] The closest microbiological analogy to the reproductively defined species is the "genospecies." Unfortunately, "(t)he genospecies, a cluster of microorganisms which can exchange genes, is much too broad [to be] a useful species concept. . . ."[203]

Taxonomists have flippantly classified themselves into two groups: "splitters" and "lumpers." "Splitters" split traditional species into many new species, and "lumpers" lump them back together.[204] Most patent application writers are "splitters." As Silvestri and Gottlieb remarked, sympathetically,

> Because the species is the taxon usually accepted for process patents in the microbiological industry, there is an inevitable pressure to proliferate the number of species. It might be recommended that patenting of subspecific taxa should be allowed. This action would relieve the pressure for creating more species, and yet preserve the economic advantage that leads to the development of microbial industries in various countries.[205]

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[198] J. Locke, *An Essay on Human Understanding*, book III, ch. 6. (1689).

[199] E. Mayr, *Principles of Systematic Zoology* 26-28 (1969).

[200] Cowan, *The Microbial Species*, in Microbial Classification, 443 (1962).

[201] Id., 451.

[202] Id., 440.

[203] Woodruff, Importance of the Producing Organisms in Obtaining Patent Protection for Fermentation Processes in Genetics of Industrial Microorganisms, 403, 405 (1970).

[204] Mayr, *supra* note 199 at 238.

[205] *Supra* note 197 at 112.

Other commentators have also suggested that the taxonomy of industrial microorganisms has been unduly influenced by patent considerations.

The late John V. Whittenberg of American Cyanamid remarked that "(t)he proposed establishment of a new species of microorganism may be based on an honest misinterpretation or erroneous observation of data or it may be the result of an obvious attempt to create a new species, regardless of the weight of scientific authority.[206]

Professor Waksman, referring to the tendency toward attaching "undue importance" to the "economic property" of a new culture, and the consequent proliferation of new species, states

> It is commonly believed that to characterize a species, . . . it is desirable to describe a large number of properties. This procedure is not always followed. . . . It is easier to create a new species than to attempt to correlate the characteristics of a freshly isolated culture with those of known species already described in the literature. This problem has become particularly acute when Company A, for example, presents claims that to produce the same antibiotic or vitamins it is using a different species than that claim in the patent granted to Company B. This is done, of course, to avoid patent infringement.[207]

Professor Waksman also noted the existence of countervailing forces: "the fact that the creation of a new species may facilitate the patent situation serves to aggravate [the splitting of species]. On the other hand, the importance of a particular biochemical product may offer the temptation of grouping all cultures producing such a substance into a single species."[208]

The PTO has tended to regard Bergey's *Manual of Determinative Bacteriology* with the same slavish adulation which

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[206] J. V. Whittenberg, Microbiological Patents in International Litigation, in 13 Adv. Applied Microbiol 283, 384 (1970).

[207] S. A. Waksman, Species Concept Among the Actinomycetes with Special Reference to the Genus Streptomyces, 21 Bacteriol Rev. 1 (1957).

[208] Id., at 5.

the western medieval world paid to Aristotle. Bergey's manual groups organisms into a hierarchial structure on the basis of a limited number of differentiae, with a bias toward those characters which are readily observable. While Class 435's cross-references to Bergey's manual are invaluable in searching the patent files for prior art, Bergey's manual should not be viewed as an oracle on validity and infringement issues.

Different hierarchial systems may be used to classify the same assemblage of strains. Thus, Waksman and Henrici classified the species of the genus *Streptomyces* according "the ecology of the organisms, production of soluble pigments in organic and synthetic media, and [to a lesser degree] manner of sporulation.[209] Krassilnikov, on the other hand, based his classification upon "manner of sporulation, shape of spores, pigmentation of cultures." Baldacci emphasizes the color of the vegetative and aerial mycelia in dividing the genus into "series," and divides species based upon enzymatic and antibiotic activity.

Rehacek has described the taxonomy of the industrially important actinomycetes as an "arbitrary" grouping of organisms. He observes that "it is extremely difficult to find a [chlortetracycline-producing] strain which completely fits Duggar's description of *Streptomyces aureofaciens.* No two strains of any species are completely identical but each differs from the other in any number of subtle traits, thus giving a degree of individuality to the strain."[210]

In the same vein, Professor Waksman has made reference to the "great variability" of the Actinomycetes, "especially when grown on media of different chemical composition and under different environmental conditions." He also has observed that "spontaneous mutations" are produced in this group of organisms with "ease."[211]

Patent attorneys have, in essence, sought to elevate the antibiotic-producing properties of the patent strains to the digni-

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[209] Waksman (Appendix).

[210] Rehacek, *Distinction Between Microorganisms in Examination for Novelty,* in Genetics of Industrial Microorganisms, 423 (1970).

[211] Waksman at 3.

ty of a species or genus-differentiating character. As Stoy points out,

> For scientific purposes, the microorganisms are usually not classified from the standpoint of a desirable metabolite since the ability of producing the metabolite is no stable, strictly characteristic property. In the patent right, however, where the production of the metabolite is usually the only reason why the fermentation is carried out, the said ability is of primary importance.[212]

Taxonomists have debated whether the formation of antibiotics should be used as a taxonomic character.[213] Opponents reason that antibiotic activity varies from culture to culture, and that the same antibiotic is often formed by several otherwise distinct species. Baldacci points out that virtually all of the conventional taxonomic characters are in part subjective and variable, and that by redefining the species boundaries the second objection might be removed. Baldacci notes, however, that it would be difficult to classify known species producing several different antibiotics, and that all classification would require the aid of a chemist.[214] Baldacci would use antibody formation as a *subspecies* differentiator.

Baldacci, aware of the "species-splitting" effect of the patent laws, suggests that "the protection of a strain could also be achieved at taxonomic ranks lower than that of species, since these are already recognized by microbiologists. . . ."[215] Baldacci also suggested that subspecies be differentiated on the basis of their antibiotic activity, so in essence Baldacci favors patents directed to "antibiotic-producing organisms of Genus A, species B." Stoy appears to favor a similar approach: "Among all microorganisms conforming to the taxonomic specification disclosed, only the use of such is protected that produce the

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[212] Stoy, *supra* note 195, at 398.

[213] Rehacek, *supra* note 210 at 424 (1970).

[214] E. Baldacci, *The Classification of Actinomycetes in Relation to Their Antibiotic Activity*, in 3 Advances in Applied Microbiology 257 (Umbreit ed., 1961).

[215] Baldacci, 263; *see also* Baldacci at 275-276.

defined substance."[216]

Woodruff argues that in some instances a microbiologist may be entitled to a supraspecies claim, if he can describe how to identify the desired organisms:

> In certain inventions of broader scope a new discovery may apply to a complete species or an even broader class of microorganisms in which case the cultures deposited become only typical examples of organisms which can be employed successfully in the new invention. The written specification must clearly define the limits of the microbial class which will react favorably to the invention. Certain new discoveries are of such import and so widely applicable that limitation to a single species provides inadequate protection. In this latter case, a patent specification must indicate clearly how one can obtain an organism from nature which responds to the invention, and patent claims are extended to any microorganism recoverable by the disclosed means.[217]

He also points out that if claims are interpreted too narrowly, the industry may be caught in a rip tide toward trade secret protection.

> The possibility of interspecies isolates, now accepted by many taxonomists, compounds the industrial microbiologists dilemma. Unless he can describe the microbiological limits of an invention so that no exception exists, the protection granted by a patent is of little practical value; thus there is no recourse for industry to recover the costs expended on research but to retreat to secrecy. The fact that the species concept covers 99 percent of all natural isolates is of little value if the remaining 1 percent provides opportunity for a laboratory which has conducted no research and made no basic discoveries to practice a publicly disclosed invention free of infringement penalties.[218]

When the classification of a cluster of new isolates or mutants in a particular genera is rendered arbitrary by its atypical characteristics, limiting the scope of the claim to the strains

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[216] Stoy, 398.

[217] Woodruff, *supra* note 203 at 404.

[218] Woodruff, id. at 406.

traditionally included in the recited taxon may be shortsighted.

According to Woodruff, "(a)n experimental definition of the species concept for each patent" could be used to overcome the problem of interspecies isolates.[219]

In connection with litigation, several Merck researchers attempted to determine which of the glutamic acid-producing strains listed in the 1977 ATCC Catalog or referred to in pre-1964 patents and patent applications might fall within the scope of U.S. Patent No. 3,003,925, nominally covering the cultivation of Micrococcus glutamicus, a new species with unusual characteristics, possibly related to the genera Brevibacterium, Corynebacterium, Microbacterium, Arthrobacter, or Bacterium.

Seven of the eleven glutamic-acid productive genera were deemed immediately excludable. This left the genera Brevibacterium, Corynebacterium, Microbacterium, and Micrococcus. The characteristics of three "commercial" species, B. divaricatum, C. lilium, and C. callunae, were compared with those of M. glutamicus. Some sixty characteristics were compared. The most obvious difference was in shape, since M. glutamicus is spherical and the others were rodlike. More modest differences in colony pigmentation, citrate utilization in Koser's medium, and acid production in galactose and glycerol media were found. "The cultural differences described are minor, but were adequate to support differences of opinion concerning classification which were only settled in the United States as the result of [an] expensive patent infringement suit. . . . As an outcome of the extensive work, glutamic acid processes employing *B. divaricatum, C. lilium,* and *C. callunae* were deemed to be within the scope of the claims of U.S. Patent 3,003,925.[220]

There are a number of theoretical approaches to providing an objective test of equivalency which might prove fruitful. Numerical taxonomy is a mathematical technique in which each of a large number of organisms is identified in terms of a large number of traits, and the organisms are then grouped

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[219] Id.

[220] Id.

into similarity clusters derived by mathematical analysis of the traits. The early literature refers to it as "Adansonian classification." Many families of organisms have been studied by these methods, and statistical flaws in the earlier studies have been rectified by later researchers. An objective measure of the similarity of two strains could be derived by Adansonian methods.[221]

Sneath indicates that "a few strains labelled *Nocardia* were found in the clusters" of *Streptomyces* species, showing how classical taxonomy can distort the degree of similarity between strains.

These similarity values must be examined with caution. In atypical strains on B. cereus, B. megaterium, B. circulans, B. brens, and B. subtilus, the degree of similarity with the type of strains may be only 50 to 60 percent.

The value of numerical taxonomy to the patent attorney can be overstated. In its early years, some specialists believed

> [T]hat numerical taxonomy carried to its highest order of development . . . will result in definition of clearly defined species clusters and complete elimination of intermediate forms. If this view proves true, . . . the industrial microbiologist . . . will be able to define with certainty the limits of a species which is the subject of an inventive discovery.[222]

Woodruff warns, however, that "(r)esearch in microbial genetics makes it clear that the optimism of the early numerical taxonomists was not well founded.[223] Nonetheless, Sneath believes that the technique yields "stable, precise taxonomies based on objective criteria.[224]

Another approach is molecular taxonomy.

Woodruff and his co-workers found "that the base pair ratios of microbial DNA, as expressed by Tm values, can provide supporting, though not conclusive, evidence of similarities. Where significantly different Tm values are observed organ-

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[221] P.H.A. Sneath, The Construction of Taxonomic Groups, in Microbial Classification, 289, 321 (1962).

[222] Woodruff at 405.

[223] Id.

[224] Sneath, *supra* note 221.

isms can be held noninfringing."[225] As they explain in their article, there are two types of base pair interactions in the double stranded DNA molecule. The guanine-cytosine (GC) pairs are more resistant to strand-separating forces than are the adenine-thymine (AT) pairs. The Tm value is the temperature at which heated double helix strands of DNA will unwind into disordered single strands, and is correlated with the GC percentage. Thus, Woodruff reported the following GC percentages:[226]

M. glutamicus (soil isolate)	53.9%	B. vitarumen 69.3
B. divaricatum	53.8%	A. globiformis 65.8
		E. coli 50.7
		M. lysodeikticus 72
		C. xerosis 57.5

According to Woodruff, "(a)ll cultures which by analysis have a GC range within a narrow range of deposited patent examples, which by conventional taxonomic study are generally similar to a cultural description of a typical strain published in a patent specification, and which fall within the range of cultural variation of newly isolated microorganisms from nature should be accepted as within the scope of a fermentation process patent of species breadth. It is immaterial what species name is assigned by different research workers.[227]

It is also possible to determine the degree of similarity of two organisms by hybridizing their DNA,[228] but this is a more extensive laboratory task than GC analysis. Precise determinations of genetic homology have, nonetheless, been performed.[229]

Woodruff's "final test" for the validity of the patent's species concept was to utilize the description of the organism in the patent as a guide to the choice of producing organisms, *i.e.*, to actually attempt to utilize the teaching of the patent. Relying

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[225] Woodruff at 406.

[226] Id., 413-415.

[227] Woodruff at 417.

[228] Pelczar, et al., Microbiology 44 (4th ed. 1977).

[229] *E.g.*, Izard et al., DNA Relatedness Between *Enterobacter cloacae* and *Enterobacter amnigenus* Sp. nor., 31 Int'l J. Sys. Bacteriol 35 (Jan. 1981).

on seven characteristics of the M-glutamicus strain described in U.S. Patent 3,003,925, Woodruff examined 300 animal feces isolates. One hundred-eighty-two did not satisfy the search description. Forty-nine of the "passing" cultures were tested for glutamic acid producing activity. Yields ranged from 7 to 46 percent, with the median in the 31 to 35 percent range. Only two produced less than 10 percent yield.[230]

Woodruff's analyses suggest that it might be possible to advance a "fingerprint" claim to an organism, *e.g.*, "a culture of an organism having a GC percentage of 50 to 55 percent and the ability to produce glutamic acid with a yield of 10 percent or more." This possibility should be explored by the profession.

The ground swell in favor of the use of the "new taxonomy" may even have reached into the courts.

In *Novo Industri A/S v. Travenol Laboratories, Inc.*,[231] the court upheld a patent relating to the preparation of a milk-coagulating enzyme by cultivating the fungus *Mucor miehei* Cooney et Emerson. A prior art patent taught that the usually heterothallic *Mucor pusillus* Lindt also produced a milk-coagulating enzyme (though not the same one), but that some of the 150 to 200 species of genus *Mucor* do not produce good milk coagulating enzymes. Mucor Miehei, a homothallic species, produced "different and highly superior results in comparison with those obtained with *Musor pusillus.*"

Defendants argued that "the sole distinguishing characteristic between *Mucor miehei* and *Mucor pusillus* was sexuality (*i.e.*, homothallic vs. heterothallic). However, the Court found that:

> [T]he classification of an organism as a *Mucor miehei* or a *Mucor pusillus* cannot be based on any single characteristic or property. Rather, the Court finds that one of ordinary skill in the art would evaluate all the distinguishing characteristics discussed by Cooney and Emerson [in their taxonomic treatise on Thermophilic Fungi].

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230 Woodruff at 415-416.

231 Civ. Action No. 77-C-2778, Supplemental Findings 5, 8-20 (N.D. Ill. March 25, 1981) (Grady, J.), aff'd, 24 PTCJ (BNA) 86 (7th Cir. 1982).

The bottom line is that any microbiological litigation will resolve itself into a battle of the experts:

> Any competent microbiologist could, in the present state of our knowledge, produce evidence that two similar organisms were not in fact identical, or indeed marshall an impressive army of tests to suggest that they were the same if so required.[232]

§ 4.04 Nonobviousness, Infringement, and Similar Nucleotide Sequences

DNA is a very unusual, high-molecular weight organic polymer which, because of its properties, is virtually the *sina qua non* of life itself. What makes it a polymer *sui generis?*

> [A]lthough it is true that DNA is a polymer of only four different kinds of monomeric building blocks, it is unlike any other polymer in that the exact position of each of the building blocks in a molecule consisting of thousands of blocks is of critical importance. Moreover, differences in the sequences of building blocks (base pairs) from one DNA molecule to another can have profound functional consequences. Alteration of a single base pair out of the 5,000,000 base pairs in E. coli DNA can determine whether the bacterium can produce a particular enzyme, can grow in a particular environment, or can metabolize particular compounds. In contrast, a typical organic polymer used in the plastics or textiles industries has only one kind of repeating building block, so it is the nature of the quite different sequence which specifies the exact same hormone and use it to produce the hormone without infringing on the patent? Can the second sequence be patented? It should be noted that it is not unreasonable to assume that in some cases a second sequence will be measurably better than the first one. It could be better in terms of the case with which it itself can be synthesized, or it could be better in terms of the efficiency with which it codes for the hormone in the cell.[233]

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[232] J. R. Norris, The Microbiologist and the First European Patent Convention, Process Biochemistry 29, 30 (June 1977).

[233] Jackson, Patenting of Genes: What will the Ground Rules Be?, in ASM, Patentability of Microorganisms: Issues and Questions, 23 24-27 (1981).

Certainly, inducing a point mutation in an unexpressed segment of the gene sequence, or substituting a new base pair for its equivalent, normally would not be sufficient to avoid infringement.

The Manis patent claim[234] referred to a restriction map of the claimed plasmid. Would eliminating a nonunique restriction site (*e.g.*, 9.0 Xho I) be sufficient to avoid infringement? What about eliminating a unique restriction site (*e.g.*, Bgl II 0.0/9.2)?

According to Jackson, most vector DNA molecules are variations "on one of three basic naturally occurring DNA molecules. What degree of variation is going to constitute novelty . . . or [avoid] infringement . . . ?"

It is likely that useful gene sequences will be characterized long before their usefulness is recognized. Does the preexisting knowledge of the sequence preclude a patent to he who recognized its utility? An argument to the contrary might be based on the *Kratz* case, since "2M2PA" was a known ingredient of strawberries before its flavor was recognized:

> Even if the bare lists of compounds found in strawberries were in the prior art, those extensive lists are quite mute in directing one having ordinary skill in the art to any particular compound for any purpose. While recognizing that obviousness does not require complete predictability, In re Kronig, 539 F.2d 1300, 190 USPQ 425 (CCPA 1976), we would consider it necessary even once 2M2PA is known, that the prior art itself further provide same foreseeability or predictability that the compound is a significant strawberry flavor ingredient.[235]

RDNA molecules consist of three functional parts: (1) the vector DNA, by which the molecule is stably replicated and by whose phenotypic expression a transformed organism is recognized, (2) the structural DNA, which produces the desired proteins, and (3) the regulatory DNA, which control the level of expression of the structural genes, or the replication pro-

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[234] Manis, U.S. Patent No. 4,273,875 [1981].

[235] In re Kratz, 201 U.S.P.Q. 71, 76 (CCPA 1979).

cess.[236] Different vectors and regulatory elements will be developed in the years ahead, and combined with a variety of structural genes. The desirability of patent protection is clear, though the ground rules for patenting gene sequences are still uncertain.

There is a tendency for those new to the molecular biology art to regard the various promoters, terminators, enhancers, attenuators, repressors, inducers, structural genes, replicons, vectors, enzymes and hosts as recipe ingredients, to be combined willy-nilly by the researcher "chef." Assuming that none of the components are novel, it can always be argued that it was obvious to try the particular combination utilized.

Unfortunately for those trying to achieve commercially important ends, but fortunately for those trying to solicit patents on the means to those ends, life is not so simple. The structural gene must be synthesized or isolated in a complete form. When the gene expresses a polypeptide which is a minor cellular constituent, this may require a fair amount of cajoling. The gene must then be incorporated into a transfer vector, and then the promoter must be operably linked to it. If it is desired to express the gene in a different host than the one in which the transfer vector was maintained, the necessary origin of replication must be supplied. The performance of these manipulations may be hampered by the presence of inconvenient restriction sites on the gene itself. Transcription of the gene into mRNA may be hindered by a shortage of a particular tRNA in the particular host. Transcription of the gene into mRNA also may be hindered by negatively acting regulatory sequences unwittingly imported into the plasmid. The regulatory sequences may also behave differently in a heterologous (foreign) host. If the gene has introns, it cannot be properly expressed in a host lacking the mechanism for splicing out the hnRNA transcript of the intron sequence. The mRNA may be degraded by the host. Translation of the mRNA into protein may be incomplete. The protein may be degraded by host enzymes. Or the host may lack the mechanism needed to modify the protein to obtain the desired biological activity. Or the protein may lack the signal peptide which would tell the host to

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[236] Jackson, *supra* at 27.

secrete it into the world beyond. These are just a few of the problems of real-life molecular biology.

§ 4.04A Infringement of Biotechnology Patents: Claim Analysis

In interpreting claims to biotechnology inventions, one sometimes encounters limitations which can be interpreted either as structural limitations or as process limitations. One example is the word "mutant": is a "mutant protein" one created by mutation of the corresponding gene, or is it a protein having an amino acid sequence which is similar to but not identical with that of the native protein, however that protein is obtained? Is a "synthetic protein" one identical to the natural protein though obtained by artificial means, or is it a protein which necessarily differs in structure from the natural protein by virtue of its synthetic origins?

An issue of this kind was raised in *Scripps Clinic and Research Foundation v. Genentech, Inc.*[236.1] Scripps argued that its claims to "a human VII:C preparation" of specified purity covered any sufficient pure preparation of a protein having "the functional and structural characteristics" of Factor VIII:C "as it occurs naturally in humans." The record showed that Genentech's Factor VIII:C gene was a cDNA complementary to naturally occurring messenger RNA for Factor VIII:C. This cDNA transcript of the human gene was expressed by Genentech in a baby hamster kidney cell. Genentech argued that the term "human" limited Scripps' claims to Factor VIII:C derived from human blood plasma. This issue was resolved in part by a somewhat loose application of the doctrine of claim differentiation. The court observed that Scripps had presented product-by-process claims which recited that the Factor VIII:C is filtered "from a plasma or commercial concentrate source." The weakness of this argument is that even reading "human" as desired by Genentech, the product claims would still have been different in scope from the product-by-process claims.

[236.1] 3 U.S.P.Q.2d 1481 (N.D. Cal. 1987), on reconsideration, 6 U.S.P.Q.2d 1019 (N.D. Cal. 1988).

The court also pointed to passages in the prosecution history in which Scripps pointed to differences between human Factor VIII:C and bovine Factor VIII:C (which was known in the art) in both amino acid sequence carbohydrate content and natigencity. It suggested that Scripps' reliance on structural differences rather than on differences in origin indicated that "human Factor VIII:C" was "descriptive not of its derivation from human plasma but of its fundamental characteristics peculiar to the species."

This author feels that a better argument for the court's construction of the product claims was that a limitation to Factor VIII:C "derived from human plasma" would have had no differentiating effect if such Factor VIII:C was not somehow *structurally* different from the known bovine Factor VIII:C. A disguised product-by-process claim is no more valid than an avowed product-by-process claim when it attempts to reach a known product.

Another problem with a term like "Factor VIII:C" is that, if not defined by the specification, it leaves open the question of what molecular species are covered by it. Genentech's European Application defined "human Factor VIII" as a protein capable of functioning like human Factor VIII. Thus, it must be able to correct human factor VIII deficiencies by catalyzing the conversion of Factor X to Xa in the presence of Factor IXa, calcium and phospholipid, and it must be capable of correcting the coagulation defect in plasma derived from hemophiliacs. Also, it must have immunological properties which are substantially identical to human plasma factor VIII." Thus, analogues of human Factor VIII could be embraced by Genentech's claims.

While the Scripps patent did not set forth what was meant by "Factor VIII:C," Scripps nonetheless succeeded in obtaining summary judgment that Genentech's recombinant Factor VIII:C infringed.

Genentech's preparation differed modestly from that of Scripps. First, Genentech's Factor VIII:C allegedly was of reduced polymorphism. Second, the glycosylation of Factor VIII:C by Genentech's hamster cells would have been different than that of Factor VIII:C from Scripps' human plasma. Nonetheless, the Court found that Genentech's recombinant

Factor VIII:C was "structurally and functionally the same" in all material respects and therefore qualified as "human VIII:C" within the meaning of the claims.

Several interesting infringement issues were considered in *Hybritech, Inc. v. Abbott Laboratories.*[236.2] An exemplary claim of the patent is reproduced below:

> 19. In an immunometric assay to determine the presence of concentration of an antigenic substance in a sample of fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, the improvement comprising employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.

Abbott, in some of its products, used Fab fragments of antibodies, instead of intact antibodies.[236.3] The court noted that "there is testimony in the record, however, that Fab fragments do the same thing in essentially the same ways as the whole antibody." It also observed that Abbott had not thought it necessary to notify FDA of the substitution and had not expected any customer reaction. On this record, the court's ruling that Hybritech was likely to succeed on the merits on the issue of infringement under the "doctrine of equivalents" was not surprising.

The claims also contain a quantitative limitation as to affinity, "at least about 10^8 liters/mole." By "affinity," the Court said, was meant "functional affinity" (avidity for an antigen) as distinct from "intrinsic affinity" (affinity for a particular epitope of an antigen). The affinity of one of Abbott's hCG antibodies was 4.7 or 4.8 $\times$ 10^7, which is, of course, less than 10^8. The court held that this difference—less than half an order

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[236.2] 4 U.S.P.Q.2d 1001 (C.D. Cal. 1987) (on motion for preliminary injunction).

[236.3] Id. at 1012-13.

of magnitude—was no greater than the two-or-three-fold measurement errors inherent in affinity determinations and was not significant. The word "about" in the claim also supported its relaxation of the 10^8 minimum.

A third issue was posed by Abbott's use of blends of monoclonal antibodies in certain assays.[236.4] The court held that these assays literally infringed the claims. In doing so, it relied on two aspects of the patent. First, the claims were written in an "open" format (*i.e.*, A method . . . comprising . . ."). Second, the specification referred to the use of "at least one and usually two *or more* different monoclonal antibodies." [Emphasis by the court.]

§ 4.05 Infringement of "Biotechnology" Patents: Additional Questions

[1] The "Experimental Use" Defense

In *Whittemore v. Cutter,* Justice Story declared "it could never have been the intention of the legislature to punish a man, who constructed . . . a machine merely for philosophical experiments. . . ."[237] Given the research-intensive character of the biotechnology industry, it is likely that companies who are utilizing patented cultures or method in their own R&D programs will raise the "experimental use" defense when sued for patent infringement.

One line of cases takes an expansive view of the "experimental use" doctrine. *Ruth v. Sterns-Roger Manufacturing Company* involved a patented flotation machine. In the accounting against a "contributory infringer," Ruth sought to include parts sold to the Colorado School of Mines. The Special Master found that these parts "were for use in laboratory machines used for experimental purposes.[238] Similarly, in *Chesterfield v. United States,* a patented cobalt-nickel alloy was apparently used by the Government "only for testing and for experimen-

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[236.4] Id. at 1012.

[237] 29 F. Cas. 1120, 1121 (No. 17,600) (CCD Mass. 1813).

[238] 13 F. Supp. 697, 713 (D. Colo. 1935) rev'd on other grounds 87 F.2d 35 (10th Cir. 1936).

tal purposes."[239] Finally, in *Akro Agate Co. v. Master Marble Co.*, a West Virginia Judge declared that defendant's brief, *experimental* flirtation with the use of offset grooved rolls in a marble-forming machine was not an infringement.[240] Taken together, these cases show that the universities, the government, and industry are permitted to invoke the "experimental use" defense.

The word "experimental" does not, however, guarantee immunity. Professor Robinson pointed out that the patented product may be intended for experimenters. According to his 1890 treatise:

> Where [the invention] is made or used as an experiment, whether for the gratification of scientific tastes, or for curiosity, or for amusement, the interests of the patentee are not antagonized, the sole effect being of an intellectual character in the promotion of the employer's knowledge or the relaxation affected to his mind. But if the products of the experiment are sold, or used for the convenience of the experimenter, or if the experiments are conducted with a view to the adaptation of the invention to the experimenter's business, the acts of making or of use are violations of the rights of the inventor and infringement of his patent.[241]

If adopted, Robinson's view severely limits the scope of the "experimental use" defense.

The defense was further limited by two Court of Claims cases. In *Douglas v. United States,*[242] Trial Judge Cooper tried to harmonize the decided cases by declaring that when the experimental use was in connection with the user's business, only a sparing, isolated use would avoid infringement, and then under the principle *de minimis non curat lex.* In *Douglas,* the patented jet engine devices were used for four years of systematic testing for governmental purposes, rather than "for amusement, to satisfy idle curiosity, or for philosophical industry." In *Pitcairn v. United States,* the government unsuc-

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[239] 159 F. Supp. 371, 375 (Ct. Cl. 1958).
[240] 18 F. Supp. 305, 333 (N.D. W.Va. 1937).
[241] 3 Robinson, *The Law of Patents for Useful Inventions,* 898 (1890).
[242] 181 U.S.P.Q. 170, 176-177 (Ct. Cl. Trial Div. 1974).

cessfully contended that rotary-wing aircraft were noncompensably used for "testing, evaluational, demonstrational or experimental purposes," in the face of the judge's belief that such purposes are part of the business of the Government.[243]

In *Roche Products, Inc. v. Bolar Pharmaceutical Co.* (April 23, 1984), the CAFC held that the owner of the patent on the drug fluazepam was entitled to a remedy against a generic drug manufacturer who, in the twilight year of the patent term, imported flurazepam solely for use in obtaining stability and bioequivalency data to support a New Drug Application. In remanding the case to the court below to fashion an appropriate remedy, the court indicated that it thought that the requested sanction—confiscation of the data Bolar generated for FDA using the infringing material—was too harsh.

In ruling against *Bolar* on the issue of "experimental use," the CAFC followed court of claims precedents, declaring: "Bolar's intended 'experimental' use is solely for business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry." Rather, it found that *Bolar* had engaged in an inquiry having "definite, cognizable and not insubstantial commercial purposes."

New 35 U.S.C. §271(e)(1) in part overrules *Bolar.* It provides that:

> It shall not be an act of infringement to make, use or sell a patented invention (other than a new animal drug or veterinary biological product. . . .) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs.

However, the new Act also extended the concept of infringement in 35 U.S.C. §271(e)(2):

> It shall be an act of infringement to submit [a New Drug Application or Abbreviated New Drug Application] for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use or sale

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[243] 188 U.S.P.Q. 35, 47 (Ct. Cl. Trial Div. 1975).

of a drug claimed in the patent or the use of which is claimed in a patent before the expiration of said patent.

35 U.S.C. §271(e)(2) is specifically limited to drugs. It is clearly prompted by new 21 U.S.C. §355(b)(2) and (j)(2) which require that Paper NDA applicants and ANDA applicants certify the patent status of the drug and the desired indications and notify the patent holder if they regard a patent seemingly infringed to be in fact invalid and noninfringed. The patentee then has forty-five days to sue. Under the former language of 35 U.S.C. §271, there would have had to have been some making, using or selling of the invention in the United States to provide a basis for suit. Such a basis would have been lacking if the application for FDA approval were based on published literature by others and/or on foreign clinical studies. 35 U.S.C. §271(e)(2) provides an independent basis for suit. The relationship of 35 U.S.C. §271(e)(2) to 21 U.S.C. §§355(b)(2)(A)(iv) and (c)(3)(C) was recognized in *Scripps Clinic and Research Foundation v. Genentech, Inc.*[243.1]

The first judicial interpretation of new 35 U.S.C. §271(e)(1) appeared in *Scripps.* Scripps held U.S. Patent No. 4,361,509 and Reissue No. 32,011 relating to the purification of Factor VIII:C. Genentech used the claimed process to produce Factor VIII:C, which it sequenced. With the knowledge of the polypeptide sequence, it successfully devised a probe against the Factor VIII:C gene, cloned the gene, and began producing Factor VIII:C by a noninfringing rDNA process. Genentech also used the natural Factor VIII:C derived by the Scripps process as a reference in establishing before FDA the bioequivalency of its recombinant product.

The court concluded: "Defendant has used the Factor VIII:C product to determine the amino acid sequence and to assist it in cloning the gene responsible for Factor VIII:C. It may well be that this will eventually lead to the submission of data to governmental agencies, but that was not the sole purpose of these activities. To apply §271(e)(1) to those circumstances would be to permit the exception to follow the rule."

Judge Schwarzer did not explain whether merely purifying

[243.1] 231 U.S.P.Q. 978 (N.D. Cal. 1986).

natural Factor VIII:C to act as a reference in FDA-dictated bioequivalency studies of recombinant Factor VIII:C would be excused by §271(e)(1); this author believes that it would be.

Subsequently, Genentech sought reconsideration of the 1986 order, arguing that all of its uses of Factor VIII:C bore "some reasonable relationship" to FDA testing purposes.[243.2] The court reviewed the legislative history of Sec. 271(e)(1), which stated, "the only activity which will be permitted by the bill is a limited amount of testing so that generic manufacturers can establish the bioequivalency of a generic substitute." The court found that Genentech used Factor VIII:C in preparing Genentech's European patent application and in performing Genentech's obligations to Cutter under an agreement to develop a process for manufacturing Factor VII:C on a commercial scale, and that the agreement contemplated the marketing of recombinant Factor VII:C outside the United States before expiration of the Scripps patent. Relying on the "solely" stricture of Sec. 271(e)(1), the court denied Genentech's motion.

There is some question as to the type of patentable products covered by 35 U.S.C. §271(e)(1). The Food, Drug and Cosmetic Act, which regulates drugs, also regulates medical devices, foods, and cosmetics. However, a district court refused to extend the 271(e)(1) defense to medical devices. The Public Health Service Act regulates biologics which have been deemed to be drugs for FDCA purposes. It is thus plausible to argue that uses of a patented invention which are reasonably related to the development and submission of information to the FDA regarding both conventional drugs and biologics (other than the statutorily excepted veterinary drugs and biologics) are protected uses.

In *Paper Converting Machine Co. v. Magna-Graphics Corp.* (September 28, 1984), the CAFC held that when a substantially complete machine was assembled and tested during the life of the patent with the view to completing and selling it as soon as the patent expired, the assembly constituted an infringing

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[243.2] Scripps Clinic & Research Found. v. Genentech, Inc., 3 U.S.P.Q.2d 1481, 1493 (N.D. Cal. 1987).

Eli Lilly and Co. v. Medtronic, Inc., 35 PTCJ (BNA) 170 (Dec. 24, 1987).

"making" of the patented apparatus. Like *Roche*, this decision liberally interpreted "the temporal limits of the American patent grant."

[2] Contributory Infringement

Just by looking at a chemical, it is impossible to determine whether it has been manufactured by a patented fermentation process rather than by conventional synthetic methods. For this reason, it may be difficult to identify the direct infringers. It is far easier to locate the companies which are supplying the necessary microbial culture.

In certain fields of the microbiological industry, it may be unprofitable to sue direct infringers, *e.g.*, the farmers who use a patented bacterial insecticide; the amateur winemakers who use a patented "all-purpose" wine yeast strain; the bakers who use a patented "baker's yeast." Once again, the culture suppliers are the better target.

"Infringement" is defined by 35 U.S.C. §271:

> (a) Except as otherwise provided in this title [35 USCS §§1 et seq.], whoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.
>
> (b) Whoever actively induces infringement of a patent shall be liable as an infringer.
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> (c) Whoever sells a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

The case of *Sing v. Culture Products, Inc.*[244] is instructive. Sing received a patent containing the following claim:

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[244] 204 U.S.P.Q. 848 (S.D. Mo. 1979).

[A]dding to the cottage cheese, or its creaming mixture, sufficient culture preparation of *Streptococcus diacetilactis,* said culture preparation selected from the group consisting of freeze dried culture, frozen concentrated cells, and freeze dried concentrated cells, to cause a concentration of cells per gram to 2 x 10^6 cells per gram of cottage cheese.

Use of this prepared concentrate obviated the need for dairies to engage in the "technically difficult task" of properly culturing *S. diacetilactis.*

Plaintiff had the culture concentrates prepared for him by Great Lakes Biochemical Company, which, on plaintiff's instructions, labeled it as being "for use in the method of U.S. Patent No. 3,968,256," and supplied it together with the patent's instructions for its use. Defendants bought the Great Lakes product, relabelled it "Lacto-Life Culture Dressing" and sold it to dairies accompanied by directions "identical in all respects to the instructions issued by plaintiffs." The dairies used it to produce cottage cheese ("only two isolated incidents of use of Lacto-Life in the manufacture of sour cream were shown"). The Court held that defendant's customers infringed plaintiff's patent; that "Lacto-Life" was especially adapted for use in the infringement; and that defendants' culture was not a staple article suitable for *substantial* noninfringing use.[245]

The Court also held Culture Products, Inc. liable under 35 U.S.C. §271(b), since it supplied directions for use which, when followed, resulted in direct infringement of the patent dairies.[246]

[3] Section 337 Actions

If a patented process is practiced outside the United States there is no infringement.[247]

Some solace is given to patentees by Section 337 of the Tariff

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[245] Id., 852-853.
[246] Id., 853.
[247] 35 U.S.C. §271.

Act.[248] Under Section 337, a "domestic industry" endangered by the "unfair acts" of an importer may seek an exclusion order through a proceeding before the International Trade Commission. Import of a product produced by means of a process covered by a domestic patent is an "unfair act," and the domestic industry is that which practices the process covered by the claim—even if it be only the patentee. Certain economic proofs must be set forth by the patentee in an ITC Proceeding, but the inconvenience thus experienced may be set against the speed with which the ITC acts in the usual case.

This author is not aware of any Section 337 cases directly involving the fermentation industry. However, there are hints that Stanford is prepared to invoke Section 337 with regard to the Cohen and Boyer patent. According to a Stanford press release of August 3, 1981:

> Initially [Stanford's patent attorney] was concerned that the patent methods might be used overseas to produce products for sale in the U.S. without need for a license. However, pursuant to the law administered by the International Trade Commission, anyone who uses the patent methods overseas, will need a license from us to import the resulting products into the U.S., he observed.

On February 3, 1988, the International Trade Commission instituted an investigation[248.1] into whether the importation of certain recombinant erythropoietin was an unfair act under Section 337 of the Tariff Act. The investigation was prompted by the complaint of Amgen, Inc., owner of a patent on genetically engineered host cells used in the production of recombinant erythropoietin. Chugai Pharmaceutical was accused of using such cells *in Japan* for the production of recombinant erythropoietin for import into the United States.

The traditional Section 337 action relates to the importation of a *patented product* into the United States. Amgen's patent does not include any claims to erythropoietin *per se*. By special dispensation, Congress created a cause of action under Section 337a when a product, produced abroad by a process when if

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[248] *See generally* Patent Resources Group, ed., *International Trade Commission Patent Practice* (1979).

[248.1] In re Certain Recombinant Erythropoietin, 337-TA-281.

practices here would infringe, is imported. But Amgen's patent does not claim the process, either. Rather, what Amgen owns is a right to exclude others from making, using or selling in the United States cells genetically engineered to produce erythropoietin. There is no other rational use of these cells.

The Achilles' Heel of Amgen's case is that if the definition of "unfair act" in Section 337 is so broad as to embrace cells used in an unpatented process of making an unpatented protein, why would it not also include use of a patented process to make an unpatented product? Yet Congress found it necessary to enact Section 337a to give process patent owners relief against the importation of products made abroad according to U.S.-patented processes.

Since recombinant DNA technology is often used to produce proteins already available (though in small quantities) in purified form, and therefore unpatentable, and since the *Durden* doctrine has made it more difficult to patent manufacturing processes, claims to transformed cells and expression vectors have gained in importance. Thus, the industry will watch the Amgen/Chugai investigation with interest.

[4] The "Exhaustion" Defense

When a patented product is purchased from one authorized by the patent owner to sell it, the purchaser may use or resell it without restriction. The patent monopoly is exhausted.[249] The purchaser has the right to repair the product, but not the right to reconstruct it,[250] as he is not impliedly licensed to "make" the product.

When the purchase is of a product which can be used only in a patented process, the seller's process patent monopoly is exhausted.[251] If the process has a noninfringing use, no license

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[249] Adams v. Burke, 84 U.S. (17 Wall.) 453, 456-457 (1873); Keeler v. Standard Folding Bed Co., 157 U.S. 659 (1895).

[250] Aro Mfg. Co. v. Convertible Top Replacement, 365 U.S. 337 (1961) and 337 U.S. 476 (1964).

[251] Edison Electric Light Co. v. Peninsular Light, Power & Heat Co., 101 F. 831, 837 (6th Cir. 1900); United States v. Univis Lens Co., 316 U.S. 241 (1942).

will be implied.[252]

These rules, difficult enough to apply to mundane apparatus and chemicals, become a source of bedevilment when applied to microbiological invention. Organisms, left to themselves, will multiply, while fecundity is not a notable characteristic of vacuum tubes or chemical solutions. If a patentee sells a subculture of a patented culture, and the purchaser propagates the organism in a nutrient medium, is the latter "using" the culture or is he "making" more of it? Since it is impossible to use a microbial culture (other than microbial food products or "killed" vaccines) without permitting cell division to take place, the sale of the subculture must be construed as an implied license to cultivate the organisms.

It may be argued that it would be inappropriate to hold, however, that the purchaser may then sell subcultures of the subculture he received from the patentee, in competition with the latter. The Second Circuit indicates that "implied" license is a license implied-in-fact, rather than one implied-in-law:

> The burden was upon the appellees to establish that the parties agreed, by a meeting of the minds, that the licenses contended for should be granted. The mere sale imports no license, except where the circumstances plainly indicate that it did, or except where good faith required it, or where it cannot be doubted that the vendee understood that they were getting a license.[253]

A closer question is whether the licensee may resell his entire stock of the patentee's culture to another. An analogy may be drawn to a situation covered by the most recent amendment to the Copyright Act:

> Notwithstanding the provisions of Section 106, it is not an infringement for the owner of a copy of a computer program to make or authorize the making of another copy or adaptation of that computer program provided:

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[252] United Nickel Co. v. California Electric Works, 25 F. 475 (C.C. Cal. 1885); Popsicle Corp. v. Weiss, 40 F.2d 301 (S.D.N.Y. 1929).

[253] General Electric Co. v. Continental Lamp Works, Inc., 280 F. 846 (2d Cir. 1922).

(1) That such a new copy or adaptation is created as an essential step in the utilization of the computer program in conjunction with a machine and that it is used in no other manner, or

(2) That such new copy or adaptation is for archival purposes only and that all archival copies are destroyed in the event that continued possession of the computer program should cease to be rightful.

Any exact copies prepared in accordance with the provisions of this section may be leased, sold, or otherwise transferred, along with a copy from which such copies were prepared, only as part of the lease, sale, or other transfer of all rights in the program. Adaptations so prepared may be transferred only with the authorization of the copyright owner.[254]

Another interesting question is whether purchase of the culture exhausts the monopoly insofar as the purchaser's *mutated* strain is concerned. The situation is comparable to instances in which the patented product is reconstructed for a special purpose.[255] It may also be compared to the *adaptation* of a copyrighted computer program.

[5] The "Catalyst" Defense

In an interesting paper, Jorge Goldstein suggested that if a patent claimed a microorganism per se, and described a particular use for it, that "if a new use for the microbe were later discovered, it might turn out not to be dominated by the original patent if the same is given a narrow 'catalyst-type' interpretation."[256] He thus referred to the peculiar line of case law limiting the scope of product claims on catalysts. *Ziegler v. Phillips Petroleum* (1973) involved two patents on polymeriza-

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[254] P.L. 96-517 §10(a), 17 U.S.C. §117 (as amended).

[255] Compare Miller Hatcheries, Inc. v. Buckeye Incubator Co., 41 F.2d 619, 621-622 (6th Cir. 1942); Wilbur-Ellis Co. v. Kuther, 377 U.S. 422 (1964); with George Close Co. v. Ideal Wrapping Machine Co., 2 F.2d 532 (1st Cir. 1928); National Phonograph Co. v. Fletcher, 117 F. 149 (E.D.N.Y. 1902).

[256] J.A. Goldstein, The Scope and Enforcement of Biotechnology Patents, in ATCC Biotechnology Patent Conference Workbook, 54, 58 (1983).

tion catalysts disclosed to be useful in the polymerization of ethylene.[257] The defendant used similar catalysts in the polymerization of butadiene and propylene. The Fifth Circuit held that the *Ziegler* product claim to the catalyst was not infringed by the defendant's use of a similar polymerization catalyst in the polymerization of butadiene.

Dr. Goldstein suggests that a "new reaction for a patented enzyme may be considered . . . to fall outside a claim to an enzyme per se."[258] Enzymes, of course are biological catalysts, so the analogy is a strong one. Indeed, a microorganism used to ferment a substrate into a desired product has some characteristics in common with catalysts, so that application of the *Ziegler* approach to microorganisms has some merit. But is *Ziegler* good law?

Most commentators have referred to the so-called "all uses" doctrine: a product patent claim covers all uses of the patent, whether envisioned by the patentee or not. Rightly or wrongly, some courts have restricted the sweep of this doctrine. In *Kaz Mfg. Co. v. Chesebrough-Ponds, Inc.* (1963), the Second Circuit colorfully suggested that "one who constructs a patented wall safe but uses it only to anchor his boat would not be a patent infringer since such use would not be for the purpose of utilizing the teachings of the patent." In much the same vein, the *Ziegler* court said that it was restricting the patentee to the uses of his catalyst which it regarded as "the basic teaching and actual invention."[259] Still, while the Fifth Circuit said that it was "not holding as a matter of law that the patentee of a chemical catalyst is protected in his monopoly only so far as he specifically claims the reactions in which the catalyst finds use,"[260] in seeking to give "effect to the real invention," it seemed to many scholars to hold the "all uses" doctrine inapplicable to chemical catalysts.

The *Ziegler* case has received a considerable amount of criticism, much of it justified. However, a close examination of the facts in *Ziegler* will put the holding, if not the dicta, in a better

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[257] 177 USPQ 481 (5th Cir. 1973).
[258] Goldstein, *supra* note 256, at 58.
[259] 317 F.2d 679, 137 USPQ 588 (2d Cir. 1963).
[260] Ziegler, *supra* note 257, at 491.

light. First, the *Ziegler* claims were not literally infringed.[261] The court was thus evaluating infringement under the doctrine of equivalents. In declaring that "the proper construction of a patent claiming a chemical catalyst system, therefore, looks not only at the components of the system but also at the reaction or reactions catalyzed and the reaction products,"[262] the court merely required that the two catalytic systems "perform substantially the same function in substantially the same way to obtain the same result," as mandated by the holding of the Supreme Court in *Graver Tank & Mfg. Co. v. Linde Air Products* (1950).[263]

The next point made by the Court was less convincing. The patent, rather than claiming the catalyst as a "composition of matter," spoke of it as a "polymerization catalyst." Thus, reasoned the court, it was not enough to find a similar compound used by *Phillips;* it was necessary to find that the compound functioned as a catalyst in order to find infringement. Moreover, the Court argued, because of the highly specific activity of a catalyst, it was not logical to consider the composition of the catalyst apart from its use. "A catalyst system . . . has both composition of matter and process characteristics, and to pigeonhole the '332 patent's invention as one or the other would be needlessly formalistic, and might produce a distorted view of the true patented invention." (The answer, of course, is that patent claims, like deeds to property, are necessarily formalistic, and that if the scope of the claim is inconsistent with the disclosure, the proper approach is to strike down the claim under 35 U.S.C. §112, rather than to interpret it artificially.)

Third, *Ziegler's* specification did not make any discernible attempt to suggest, even in a general way, that his catalytic composition could be used to polymerize any polymer other than ethylene. The '332 patent was titled *Polymerization of Ethylene,* and all of its examples dealt with ethylene. Indeed, it may be that the "catalyst" exception was merely an attempt to construe the claim narrowly enough to save it from attack under §112 for lack of enablement.

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[261] Id., 490.

[262] Id., 491.

[263] 339 U.S. 605, 85 USPQ 328 (1950).

Finally, the Court did hold that *Ziegler's* '115 patent was infringed by the *Phillips* polypropylene production process. The '115 patent had a vaguer title and indicated that the invention was a polymerization catalyst for lower olefins, particularly ethylene. Propylene is, of course, a lower olefin.

There is certainly a risk that the "catalyst" exception will rear its ugly head in biotechnology patent litigation. The best way to exorcise this specter is to give it no excuse to appear. The *Ziegler* court observed that the '115 patent's references to ethylene were almost always preceded by "such as;" this is a painless preventative measure.

§ 4.06 Patentability of Biotechnical Processes

The decision of *In re Durden*[264] inspired a flurry of rejections of process claims by the PTO. *Durden* affirmed an examiner's rejection of a claim to a process of making certain carbamate esters from certain oximes. The patentability of the oxime starting materials and the carbamate ester products was conceded. The rejection was based on the Punja reference, which disclosed the same process applied to different (but similar) reactants.

Applicants' brief conceded that "the claimed process, apart from the fact of employing a novel and obvious starting material and apart from the fact of producing a new and nonobvious product, is obvious." Nor did they argue that "differences in the chemical structure of either the starting oxime compound or the product produced would be expected to affect the reaction in any way which might render the claimed process nonobvious."

The CAFC remarked, "the issue to be decided is whether a chemical process, otherwise obvious, is patentable *because* either or both the specific starting material employed and the product obtained, are novel and nonobvious." Its answer was, "Not necessarily."

Before affirming the rejection, it considered and contrasted

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[264] In re Durden, 763 F.2d 1406 (CAFC 1985).

the decisions of its predecessor court in *Kuehl,*[265] and *Albertson.*[266] *Kuehl* involved a hydrocarbon cracking process employing a newly invented catalyst, ZK-22. The process claim was vindicated by the CCPA. The *Durden* court explained that the cracking process in *Kuehl* "was not predictable on the basis of mere possession of the catalyst."

This statement was unfortunate, as it suggested that in evaluating the patentability of a fermentation process, the organism must be deemed a part of the prior art. In *Kuehl,* the CCPA said one must determine whether it was obvious to use ZK-22 to crack hydrocarbons without reference to knowledge of ZK-22 or its properties.

Indeed, *In re Mancy* squarely considered the patentability of fermentation methods using novel organisms. In reversing the rejection of a process claim, the CCPA declared

> Under §103 neither a novel product made by, nor a novel product used in, the process can be treated as prior art. In the method-of-use cases, such as *Kuehl,* the novelty of the starting material may itself lend unobviousness to the process.[267]

It was more skeptical of ascribing patentability to a process merely because it produced a novel product. In genetic engineering applications, it is common to see claims to "a process of producing polypeptide P which comprises cultivating the transformed host of claim 1 under conditions favorable to expression, of polypeptide P, and recovering polypeptide P." It can be argued that the "transformed host" is, like the oxime in *Durden,* a novel starting material, but that the process itself, given possession of the novel starting material, is purely conventional.

The loss of the process is of little commercial significance if the product may be claimed. If the product, however, is "old," then the assignee may find it difficult to fend off foreign competition. If neither the process nor the product is patented in the United States, then the product may be produced abroad and imported into the United States without commit-

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[265] In re Kuehl, 475 F.2d 658 (CCPA 1973).

[266] In re Albertson, 332 F.2d 379 (CCPA 1964).

[267] In re Mancy, 499 F.2d 1289, 1293 (CCPA 1974).

ting an "unfair act" under either 19 U.S.C. §1337 or 19 U.S.C. §1337a.

Durden does not render unpatentable the application of a conventional process to a novel material, provided that the result is, to some degree, uncertain. *In re Coleman* is instructive. The conventional monosulfonation process was applied to hydrocarbon gas oil feedstock. Applied blindly, the process experienced the problem of inadvertent polysulfonation. This problem was overcome by judicious feedstock selection. As the *Coleman* court said, "one may look at a starting material to the extent that it affects the process."[268]

Thus, in a genetic engineering case, one could ask: Is the mRNA transcript stable? Is the protein vulnerable to the transformed host's proteases? Can the host process and secrete it properly? Can the desired polypeptide be recovered easily from amidst the host's other metabolic products? These are the kinds of uncertainties which overcome the supposed obviousness of the process.

Durden-type issues also arise in the immunological arts, as was pointed out by a dictum in *Ex parte Goodall:* "even were claims to appellants' hybridoma and antibody found to be allowable, the patentability of the processes of producing the hybridoma and the antibody and using the antibody would still be in question,"[269] citing *Durden.*

§ 4.07 Patentability of Biotechnology Inventions Derived by Screening Procedures

Many biotechnology inventions are the fortunate result of a tedious screening procedure. Field isolates are plated out onto various media and screened for useful properties. Organisms of interest are barraged with mutagenic agents and then screened once more. If a strain that produces small quantities of desirable antibiotic is available, should one be able to patent a superior strain derived by the conventional process of mutation and selection?

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[268] In re Coleman, 621 F.2d 1141, 1145 (CCPA 1980).

[269] 231 U.S.P.Q. 831 (BPAI 1986).

Similar questions are prompted by developments in molecular biology. Numerous techniques exist for fishing out a desired gene from a complex population of nucleic acids. For example, complementary DNAs are synthesized, using the messenger RNAs of a cell as templates. These are cloned, creating a "cDNA library." Information about the amino acid sequence of the protein of interest, and about the codon preferences of the cell in question, is used to design a nucleic acid probe which, hopefully, will hybridize preferentially with the cDNAs which encode all or part of the desired protein.

In Europe, these issues have been raised twice in *inter partes* proceedings. In the Biogen case, it was held that a recombinant alpha interferon molecule was unpatentable over art teaching the N-terminal sequence of the protein and how sequence data could be used in probe design. In the Genentech case, the court was unwilling to hold that Genentech's recombinant tPA was obvious.

In the United States, the application of 35 U.S.C. 103 to monoclonal antibody development has engendered considerable interest and uncertainty.

The splenocytes are used to make hybridoma cell lines which produced monoclonal antibodies. The antibodies differ in type, specificity, and affinity for the antigen of interest, and screening is therefore necessary.

In *Ex parte Old*,[270] claims were presented to monoclonal antibodies recognizing certain human renal cell antigens (claim 9). It appears that these antigens were characteristic of malignant renal cells. The Examiner argued that Old's monoclonal antibodies were obvious in view of (1) Ueda's polyclonal antibodies recognizing human renal cell antigens; (2) Kohler and Milstein's generic technique for preparing monoclonal antibodies; and (3) Dippold's demonstration that monoclonal antibodies against a cancer antigen (melanoma) could be prepared by that technique.

The Board reversed the rejection under 35 U.S.C. §103. "Hybridoma technology is an empirical art in which the routineer is unable to foresee what particular antibodies will be produced and which specific surface antigens will be recognized

[270] 229 U.S.P.Q. 196 (BPAI 1985).

by them. [I]t may be 'obvious to try' the Kohler-Milstein technique as applied to malignant renal cells, but such is not the standard under which obviousness under 35 U.S.C. 103 must be established."

Examiner-in-Chief Merker, dissenting, characterized Old's work as "the application of admittedly known standard techniques to admittedly known renal cancer cell lines to produce expected hybridomas which produce expected monoclonal antibodies."

But are they "expected"? There is an unfortunate lack of attention to detail in both opinions in the *Old* case. What was the nature of the antigens recited in claim 1? How common were they in normal renal cells? How common were they in malignant cells? Did the prior art recognize that they were cancer markers? Were they available in a state of purity typical of that used in the hybridoma art?

One can visualize a variety of claims: (a) a monoclonal antibody that recognizes a *renal cell* antigen; (b) a monoclonal antibody that recognizes a *renal cancer* antigen; (c) a monoclonal antibody that recognizes a renal cancer antigen and *does not cross-react* with normal renal cells; (d) a monoclonal antibody to the *cell surface* renal cancer cell marker; and (e) a monoclonal antibody that recognizes a *particular* renal cancer marker. It becomes easier and easier to recognize patentability as one moves from (a) to (e).

The dissent does touch on these points. Merker argues that the applicant failed to differentiate the claimed monoclonal antibodies "either among themselves or from other monoclonal antibodies which recognize renal cancer antigens."

The point would be a significant one if monoclonal antibodies for renal cancer cell antigens were prior art. Merker points to a textbook,[271] but that reference was published in 1982, while the Old application was filed on August 31, 1981. It thus appears to be merely evidence of nearly simultaneous invention by others. Against this relatively weak evidence of obviousness must be set the countervailing evidence relied on by the majority: a long-felt, relatively unsolved need for monoclonal antibodies to cancer antigens.

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[271] McMichael & Fabre, *Monoclonal Antibodies in Clinical Medicine*, 111-29 (1982).

Even without outright prior invention, there was a plausible obviousness case against the David patent in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*[272] High affinity monoclonal antibodies were known. Monoclonal antibodies had been used in competitive assays. Sandwich assays using polyclonal antibodies were conventional and the importance of affinity was recognized. The use of monoclonal antibodies in immunoassays was generally advocated. Nonetheless, these teachings were dismissed by the Federal Circuit as mere "invitations to try monoclonal antibodies in immunoassays" that did not "suggest how that end may be accomplished."

The *Hybritech* case shows the importance of presenting claims of different breadth.

Contemporaneous development of a biotech invention may be indicative of obviousness. In *Hybritech v. Monoclonal Antibodies, Inc.*, the trial court declared that the alleged invention "was contemporaneously developed by at least five different groups of workers in the field." If contemporaneous development always was indicative of obviousness, there would be no need for interference proceedings. The Federal Circuit discounted these developments in *Hybritech* as not being truly contemporaneous, the first being more than a year after Hybritech's filing date. It also thought that there was strong countervailing evidence of nonobviousness (commercial success; unexpected advantages).

The obviousness of a sandwich assay using monoclonals was again considered in *Hybritech, Inc. v. Abbott Laboratories.*[273] The court accepted one of Abbott's premises: that there was a great deal of interest in using monoclonal antibodies in place of polyclonal antibodies in various assays. However, it also was impressed by the misgivings also prevalent at the time:

> In particular, those skilled in the art seemed to be aware of two major problems for this particular use of monoclonal antibodies. One of them was that the monoclonal antibodies might be too specific; they might be too sensitive. The other disadvantage

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[272] Hybritech, Inc. v. Monoclonal Antibodies, Inc., 227 USPQ 215 (N.D. Cal. 1985), rev'd, 231 USPQ 81 (App. No. 86-531, decided Sept. 19, 1986).

[273] 4 U.S.P.Q.2d 1001, 1009 (C.D. Cal. 1987).

was that it would be difficult to obtain suitable antibodies with sufficiently high affinities.

It is difficult to harmonize the Board's decision in *Old* with its subsequent holdings in *Ex parte Ehrlich, Ex parte Goodall,* and *Ex parte Allen.*

In *Ehrlich,*[274] claim 4, which was directed to "monoclonal antibodies specific for human fibroblast interferon," was rejected as obvious in view of three teachings of the prior art: (1) that human fibroblast interferon and human leukocyte interferon are antigenic (Stewart; Ganfield), (2) that monoclonal antibodies specific to known antigens may be produced (Kohler & Milstein), and (3) that the technique of Kohler and Milstein could be applied successfully to the production of monoclonal antibodies specific for human leukocyte interferon. The Board held that "the success of Secher in obtaining monoclonal antibodies specific for one type of human interferon, while overcoming the problems disclosed in the reference, would have led one to produce monoclonal antibodies specific to human fibroblast interferon using the *same* method with a reasonable expectation of success."

The Board carefully eschews the perilous words "obvious to try." But the standard applied in *Ehrlich* is clearly the same as the one advanced unsuccessfully by the Examiner in *Old:* "obvious to try with a reasonable expectation of success."

In *Ex parte Goodall*[275] the Board affirmed a rejection of a claim to a monoclonal antibody over the antibody over the antibody of another even when there was no direct evidence that the antibodies were similar. The Board inferred similarity from the identity of the antigen, mouse line, myeloma cell line and (possibly) the fusion protocol used to obtain the antibodies, despite differences in the inoculation protocol. The Board found that there was a "predominance of similarities" between the two production methods. It concluded that the processes were sufficiently similar so that the antibodies produced could reasonably be expected to be the same.

The Board further refined its standard of nonobviousness in

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[274] 3 U.S.P.Q.2d 1011 (B.P.A.I. 1987).
[275] 231 U.S.P.Q. 831 (BPAI 1986).

Ex parte Allen, where it found that "one of ordinary skill in the art would have a reasonable expectation that the Stanley, et al., method would be successful in inducing polyploidy in *Crassostrea gigas* oysters based on the success by Stanley, et al., with *Crassostrea virginica* oysters and the recommendation by Stanley, et al., to utilize the method with cultured oysters" generally. Indeed, the Board was willing to say that the expectation of success was "strong."

In *Ehrlich,* the Board cited a line of cases holding that "obviousness under 35 U.S.C. 103 does not require absolute predictability." In *In re Moreton*[276] the court found that a prior art reference taught that monocresyl diphenyl phosphate was a good lubricant. The claim was to the use of certain triaryl phosphates as lubricants for steel-on-steel, steel-on-bronze and steel-on-butyl rubber surfaces in the hydraulic system of an aircraft. The court felt that as a known lubricant, its use would be suggested. Indeed, it went so far as to say that "if the steel-on-butyl rubber surfaces presented any real problem in the sense of deterioration of the seal by the hydraulic fluid, we can see nothing patentable in testing the available fluids, which include those claimed, in order to determine which one or ones would not adversely affect the particular synthetic rubber being used."

While *In re Farnham* followed *Moreton* in general principle, the court found that "appellants' invention does in fact involve something more than the selection of a known catalyst and its use in place of another in a known reaction to produce Bisphenol A." Specifically, Farnham used a cation exchange resin instead of soluble acid as a catalyst. The advantages of resin catalysts were well known, and were similar to those soluble acids. However, Farnham discovered that the desired reaction required pretreatment of the resin catalyst to reduce its water content. The rejection of claims limited to the dry catalyst were reversed, whereas the rejection of the broader claims was affirmed.

While 35 U.S.C. 103 does not require "complete predictability," it does mandate something more than it be "obvious to

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[276] 288 F.2d 708, 129 U.S.P.Q. 272 (CCPA 1961).

try" the claimed expedient. *In re Geiger*[277] reversed a rejection of a claimed method for treating cooling water systems employing a three component antiscaling composition. The components were known antiscaling agents, but had not been used in the claimed combination. The court ruled that the Examiner had failed to establish even a *prima facie* case for obviousness since the references did not suggest the combination. That persons skilled in the art "might find it obvious to try various combinations of these known scale and corrosion prevention agents" was considered irrelevant. Judge Newman, concurring in the result, deemed that the references did teach the combination, but that *prima facie* obviousness was overcome by the demonstrably exceptional corrosion inhibition exhibited by Geiger's composition.

More recently, the Federal Circuit observed in *In re Fine*[278] that "whether a particular combination might be 'obvious to try' is not a legitimate test for patentability." There, in a claimed apparatus for detecting nitrogen compounds in the air, the P.T.O. took the position that it would be obvious to substitute the Warnick nitric oxide detector for Eads' sulfur dioxide detector in the Eads System. The court ruled that there was no suggestion in Eads to use his arrangement to detect nitrogen compounds; indeed, his sulfur compound detector was adversely affected by the presence of nitrogen compounds in the sample.

In re Antonie involved a waste water treatment device with a claimed ratio of tank volume to contractor area. The court remarked, "The PTO and the minority appear to argue that it would always be *obvious* for one of ordinary skill in the art *to try* varying *every* parameter of a system in order to optimize the effectiveness of the system even if there is no evidence in the record that the prior art recognized that particular parameter affected the result." It criticized that approach as one which over emphasizes the "routine nature of the data gathering required to arrive at appellant's discovery, after its existence became expected," in contravention of 35 U.S.C. 103's stricture that "patentability shall be negatived by the manner

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[277] 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987).

[278] 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

in which an invention was made." It also pointed out that the invention as a whole is what must be measured against the standard of 35 U.S.C. 102.

In *Ehrlich* and *Allen*, the Board has advanced a new rubric: "obvious to try, with a reasonable (or strong) chance of success." But a "chance of success" analysis is ever in danger of being colored by hindsight: knowing that a screening procedure was carried out successfully, is one likely to assign it a *low* chance of success?

Subsequently, the Federal Circuit clarified the standard of patentability in a case (*In re O'Farrell*) involving recombinant DNA, not monoclonal antibodies.[278.1] O'Farrell claimed the use of a fused gene as a means of producing a foreign protein in bacteria. A foreign gene was placed behind a substantial portion of an indigenous gene without an intervening stop codon. Thus, transcription of the indigenous gene resulted in readthrough transcription of the foreign gene and translation of the mRNA transcript into a chimeric protein. The prior art showed fusion of a beta-galactosidase gene to a ribosomal RNA gene and transcription of the fused gene. There was also evidence that the mRNA transcript was translated into a higher molecular weight analogue of beta-galactosidase, presumably incorporating amino acids encoded by the ribosomal RNA gene.

When the claims were rejected, O'Farrell argued that there was no basis for predicting that a normally translated eukaryotic sequence could be successfully expressed, since ribosomal RNA is not naturally translated into protein. The rejection was categorized as an attempt to apply an improper "obvious try" standard.

The Federal Circuit acknowledged that it was improper to reject a claim when what was "obvious to try" would have been "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." It also thought it improper to denounce as obvious the exploration of a promising new

[278.1] In re O'Farrell, Appeal No. 87-1486 (Fed. Cir. August 10, 1988).

field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

On the other hand, Judge Rich wrote, obviousness does not require absolute predictability of success: "For obviousness under Sec. 103, all that is required is a reasonable expectation of success." The prior art (indeed, a single reference) was found to contain (1) detailed enabling methodology for practicing the claimed invention, (2) a suggestion to modify the prior art to practice the claimed invention, and (3) evidence suggesting that it would be successful. The presence of these three ingredients made it clear that the Board's inference of a "reasonable expectation of success" was not a hindsight reconstruction of the claimed invention.

§ 4.08 Standards of Inequitable Conduct in Biotechnology Patent Prosecution and Litigation

In *Scripps Clinic and Research Foundation v. Genentech, Inc.*,[279] Scripps obtained summary judgment that its conduct in prosecuting claims to monoclonal antibodies specific for Factor VIII:RP had not been inequitable. The claims required that the antibodies bind a Factor VIII:RP/VIII:C complex and remain bound to the VII:RP when subjected to a saline solution elution and when said antibody is bound to a substrate. Scripps had failed to directly disclose an abstract to the Examiner, which the Examiner relied upon in rejecting those claims. Meyer Abstract reported the production of monoclonal antibodies specific for Factor VIII:RP, but did not disclose that these antibodies could be bound to a substrate to form an immunosorbent for the isolation and purification of Factor VIII:C from the VIII:C/VIII:RP complex. The claims were withdrawn when the Examiner demanded that Scripps test Meyers's antibodies for the aforementioned properties. The court gave great deference to a PTO ruling that "lacking such disclosure, the Meyer abstract did not appear material to the examina-

[279] 3 U.S.P.Q.2d 1481, 1494-97 (N.D. Cal. 1987), on reconsideration, 6 U.S.P.Q.2d 1018, 1022-23 (N.D. Cal. 1988).

tion" and that the meat of the abstract was summarized in the Muller article, which was presented to the Examiner.

CHAPTER 5

Disclosure of Microbiological Inventions Under U.S. Utility Patent Law

§ 5.01 Overview of the Disclosure Requirements

By virture of 35 U.S.C. §111, the application for patent must include "a specification as prescribed by § 112." The format of the specification is not described by § 112, other than a statement that it must "conclude with one or more claims." Rule 77, however, states that "the following order of arrangement should be observed in framing the invention":

(a) Title of the invention. . . .
(c) (1) Cross-reference to related applications. . . .
(d) Brief summary of the invention.
(e) Brief description of the several views of the drawings, if there are drawings.
(f) Detailed description.
(g) Claim or claims.

(h) Signature. . . .
(i) Abstract of the disclosure.
(j) Drawings.

Section 112 consists of three paragraphs. The first paragraph sets forth what must be disclosed in the body of the specification, while the other paragraphs deal only with the claims. The first paragraph reads as follows

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Particular attention will also be called at this time to Rule 73, describing the "summary of the invention," and to Rule 71, describing the "detailed description":

> §1.73 Summary of the invention.
>
> A brief summary of the invention indicating its nature and substance, which may include a statement of the object of the invention, should precede the detailed description. Such summary should, when set forth, be commensurate with the invention as claimed and any object recited should be that of the invention as claimed.
>
> §1.71 Detailed description and specification of the invention.
>
> (a) The specification must include a written description of the invention or discovery and of the manner and process of making and using the same, and is required to be in such full, clear, concise, and exact terms as to enable any person skilled in the art or science to which the invention or discovery appertains, or with which it is most nearly connected, to make and use the same.
>
> (b) The specification must set forth the precise invention for

which a patent is solicited, in such manner as to distinguish it from other inventions and from what is old. It must describe completely a specific embodiment of the process, machine, manufacture, composition of matter or improvement invented, and must explain the mode of operation or principle whenever applicable. The best mode contemplated by the inventor of carrying out his invention must be set forth.

(c) In the case of an improvement, the specification must particularly point out the part or parts of the process, machine, manufacture, or composition of matter to which the improvement relates, and the description should be confined to the specific improvement and to such parts as necessarily cooperate with it or as may be necessary to a complete understanding or description of it.

Note that the Rule 71 demands that the specification "describe completely a specific embodiment." There is no direct statutory support for this demand, which is only obliquely and partially supported by § 112's, "best mode" disclosure requirement. The disclosure of a "working example" does, however, make the specification clearer to persons skilled in the art, and in most cases is a practical necessity.

Note also that it is important that there be a correspondence between the claims and the specification. Under the second paragraph of § 112, only what has been described as applicant's invention may be claimed. Once the application has been filed, "no amendment shall introduce new matter into the disclosure of the invention." Undisclosed matter can be disclosed only in a separate, continuation-in-part application.

[1] Functions of 35 U.S.C. §112

The first paragraph of 35 U.S.C. §112 is a "disclosure" requirement, serving three functions which are easily confused.

First, it requires the inventor to delineate what he contemplates to be his invention when he files his application. The filing date of a patent application is the prima facie date of invention in determining questions of novelty, priority, and nonobviousness, as well as the reference date for the applica-

tion of the "statutory bar" provisions. The requirement that the specification contain a "written description of the invention" ensures that the invention is well-defined, *i.e.*, that it "is fully capable of being reduced to practice," as of the date of filing.

Second, from the date the patent issues, the patent specification adds to the storehouse of knowledge in the art, and serves as a springboard for further invention.

Finally, after the patent expires, the patent specification teaches the public how to practice the invention.

Traditionally, the disclosure requirement is subdivided into three elements: a "description" requirement; an "enablement" requirement; and a "best mode" requirement.

[2] Differentiating the "Description" Requirement and the "Enablement" Requirement

Ordinarily, it is difficult to differentiate the requirement that the applicant describe his invention from the other elements of the "disclosure" requirement.

It comes into play as a distinct entity when an applicant seeks to advance claims which are broader or narrower than those which he originally filed. This may occur (1) when the applicant amends a claim; (2) when the applicant files a continuation application, claiming the benefit of his earlier filing date under 35 U.S.C. §120; or (3) when the application goes into interference, and the applicant must support the interference count.[1] The description requirement is distinct from the enablement requirement, in that "(i)t is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe the invention."[2] In *Ruschig*,[3] applicants generically claimed a family of therapeutic compounds. They were not permitted to specifically claim, at a later date, one such compound—chlorpropamide—even though a general method for making compounds of the class,

[1] In re Smith, 481 F.2d 910, 914 (CCPA 1973).

[2] In re DiLeone, 436 F.2d 1400, 1405 n.1 (CCPA 1971).

[3] Application of Ruschig, 379 F.2d 990, 994-96 (CCPA 1971).

including chlorpropamide, was provided. In essence, the applicants failed to indicate that they regarded chlorpropamide as a separate invention. In an interference case, *Fields v. Conover,* the "description" requirement was justified on policy grounds, as necessary to limit the reach of pioneer patents so as not to cover inventions of others clearly envisioned by the pioneer.[4]

The inventions to be described may be novel metabolic products, new methods of using a known metabolic product, new methods for the production of a useful substance by fermentation, new fermentation media, new methods of isolating, cultivating, mutating or breeding organisms, or of manipulating DNA or RNA segments, novel strains or cultures, novel preparations containing microorganisms (such as food additives, biological control agents, or vaccines), or new methods of utilizing these organisms.

In describing these inventions, several of which may arise from a single line of research, the attorney and the inventor should be mindful of the desirability of presenting claims of varying scope. If claims of varying scope are presented, the gist of each claim should be described in the specification. Thus, an antibiotic fermentation patent might recite inventions directed to "a new substance of molecular structure *X*" "its use as an antibiotic," "its use as an antibiotic inhibiting *staphylococcus aureus,*" "a method for the production of *X* employing strains of species *Y,*" and "particularly to a method for the production of *X* employing strain *Z* of species *Y.*" Typically, the inventions are described by such language as "This invention is directed to . . ." or "It is an object of the present invention to provide . . ." or even "It is preferable to . . . ."

[3] The "Enablement" Requirement and the "Person Skilled in the Art"

The "enablement" requirement, on the other hand, requires only that the reader, a person skilled in the art, be taught how to *make* and *use* the invention described. The

[4] 443 F.2d 1386, 1392 (CCPA 1971).

substances, procedures, and organisms in question are described in greater detail, and the specification generally closes with a series of specific examples of preparation and use, having a level of detail comparable to that of a well-kept laboratory notebook record of experiments. Typically, there is a precatory warning that the examples are illustrative only, and that modifications would be apparent to persons skilled in the art.

A patent specification which is incomprehensible to a layman may nonetheless be "enabling," where the specification is thus incomprehensible merely because it speaks to those skilled in the art to which it pertains in their own language, and draws on their common body of knowledge. As the Supreme Court stated in *Webster Loom Co. v. Higgins* (1882),

> When an astronomer reports that a comet is to be seen with a telescope in the constellation of Auriga, in so many hours and minutes of right ascension, it is all Greek to the unskilled in science; but other astronomers will instantly direct their telescopes to the very point in the heavens where the stranger has made his entrance into our system. They understand the language of their brother scientist. . . . [An inventor] may begin at the point where his invention begins, and describe what he has made that is new, and what it replaces of the old. [T]hat which is common and well known is as if it were written out in the patent and delineated in the drawings.[5]

It is not always easy, however, to determine who are the skilled pupils to which the patent specification must be addressed. A problem which arises in one industry may be solved by adaptation of a solution developed in another. Or making the invention may require one kind of knowledge while using it might require another.

Suppose, for example, that a microbiologist develops, using genetic engineering techniques, an organism which will rapidly degrade an environmental pollutant. His description of the manner in which appropriate plasmids were expressed in a host organism would, in all probability, be incomprehensible to a pollution control technologist, the person who would actu-

[5] 105 U.S. (15 Otto) 580, 26 L.E. 1177, 1179 (1882).

ally use the new organism. This author would argue that the "how-to-make" disclosure should be addressed to the molecular biologist, while the "how to use" disclosure would be for the benefit of the ecologist or environmental engineer.

Thus, in *American Stainless Steel Co. v. Ludlum Steal Co.* (1923), the Second Circuit held that patents on "stainless" steel tools and cutlery provided adequate information for the metallurgist who selected the appropriate alloy, even though it did not teach the cutler that he must employ higher hardening temperatures with "stainless" steel than with other steels.[6]

The CCPA has observed that the invention of the steamboat could not have been described in terms meaningful to the sailboat builder unfamiliar with such mechanisms. In *International Standard Electric Corp. v. Ooms* (1946), the CCPA suggested that the pertinent art was one "whose adepts have the best chance of being "enable[d] . . . to make, construct, compound and use the invention."[7] Later it elaborated upon this standard, suggesting in the *Naquin* case that a patent specification may be addressed to a team of experts drawn from distinct arts, such as (in *Naquin*) computer programming and seismology.[8]

[4] Interaction of 35 U.S.C. §112 with §§119, 120

If a foreign application's filing date is to be relied on as the effective filing date of a subsequently filed U.S. application, the foreign application must satisfy *all* the requirements of 35 U.S.C. §112, even requirements not a part of the patent law of the nation where the priority application was filed.[9] Similarly, a U.S. continuation application cannot claim priority based on its parent application if the latter did not satisfy §112.

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[6] 290 Fed. 103 (2d Cir. 1923).

[7] 157 F.2d 73, 74-75 (D.C. Cir. 1946).

[8] Application of Naquin, 398 F.2d 863, 866 (CCPA 1968); accord, Ex parte Zechnall, 194 U.S.P.Q. 461 (POBA 1973).

[9] Kawai v. Metlesics, 178 U.S.P.Q. 158 (CCPA 1973)(disclosure of utility).

§ 5.02 The Relation of Culture Deposits to the "Enablement" Requirement

[1] Generally

Most readers of this treatise will be aware that microorganisms are deposited in culture collections for patent purposes. In the United States, it is slightly misleading to speak of the existence of a "deposit requirement." While amendment of § 112 to expressly require the deposit of microorganisms has been proposed by members of Congress on several occasions,[10] these proposed amendments have not been enacted. The deposit of microorganisms with a culture collection is, however, a widely followed and PTO-sanctioned approach to satisfying the "description" and "enablement" requirements of § 112, and, specifically, the statutory mandate that the specification instruct persons skilled in the art in the manner and process of making the invention. This mandate may be more aptly thought of as a "reproducibility" or "availability" requirement than as, necessarily, a "deposit" requirement.

While 35 U.S.C. §112 requires a written description, a written description alone may not make it practicable for another to practice a microbiological invention. The opinion of the Patent Office Board of Appeals in *Ex parte Kropp*,[11] which dealt with such a situation, was a milestone in the application of the "how to make" requirement to "living" inventions.

[2] The *Kropp* Dichotomy

Kropp produced an antibiotic by the fermentation activity of a "hitherto unidentified species of microorganism," of the genus *Streptomyces*, "isolated from a soil sample obtained from a farm in Pennsylvania."

The Board held that the application description, as filed, was

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[10] S. 1246 (91st Cong., 1st Sess.)(McClellan, February 28, 1969); S. 643 (92nd Cong., 1st Sess.)(1971); S. 2504 (93rd Cong., 1st Sess.)(1973); S. 2255 (94th Cong., 1st Sess.)(1975).

[11] Ex parte Kropp, 143 U.S.P.Q. 148, 149 (POBA 1959).

inherently incapable of satisfying the "how-to-make" requirement:

> The organism used as the starting material obviously cannot be reproduced from the written description nor does the specification give any source where it can be found. . . . [R]eproduction of the invention from the specification alone would require the initiation of a screening program similar to the screening programs followed in discovering antibiotics in the first instance. Such a program would involve the collection of soil samples from different sources, making cultures from the samples, isolating organisms, reculturing the isolates, and testing the resultant cultures to determine if the particular antibiotic was produced. If the organism involved in the production of the antibiotic were of very common occurrence it might be found in a relatively short time, but if it were not of common occurrence it might not be found for a very long time if found at all, and if it were a chance variation, the time before it was rediscovered might be extraordinary, or it might even never be found.[12]

The Board indicates that it would have reached a different conclusion were the organism available without undue effort to the average "person skilled in the art":

> Is appellant were dealing with a known organism which had a well defined source and which had been obtained and used by others before, or even with an organism which was merely known and available to persons skilled in the art, the present question of the sufficiency of the disclosure would not arise.[13]

The application, as filed, being non-enabling, the Board concluded that the insufficiency could not be cured by belatedly depositing the organism in a "repository recognized by the American Society of Bacteriologists, for public distribution."[14]

The ramifications of the *Kropp* dichotomy are worth exploring.

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[12] Id., 152.
[13] Id., 153.
[14] Id., 149.

[3] Deposit of "Known" Organisms May Be Unnecessary

In *Mineral Separation Co., Ltd. v. Hyde* (1916), the Supreme Court ruled that a patent specification need not be an encyclopedic recipe book for the practice of all possible permutations of an invention, provided its teachings may be followed without undue experimentation. The claimed mineral separation process had to be varied depending on the ores treated. Preliminary tests had to be made to determine the amount of oil and the extent of agitation necessary to achieve the best results. A rule of reason was applied:

> The composition of ores varies infinitely. . . and it is obviously impossible to specify in a patent the precise treatment which would be most successful and economical in each. . . . [The patent,] while leaving something to the skill of persons applying the invention, is clearly sufficiently definite to guide those skilled in the art to its successful application. . . .[15]

If the patent specification teaches those skilled in the art how to select effective strains from those publicly available, deposit of the patentee's strain might not be necessary in order to comply with the "description" and "enablement" requirements. Three cases have developed this "safe haven" for non-depositors.

In *Funk*, the Supreme Court held claims to a bacterial mixture invalid for lack of invention, without deciding whether the Seventh Circuit had correctly held that the patent was not invalid for lack of sufficient disclosure.[16] Bond had discovered that mutually noninhibitive strains of nitrogen-fixing Rhizobia bacteria existed, and, once Bond had made this discovery, the means for determining whether particular strains were inhibited were evident to bacteriologists.[17] The Seventh Circuit held that the inventor need not disclose the specific strains which may be employed if a microbiologist could readily determine the appropriate strains by making conventional

[15] 242 U.S. 261 (1916).

[16] Funk Bros. Seed Co. v. Kalo Inoculant Co., 233 U.S. 127, 132 (1948).

[17] Kalo Inoculant Co. v. Funk Bros. Seed Co., 161 F.2d 981, 985-986 (7th Cir. 1947).

tests.[18] This is not, of course, a recommendation of Bond's approach, which ran afoul of other requirements of § 112. The *Funk* case may profitably be compared with *Tabuchi v. Nubel* [, 194 U.S.P.Q. 521, 522 (CCPA 1977)], discussed *infra,* which also required experimentation on the part of the users of the patent in order to make use of the invention in question. In *Kropp,* the Board was careful to point out that *Funk* involved a mixture of *known* strains of bacteria.[19]

In a patent infringement litigation, the District Court for New Jersey held that the "Vitamin B-12" patents were valid, rejecting the contention that "the patents lack a sufficient description of the strains of organisms used to produce vitamin B-12 or vitamin B-12 active materials in terms of an identifying number for a culture deposited in a culture collection.[20] There was uncontradicted testimony that when the application was filed

> There was available at Rutgers University, in stock culture collection, a grisein producing strain of Streptomyces griseus; that this organism was suitable for the production of vitamin B-12; that it could be obtained by anyone for experimental or commercial use; and that the identification of that particular strain had been made and published by Rutgers in January 1947. There was also undisputed testimony that the grisein producing strain of Streptomyces griseus was the only strain of the microorganism mentioned in the Rutgers publication; that it was this strain that Merck requested and got from Rutgers; that this same strain has been and still is available, and that anyone requesting it would get what Merck got, namely, a strain of Streptomyces griseus suitable for the production of vitamin B-12.[21]

Moreover, the court pointed out

> In the '302 specification, reference is made to a number of different organisms within the classes Schizomycetes, Torula

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[18] Id., 987.

[19] 143 U.S.P.Q. at 151-152.

[20] Merck & Co., Inc. v. Chase Chemical Co., 155 U.S.P.Q. 139, 145 (D.N.J. 1967).

[21] Id., 146.

and Eremothecium which are useful in the production of vitamin B-12 active compositions. The specifications gives thirteen examples of the use made of a number of these organisms to produce the claimed compositions, suitable nutrients, and different recovery techniques for obtaining vitamin B-12 active compositions. A number of tests are also set forth by means of which the proper strain of organism capable of producing vitamin B-12 active compositions may be selected. Here again, the testimony establishes that a trained microbiologist, by following the teachings of the '302 patent, would be able to produce vitamin B-12 active compositions.[22]

Distinguishing *Kropp,* wherein an "extensive screening" program, "tantamount to [re]discovery,"[23] would have been necessary, the court held that a known organism, which was readily available to microbiologists from a public source, need not be identified in the specification by its culture collection catalogue number.

Tabuchi v. Nubel was a patent interference proceeding involving the following claim:

> A method for producing at least one member of the group of citric acid and (+)-isocitric acid which comprises innoculating [sic] a citric acids-accumulating and hydrocarbon-assimilating strain of a yeast belonging to the genus Candida in an aqueous culture medium containing at least one normal paraffin containing 9 to 20 carbon atoms in the molecule as the main carbon source, incubating the culture until at least one of the citric acids is substantially accumulated in the culture broth and separating the so-accumulated citric acids therefrom.[24]

Tabuchi claimed the benefit of the filing date of his first Japanese application. Tabuchi's first Japanese application mentioned several usable species: Candida quilliermondi, Candida intermedia, Candida lipolytica, Candida melibiosi, Candida parasilosis, and Candida tropicalis.[25] It did not, how-

[22] Id.
[23] Id.
[24] 194 U.S.P.Q. 521, 522 (CCPA 1977).
[25] Id., 525 n. 5.

ever, refer to any specific *strain* of the genus Candida in any public depository.

The Board rejected his claim: "since this first . . . application does not disclose . . . a specific strain of the genus Candida, we fail to see how the disclosure [therein] meets the requirements of 35 U.S.C. §112.[26]

Tabuchi successfully argued before the CCPA that

> (1) Strains of the genus Candida were known and available prior to the day on which the Japanese patent application was filed, and
>
> (2) Undue experimentation would not have been required of one skilled in the art to determine which strains of the genus Candida will product citric acid in accordance with the process defined by the count.[27]

To support its argument, Tabuchi engaged an outside expert, Dr. Kelleher, to actually carry out the screening called for by the patent. Dr. Kelleher looked at the catalogues of several culture depositories, order a selection of the *Candida* species found in the catalogues, and tested the subcultures as suggested by the application. Six of the sixteen *Candida* strains he examined were "high producers.[28] Only fifteen calendar days were required for the actual screening, and eight were spent waiting while the Candida cultures were incubated.[29]

These cases suggest that the applicant's failure to deposit his own strain may not render his claims invalid for lack of enablement if the specification teaches a means by which suitable strains, previously known to those skilled in the art, may be readily identified. Note, however, that " best mode" problems may arise if applicant's "secret" strain was manifestly superior to the "public" strains.

Care must be taken, in specifying a deposited strain as a starting material, to ensure that the deposited strain is, in fact, publicly available. Cell lines in the ATCC's Tumor Immunology Bank, for example, are available only for research purposes.

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[26] Id., 523.
[27] Id., 523-524.
[28] Id., 524.
[29] Id.

According to *Hybritech, Inc. v. Abbott Laboratories,* "it is well settled . . . the [sic, that] biological materials need not be deposited when the invention can be practiced without undue experimentation from biological materials available in the prior art."[29.1] It followed the Federal Circuit's holding that monoclonal antibodies suitable for use in the claimed assay could be obtained and screened by known methods and therefore it was unnecessary to deposit any hybridomas. It is important to note, however, that the claim was a generic claim to an assay format and not a claim to an assay for a particular analyte.

An application relating to extraction of a useful pharmaceutical from a marine invertebrate (a tunicate) was considered "enabling" in *Ex parte Rinehart,*[29.2] since the organism was readily found in identified waters.

On the other hand, in *Ex parte Hata,*[29.3] relating to a method of using "unconventional" strains of *Lactobacilli* in treating infections, the Board did not accept the unsupported opinion of appellants that usable strains were not so rare that their isolation would amount to undue experimentation. Declarations were submitted, but conspicuously absent was "an indication as to how many sources of conventional Lactobacillus were investigated and not found to contain a microorganism encompassed by the appealed claims, i.e., failures."

[4] Public Deposits Held to Overcome the Enablement Problem Posed By Previously "Unavailable" Organisms

Not long after the *Kropp* decision, the Patent Office Board of Appeals and the Commissioner of Patents indicated that public access to a deposited culture could solve the "enablement" problem posed by *Kropp.* However, because of the multiple purposes served by the "disclosure" requirements, the early ("deposit" cases diverged sharply in their view of the

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29.1 4 U.S.P.Q.2d 1001, 1011 (C.D. Cal. 1987).

29.2 App. No. 564-47 (BPAI Jan. 10, 1985), now U.S. Patent No. 4,548,814.

29.3 6 U.S.P.Q.2d 1552, 1654 (BPAI 1988).

proper timetable for deposit and release of a culture by an applicant relying on the deposit for "disclosure" purposes.

In *Ex parte Schmidt-Kastner,* the Board held that a microbiological patent application was enabling when the strains utilized had been deposited with a culture collection even though the strains would not be publicly available until the patent issued.[30] In *In re Interference A v. B v. C,* on the other hand, the Commissioner held that the deposit was evidence of the adequacy of the description on the date of filing only if "the cultures in question were freely and continuously available to the public, beginning at a time prior to the filing date of the application.[31] The question was settled by the CCPA in *In re Argoudelis.*

[5] Deposit Need Not Be Released Until Patent Issues

In re Argoudelis (1970) involved a patent on a microbiological process for the manufacture of sparsogenin and sparsogenin A, utilizing the newly isolated *Streptomyces sparsogenes* var. sparsogenes.[32] Two agar slants of this organism were deposited in the U.S.D.A.'s permanent culture collection and assigned the designation NRRL 2940. Upjohn, in depositing this organism, requested that the U.S.D.A. "withhold distribution of this organism in accordance with the United States Patent Office Rules of Practice, Rule 14, until such time as a

(*Text continued on page 5-17*)

[30] 153 U.S.P.Q. 473, 474 (P.O.B.A. 1963).
[31] 159 U.S.P.Q. 538, 541 (Commr. Pats. 1967).
[32] 434 F.2d 1390 (CCPA 1970).

United States patent is issued to us which identifies this culture by the NRRL number assigned to it."[33] The Board took the position that § 111 established "a general requirement that the specification be enabling [*i.e.*, enable others to make and use the invention] as of the filing date.[34] The CCPA held that this reliance on Section 111 was not well founded.[35]

Like the Board in *Kropp*, the CCPA recognized that "a unique aspect of using microorganisms as starting materials is that a sufficient description of how to obtain the microorganism from nature cannot be given.[36] However, the CCPA held that the Upjohn-NRRL deposit practice met the requirements of 35 U.S.C. §§111-12.

> Any person skilled in the art *with access to the pending action under Rule 14 and 35 U.S.C. §112* can reproduce the invention from the written disclosure as it was originally filed. It is not necessary that the general public have access to the culture prior to the issuance of the patent. The procedure used by appellants is sufficient to constitute a constructive reduction to practice and to entitle the appellants to the benefits of a filing date since they clearly demonstrated that they had solved all technological problems involved in producing the invention. The disclosure is sufficient to permit a thorough examination by the Patent Office and to preclude the possibility that a patent could issue without any person skilled in the art being thenceforth enabled to make and use the invention.
>
> The fact that there can be no description in words alone of how to obtain the microorganism from nature does not mean that appellants must make the microorganism available to the general public at the time of filing the application. There is no good reason why an applicant who has invented a process and product involving the use of a new microorganism must surrender his starting materials to the general public before filing, whereas an applicant in the other arts need tell the public nothing until his patent issues. We do not believe that §112 was

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[33] Id., 1391.
[34] Id., 1392.
[35] Id.
[36] Id., curiously, *Kropp* was not cited.

designed to achieve such a result.[37]

In his concurring opinion, Judge Baldwin elaborated on how the conditional deposit satisfied the "dual purpose" of § 112 by (1) ensuring the examiner that *when the patent issued* other microbiologists would be able to make and use the invention claimed, and (2) indicating that the invention claimed was fully completed (reduced to practice) *at the time the application was filed.*[38] Judge Baldwin's analysis is not entirely sound, as the U.S.D.A. did not test the agar slants with which had been supplied to determine whether the organism thereon in fact met the morphological description given by the patent application and in fact was capable of producing sparsogenin and sparsogenin A. The mere deposit certainly cannot be said to provide the same "assurance that [the] invention has reached the necessary stage of completion"[39] that a lab report would. Accordingly, it would be prudent to place a morphological description of the organism, and a detailed analysis of its fermentation products, in the specification.

[6] Deposits in Private or Foreign Depositories Permissible

The most important question left open by *Argoudelis* was whether deposit in private or foreign culture collections would satisfy § 112.

On the one hand, the court had said that "(t)he only rational ground for concern on the part of the Patent Office appears to be for the permanent availability of the deposited organisms.[40] Presumably, a private or foreign collection *could* provide this assurance. On the other hand, the CCPA recited certain "considerations" which had prompted its holding for Upjohn, without indicating their relative importance:

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[37] Id., 1393.
[38] Id., 1394-1395.
[39] Id., 1395.
[40] 438 F.2d at 1393-94.

(1) A public depository was used;
(2) The depository is operated by a department of the United States government;
(3) The depository is under a contractual obligation to place the culture in the permanent collection, to supply samples to persons legally entitled under Rule 14 and 35 U.S.C. §122 to access to appellants' application, and to supply samples to anyone seeking them once the patent issues; and
(4) There is nothing in the record to suggest that the cultures will undergo any physical changes which will render them unusable.[41]

Among the major private or foreign culture collections affected by this question were the American Type Culture Collection, Rockville, Maryland; the Commonwealth Mycological Institute, England; the Collection of the Laboratiore de Cryptogamie, France; and the Centraalbureau von Schimmelculture, the Netherlands.[42] (The *Argoudelis* decision clearly approved deposits in the U.S. government-supported NRRL and Quartermaster (QM) collections.)

In the Commissioner's Notice of April 29, 1971, now a part of MPEP 608.01(p), the PTO set forth its view of the *Argoudelis* case:

> Deposit of Microorganisms
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> Some inventions which are the subject of patent applications depend on the use of microorganisms which must be described in the specification in accordance with 35 U.S.C. 112. No problem exists when the microorganisms used are known and readily available to the public. When the invention depends on the use of a microorganism which is not so known and readily available applicants must take additional steps to comply with the requirements of §112.
>
> In re Argoudelis, et al., 168 USPQ 99 (CCPA 1970), accepted a procedure for meeting the requirements of 35 U.S.C. 112. Ac-

[41] Id., 1394.

[42] D. G. Daus, Conditionally Available Cultures, 54 J.P.O.S. 187, 188-189 (March 1972)(Daus I).

cordingly, the Patent and Trademark Office will accept the following as complying with the requirements of §112 for an adequate disclosure of the microorganism required to carry out the invention:

(1) The applicant, no later than the effective U.S. filing date of the application, has made a deposit of a culture of the microorganism in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted, under conditions which assure (a) that access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. 122, and (b) that all restrictions on the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent;

(2) Such deposit is referred to in the body of the specification as filed and is identified by deposit number, name and address of the depository, and the taxonomic description to the extent available is included in the specification; and

(3) The applicant or his assigns has provided assurance of permanent availability of the culture to the public through a depository meeting the requirements of (1). Such assurance may be in the form of an averment under oath or by declaration by the applicant to this effect.

A copy of the applicant's contract with the depository may be required by the examiner to be made of record as evidence of making the culture available under the conditions stated above.

NOTE—For problems arising from the designation of materials by trademarks and trade names, see §6.08.01(v).

In *Feldman v. Aunstrup,* the CCPA held that the 1966 conditional deposit of a fungal culture with CBS (then a private Dutch collection) satisfied § 112. The CCPA said it would be erroneous to elevate the specific facts in *Argoudelis* to the status of a rule of law. . . . [The] four factors . . . were persuasive, [not] mandatory.[43] The court pointed out that the Patent Office could obtain access to the culture *via* 35 U.S.C. §114 and 37 C.F.R. §1.93, and that the public would have access to the

[43] 186 U.S.P.Q. at 112.

"essential starting material" on the issue date.[44] The court approved the deposit of microorganisms in any collection taking "painstaking measures . . . to ensure permanent viability.[45]

[7] Possible Adverse Effects of Depositing Cultures Abroad

First, suppose that *A* is an inventor in the U.S. and *B* is an inventor abroad. Before filing his foreign priority application, *B* made a deposit with a foreign culture collection, *e.g.*, CBS. In between the date of this deposit and *B*'s foreign priority date, *A* conceived and reduced to practice the invention in question. Does 35 U.S.C. §104 prevent *B* from relying on his date of deposit as his date of invention?

35 U.S.C. §104 provides

> In proceedings in the Patent Office and in the courts, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or other activity with respect thereto, in a foreign country, except as provided in §§ 119 and 365 of this title [35 USC §§119, 365]. Where an invention was made by a person, civil or military, while domiciled in the United States and serving in a foreign country in connection with operations by or on behalf of the United States, he shall be entitled to the same rights of priority with respect to such invention as if the same had been made in the United States.

This question was not raised in *Feldman v. Aunstrup* because Aunstrup's priority date preceded Feldman's U.S. filing date. The CCPA did, however, speak of the "application filing date" as the "prima facie date of invention," while referring to the deposit as showing that the invention was "capable of being reduced to practice.[46] This at least suggests that, at least prior to the Budapest Treaty (discussed *infra*), 35 U.S.C. §104 barred reliance on the deposit to show the date of the inven-

[44] Id., 112-113.
[45] Id., 113.
[46] 186 U.S.P.Q. at 113.

tion. The Treaty leaves the answer uncertain, as it is not clear what its Article 3 is meant to accomplish.

A second danger in making a deposit with a foreign depository is that the depository might not supply subcultures as required to enable the claims presented. This could raise questions as to the validity of the issued patent. According to an APLA subcommittee, in late 1982, the ATCC requested that CBS supply a sample of Rhizopus rhizopodiformus CBS 227.75, advising that the deposit was mentioned in U.S. 4,062,-732, issued December 13, 1977. CBS replied that the authorization of the depositor would be necessary to release the culture. Subcommittee chairman Timothy Kroboth concluded, "The refusal of CBS to release the culture except on the depositor's authorization makes the deposit not publicly available in this case in which the relevant patent had been issued. Accordingly, a CBS deposit may not meet Sec. 112."[46.1]

[8] PTO May Have Authority to Require Culture Deposits With the PTO or With Government Culture Depositories

Under 35 U.S.C. §114, the PTO has the authority, "when the invention relates to a composition of matter," to "require the applicant to furnish specimens or ingredients for the purpose of inspection or experiment." 37 C.F.R. §1.94 provides for the return of the specimens to applicant, "upon demand or at his expense, unless it be deemed necessary that they be preserved in the Office."

In 1880, the PTO abandoned the general requirement that all applicants supply models or specimens. While the ancient authority of the Commissioner is preserved by § 114, it "is almost never used."[47] The Commissioner retains, however, "wide discretion as to when it is proper to require that exhibits be submitted,"[48] and conceivably could require that a microbi-

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46.1 2 Biotechnology Law Report 3 (January 1983).

47 In re Breslow, 616 F.2d 516, 522 (CCPA 1980).

48 Upton v. Ladd, 227 F. Supp. 261 (D.D.C. 1964).

al culture be submitted to the PTO for testing and examination.

Given the limited facilities of the PTO, it is unlikely that 35 U.S.C. §114 could serve as the foundation of an independent deposit requirement unless the PTO received funds for the purpose, or unless it could delegate its authority to receive the specimens to a more appropriate agency, such as USDA. Clearly, deposit of *plant* specimens with USDA could be compelled by virtue of 35 U.S.C. §164, which permits the President to direct the Secretary of Agriculture to "conduct . . . research upon special problems" on behalf of the PTO in plant patent cases. There is no comparable provision for interagency assistance in the case of utility patents, other than for drugs. 21 U.S.C. §372(d) directs the Secretary of Agriculture to conduct such research as may be required with regard to patents for drugs, upon request from the Commissioner of Patents.

(Text continued on page 5-23)

Authority to require a USDA deposit might be derived from 35 U.S.C. §6, giving the Commissioner "charge of property belonging to the Patent and Trademark Office," and giving the Commissioner general authority to "establish regulations, not inconsistent with law, for the conduct of proceedings in the Patent and Trademark Office." On the other hand, 35 U.S.C. §1 could be viewed as prohibiting the deposit of specimens outside the PTO. According to § 1, the PTO is the Office "*where* records, books, drawings, specifications, and other papers *and things pertaining to patents . . . shall be kept and preserved, except as otherwise provided by law.*" (The term "things" was substituted by the 1952 Act for the word "models" in the prior law.)

It is interesting to note that in *Feldman v. Aunstrup,* the CCPA declared that the PTO could obtain access to Aunstrup's culture by exercising its specimen-gathering authority, § 114.[49] On the other hand, in *Ex parte Argoudelis,* there is a reference to a March 30, 1959 decision by the First Assistant Commissioner of Patents, denying an applicant's request that the Commissioner order "a depositor to grant access to a culture mentioned in a patent," for "lack of authority."[50] These two rulings are as close as we have come to a decision on the § 114 issue raised in this section.

[9] Restricted Deposits Not Complying With MPEP 608.01(P) May Yet Satisfy Statutory Requirements

It should be noted that MPEP 608.01(P) is *not* a statement of the *requirements* for satisfying § 112; it is a statement of the steps which, if taken by the applicant, *guarantee acceptance* by the PTO of a culture deposition as compliance with § 112's enablement requirement.

Thus, in *Feldman v. Aunstrup,* the CCPA sanctioned a deposit which did not fully comply with the MPEP guidelines. Aunstrup made a restricted deposit in the Centraalbureau voor Schimmelcultures (CBS) on November 18, 1965. He did

[49] 517 F.2d 1351, 1354 and ns. 4-5 (CCPA 1975).

[50] 157 U.S.P.Q. 437, 441 (POBA 1966) (on petition for reconsideration).

not lift the restriction on distribution until March 20, 1969, subsequent to Feldman's effective U.S. filing date.[51] Feldman argued that as of the "effective U.S. filing date," Aunstrup had neither assured "(a) that access to the culture will be available during pendency of the patent application to one determined by the Commissioner to be entitled thereto under [37 C.F.R. §1.14]" nor "(b) that all restrictions on availability of culture so deposited will be irrevocably removed upon the granting of the patent.[52]

With regard to point (a), the CCPA declared that, under its statutory authority (35 U.S.C. §114) to require the submission of specimens, "the PTO *could* obtain access to CBS 370.65 *through Aunstrup* at any time during pendency.[53] The CCPA's complacency regarding this answer was not entirely well-founded. Under Rule 14, all of the applicants, their assignees of record, and the attorneys of record, have "access" to original applications. Under Rule 226, parties to an interference have "access" to each other's applications. The CCPA did not consider whether 35 U.S.C. §114 can be wielded by the PTO to assure access to the culture to all those who have access to the application. This author believes that the specimens required by the PTO under 35 U.S.C. §114 are properly considered to be among the "papers" relating to an application which are accessible under Rule 114. Nonetheless, the CCPA's failure to consider this situation is mildly disturbing.

With regard to point (b), the CCPA held in *Feldman* that "what is required is assurance of access (to the microorganism culture by the public upon issuance of a patent on the application) prior to or during the pendency of the application. . . .[54] In reaching this conclusion, the CCPA properly stated that Feldman erred in elevating "the specific facts in *Argoudelis* to the status of a rule of law.[55] And it is also true that the four "persuasive" factors enunciated in *Argoudelis*[56] were not held

[51] 517 F.2d 1351, 1352 (CCPA 1975).
[52] MPEP 608.01(P).
[53] 517 F.2d at 1354.
[54] Id., 1355.
[55] Id.
[56] 434 F.2d at 1394.

therein to be "necessary" or "mandatory."[57] However, it would be wrong to draw the conclusion that examiners are forbidden to make § 112 rejections against applications supported by restricted deposits. In *Argoudelis*, Judge Baldwin, concurring, stated "[n]o rejection [for lack of enablement] should be made unless the examiner is not satisfied that, *at the time a patent would issue*, its specification disclosure would be [adequate]. . . ."[58] This necessarily implies that an examiner could reject an application's claims for lack of assurance that the organism would be available to the public when issued. What *Feldman* teaches is that this ground of rejection may be *cured* simply by lifting the restriction. *The benefit of the filing date is not lost.*

[10] Failing to Lift Restrictions on a Deposit After the Patent Issues Is Likely to Render the Patent Unenforceable and/or Invalid

The argument could be made that since it is not lawful to "make, use or sell" a patented invention without the consent of the patent owner,[59] the culture—the *sine qua non* of the patented fermentation process—need not be released until the patent expires. A form of this argument was considered and rejected by the CCPA in *Argoudelis*. Judge Baldwin, concurring wrote:

> I am aware of broad statements in opinions to the effect that the teaching of the patent must be such as to "add to the sum of public knowledge" at the time the patent expires. Insofar as they might be interpreted as suggesting that a patent disclosure need not be enabling until the patent expires, such statements are incorrect and inapplicable to the issues here.[60]

It is virtually certain that, in this regard, Judge Baldwin spoke for the Court. Judge Almond declared, "It is not neces-

[57] 517 F.2d at 1355.
[58] 434 F.2d at 1395.
[59] 35 U.S.C. §271.
[60] 434 F.2d 1390, 1395 n.1.

sary that the general public have access to the culture *prior* to the *issuance* of the patent." [61] The CCPA recognized here that the *quid pro quo* contemplated as the return to the public for its patents was not merely the right to *use* the invention after expiration, but also the right to *understand* the invention upon issuance.

A similar argument was rejected in Great Britain.[62]

A related, but more difficult question is the proper treatment of a patent owner who is lax when it comes to notifying the depository of the issuance of the patent. One approach might be to hold the patent invalid, since the patent owner could have alerted the depositor during the ample time interval between his receipt of the Notice of Allowance and the date of grant. A second approach would be to refuse to enforce the patent until the deposit is released. It is possible that the courts would allow the patent owner a grace period, perhaps one based on the grace period for the payment of the issue fee, but this is not a prospect to rely upon.

Clearly, a complete refusal to provide subcultures after issuance is fatal. Are there, nonetheless, any restrictions which are appropriate? Article 5 of the Budapest Treaty suggests that governmental restrictions on export and import are acceptable if "necessary in view of national security or the dangers for health or the environment."

This would not clearly justify a private party's refusal to provide a subculture of a dangerous organism absent a statutory duty to refuse.

On May 10, 1985, Group Director Van Horn gave an advisory opinion with respect to a release form. U.S. Patents 4,396,632; 4,318,929; and 4,318,930, all relating to novel strains of *Saccharomyces cerevisiae,* made reference to strains deposited with the National Collection of Yeast Cultures (NCYC). The patent files contained declarations stating that *all* restrictions on the availability to the public of the deposited strains would be irrevocably removed upon the granting of a patent. The release form required the requesting party to (1) identify the legal entity that is causing the request to be made and (2)

[61] Id., 1393 (emphasis added).

[62] In re Dann's Application, [1966] RPC 532.

undertake not to transmit the yeast strain thus obtained to a third party. Van Horn advised that the yeast cultures must be released without these or any other restrictions.

In the "NCYC" case, the organism was innocuous. What if it was a pathogen? Could a patentee argue that supplying a known pathogen without knowing the "real" recipient could subject him to product liability if the recipient mishandled it? (Cohen and Boyer tried to exercise some discretion over who received psc101 because of their fear of the possible consequences of certain conceivable cloning experiments.) Would the PTO accept a declaration from an applicant that undertook to lift all restrictions *except* those relating to the protection of human health or the environment?

Certainly, while the CCPA in *Argoudelis* referred to "all" restrictions, it did not consider whether any particular restriction might be reasonable—such as a refusal to send a subculture of a Class 5 etiologic agent to Libya. The inventor is certainly wiser to raise the issue of the reasonableness of a restriction at the application stage, when he can always agree to forego the restriction without penalty (other than the delayed issuance of the patent). Once the patent issues, there is an estoppel arising from the file wrapper commitment which may overshadow the "reasonableness" issue.

[11] A Belated Deposit Is Permissible Under U.S. Law, But Its Advisability Is Uncertain

Until recently, the PTO took the position that if no deposits were made before the application was filed, that the application was not entitled to the benefit of his filing date. In 1982, this author argued that deposit prior to filing was not the only way to support a filing date, merely the surest way.

The *Argoudelis* opinion [at 434 F.2d 1393] stated that "(t)he procedure used by appellants is sufficient to constitute a constructive reduction to practice and to entitle appellants to the benefit of a filing date since they clearly demonstrated that they had solved all technological problems involved in producing the invention. The disclosure is sufficient to permit a thorough examination by the Patent Office. . . ." Note that the

CCPA deems this procedure to be "sufficient." It did not deem it to be "necessary." This author suggested that other procedures might satisfy the twofold standard implicit in the quoted passage. First, proof of actual reduction to practice, adduced through lab notebooks, verified samples, and corroborated testimony, should be sufficient to entitle applicants to their filing date. Second, the detailed taxonomic description of the organism is all that is normally necessary to permit examination, since the PTO does not normally inspect specimen cultures. Thus, even the failure to deposit the organism is not necessarily fatal.

This author also urged that the subsequent deposit would not constitute "new matter" under 35 U.S.C. §132 since the deposit would merely clarify and complete the taxonomic description, and the description of where the organism was found and how it was isolated.

The effect of a failure to deposit on the applicant's filing date was considered in *Ex parte Lundak* (August 21, 1984) and *In re Lundak.*[62a]

Ex parte Lundak (August 21, 1984) was heard by an eighteen-member panel which split three ways, 12-2-4. The examiner had rejected the following claims under 35 U.S.C. §112, first paragraph:

1. An immortal B-cell line WI-L2-729HF^2.
2. A hybridoma resulting from the fusion of an immunized lymphocyte and a cell line according to Claim 1.

The subject cell line was maintained, as of March 26, 1981, the filing date of the application, "at three separate locations by members of the faculty of the University of California," Lundak's assignee, these faculty members being Dr. Robert Lundak, Dr. Bruce Devens, and Dr. Richard Lubin. It also appears that it was maintained by Dr. John Lewis at the Loma Linda University Medical Center. The cell line was deposited with the ATCC on April 2, 1981. The university assignee did not undertake any of the measures which I have suggested could validate an "internal" deposit: setting up a culture col-

[62a]In re Lundak, 773 F.2d 1216 (Fed. Cir. 1985), rev'g, Exparte Lundak.

lection as a formal legal entity, having it post bond that it will comply with the terms suggested by MPEP §608.01(p), etc.[62.1] Nor did it ask, so far as the record shows, the Loma Linda Center to contract to make the cell line available to the public after the issuance of the patent.

The basis for the rejection was that *Lundak* had failed to deposit his claimed cell line at an "independent depository on or before the . . . filing date of the application."

Ex parte Lundak was the first Board decision to address the question of the use of deposits in connection with the disclosure of lymphocyte and hybridoma cell lines, as opposed to microorganisms. Not surprisingly, it found no reason to treat a novel cell line differently than a novel microorganism.

The argument of the majority opinion, written by Examiner-in-Chief Pellman, boils down as follows:

(1) MPEP §608.01(p)[62.2] states that the deposit must be made by the effective U.S. filing date in a suitable depository;
(2) The informal academic group maintaining the cell line did not meet the minimum qualifications for a PTO-permitted depository set forth in Commissioner Diamond's Memorandum on "Requirements Which Have to Be Met by International Depositary Authorities"[62.3]; and
(3) As a matter of law, an invention must be completely disclosed in an application as filed, any subsequent addition of disclosure being "new matter" forbidden by 35 U.S.C. §132.

Thus, Pellman concludes, the cell line had to be deposited on or before the date of filing of the application in a depository satisfying the requirements of MPEP §608.01(p). The Board somewhat ingenuously states that "[s]ince the procedure long followed by the Patent and Trademark Office to fulfill the enablement provision of 112 [MPEP §608.01(p)] is not con-

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[62.1] See §5.02[12].
[62.2] Appendix 1.01[1].
[62.3] Appendix 1.03[2].

trary to any statute or court decision, and since it has not been shown to be unreasonable or unfair, compliance therewith is properly required." The Board's remark puts me in mind of a comment by the famous Rumpole of the Bailey, to the effect that "highly placed coppers" are always eager to substitute "a brief hearing before the sergeant in the local Station . . . for the antiquated and unsatisfactory system of trial by jury." The "procedure long followed by the Patent and Trademark Office" was not birthed through notice-and-comment rulemaking under the Administrative Procedure Act, it was merely sanctioned by the Manual of Patent Examining Procedure, a guide for examiners. It has been held that while applicants may rely on the Manual, they are not bound by it.[62.4]

Moreover, the MPEP, by its own terms, did not require compliance with the procedure set forth therein. MPEP §608.01(p) states that the Patent and Trademark Office will "accept" a deposit of a microorganism by the effective filing date in "a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted," *i.e.*, one assuring PTO access to the culture during pendency, and unrestricted public availability after issuance of the patent. The PTO did not state that a deposit in the prescribed form was required, only that such a deposit would be assured acceptance. This distinction was apparent to the CCPA in *Feldman v. Aunstrup:* "It does not say that the Patent Office will only accept the prescribed procedure. Thus, the Notice does not purport to set forth the minimum requirements, but only a procedure which will assuredly gain PTO acceptance."[62.5]

Next, Pellman contended that the cell line, as of the date of filing, was not maintained in a culture collection which, under the Commissioner's Memorandum, would be eligible for designation by the United States as an International Depository Authority. This is, quite simply, a *non sequitur.* Under the Treaty, an International Depository Authority must be ready to accept deposits from anyone, so long as the deposits are of the kind of organisms which the IDA has stated it can maintain

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62.4 *See* In re Kaghan, 387 F.2d 398, 401 (CCPA 1967).

62.5 517 F.2d 1351, 1355 (CCPA 1975).

and the treaty formalities are complied with by the depositor.[62.6] Because it must accept deposits from all, and because it must keep the deposits confidential,[62.7] it follows that it must be "impartial and objective."[62.8] However, it does not follow that an institution cannot provide adequate assurances to the PTO that it will, itself, make the organism publicly available after the issuance of the patent and maintain it for a reasonable time thereafter.

Reliance on the MPEP, and even more so on the IDA memo, was clearly ill-founded. Closer heed must be given to the majority's treatment of *In re Glass*[62.9] as controlling authority. They cite *Glass* for the proposition that the sufficiency of the disclosure of a patent application must be judged as of the filing date of the application. With this as its major premise, and the inability of a member of the public to practice the invention as its minor premise, the Board concluded that the deposit must be made on or before the filing date of the application.

It is hard for this author to perceive *In re Glass* as "controlling authority" when the CCPA, in a later decision, *Feldman v. Aunstrup,* held that "the enablement requirement of section 112, first paragraph, does not require such assured [public] access to a microorganism as of the filing date; what is required is assurance of access . . . prior to or during the pendency of the application. . . ."[62.10] This criticism of the Board's analysis of precedent is buttressed by the fact that the CCPA in *Feldman* expressly considered *In re Glass:* "the [public disclosure] function [of 112] is only violated if the disclosure is not complete at the time it is made public, i.e., at the issue date.

62.6 Budapest Treaty, Article 6(2)(iv).

62.7 Id., subparagraph (vii) and Rule 9.2.

62.8 Id., subparagraph (iii). It is interesting to note that the latest IDA designated by the PTO, In Vitro International, Inc., is a joint venture of Intra Gene International, Inc. and the University of Michigan Micro Reference Laboratories, since the first six deposits with IVI were from the University of Michigan. 3 Biotechnology Law Report 11-12 (January-February 1984).

62.9 492 F.2d 1228 (CCPA 1974).

62.10 517 F.2d at 1355.

In re Hawkins, supra; see In re Glass. . . ."[62.11]

In the *Glass* case, the applicant attempted to rely on four patents which issued after his filing date and taught the physical conditions necessary to facilitate the growth of an artificial crystal, after the examiner rejected his claims under 112 because this teaching was not provided in the specification. The court held that these later patents could not be relied on to judge whether the persons skilled in the art were capable of practising the invention based on the applicant's teachings.

Chisum states that "[t]he Glass rule is not applied where it is clear from a nonenabling specification that the applicant is fully in possession of everything necessary to make the specification enabling prior to the date of issue."[62.12] As the CCPA in *Feldman* pointed out, *Aunstrup's* detailed taxonomic description of his Mucor miehei made it clear that that his invention was "fully capable of being reduced to practice" and therefore satisfied the so-called "second function" of Section 112, first paragraph—the one which entitles the applicant, under *In re Hawkins*,[62.13] to the benefit of his filing date.

The original *Hawkins* application incorporated by reference certain descriptive information in Hawkins pending British applications. After a 112 rejection, Hawkins bodily incorporated the British material. The CCPA held that the amendment assured that the disclosure would be complete when made public (*i.e.*, when the patent issued) and that the original reference to the methods of use disclosed in the British application assured that the invention was fully capable of being reduced to practice as of the filing date.

Distinguishing *Feldman*, the majority opinion in *Ex parte Lundak* declares,

> [a] clear distinction exists between making the deposit of a microorganism in order to comply with 35 U.S.C. 112 and assuring unrestricted public access to the culture. . . . Thus, we do not consider that the court was offering any alternative to the deposit procedure that had been found acceptable by the Patent Office. The court was merely dealing with the question

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[62.11] Id.

[62.12] Chisum, 4 Patents, sec. 7.03 [3] at 7-27 (Rel. 11-3/84).

[62.13] 486 F.2d 569 (CCPA 1973).

previously decided in the Argoudelis case [whether the deposited strain had to be publicly available prior to issuance].

It is true that *Aunstrup* had indeed deposited his strain in the CBS collection on November 18, 1965, prior to his December 2, 1965 effective filing date. As the *Lundak* Board somewhat murkily points out, the furor was over the fact that the original contract of deposit did not provide for the removal of restrictions on access upon issuance of the patent. In that sense, the *Aunstrup* holding is not controlling.

On the other hand, the Board has ignored the policy considerations addressed by *Feldman* and *Hawkins*. Both the "assurance of public disclosure by issuance" function and the "assurance of reducibility to practice by filing date" functions of 35 U.S.C. §112 were satisfied by *Lundak*.

The concurring opinion written by Examiner-in-Chief McKelvey took a different view of *Feldman*. McKelvey argued that the PTO must be assured of access to the organism during the pendency of the application because 35 U.S.C. §114 authorizes the PTO to require samples. He conveniently forgets that 35 U.S.C. §114 says that the Commissioner "may require the applicant to furnish specimens. . . ." It does not state that the applicant must enter into a contractual agreement requiring a third party to provide specimens to the examiner upon request. If an examiner made a request for a specimen, and the request was refused, the examiner could, quite properly, reject the application at that time. But I see nothing in 35 U.S.C. §114 requiring an applicant to be "on red alert" waiting for such a request to be made. The concurring opinion written by Examiner-in-Chief Rzucidlo properly states that "access to the cell line by the PTO is assured by 35 U.S.C. 114 during the pendency of the application before the Office."

In any event, McKelvey would have found that *Lundak* had failed to prove that the PTO would have access to the cell line throughout the examination. Since *Lundak* had not assumed a contractual obligation to maintain the cell line, McKelvey was unwilling to assume that it was maintained by *Lundak* personally beyond the date of his last declaration. McKelvey was unwilling to assume that the cell line would be maintained in the future by ATCC since, according to McKelvey, *Lundak*

had failed to prove that the cell line deposited with the ATCC was the same as the cell line maintained originally by him.

McKelvey also would have found that *Lundak* had not yet provided assurance of the availability after issuance of the claimed cell line from ATCC because of this "chain-of-custody" problem.

Only the concurring opinion of Rzucidlo gave full consideration to the policy arguments in *Feldman*. It quickly, of course, found that the belated ATCC deposit was timely compliance with the "public disclosure" function of Section 112. Moving to the second function, Rzucidlo noted that there had not been any criticism by the examiner of the adequacy of the taxomomic description of the cell line or of the culture conditions under which it could be maintained. He also noted that "the majority does not say that the cell line was not in existence or that the cell line was not available, through applicant, to the examiner. Rather the majority focuses on deposition in an independent depository prior to filing." According to Rzucidlo, "there does not appear to be any statutory or case law basis for this supposition on the part of the majority."

An important insight is offered by Examiner-in-Chief Rzucidlo's opinion: it is important to distinguish between enablement per se and proof of enablement. In questioning the enablement of the application, says Rzucidlo, the examiner is questioning "the existence of a pure cell culture as of the filing date of the application." In requiring deposit in an independent depository, the examiner is insisting that such a deposit "is the sole means by which evidence of enablement can be presented by an applicant." Rzucidlo and his colleagues concluded that while a deposit may be "the most desirable form in which such evidence can be presented, it is not the exclusive way. . . ."

Why, then, was this a concurring rather than a dissenting opinion? Like the McKelvey coterie, Rzucidlo's group thought that the submitted declarations were inadequate. They would not accept *Lundak's* declaration alone; they expected corroboratory applications from the other laboratories and from ATCC regarding the receipt of the specimen culture and its maintenance conditions.

How would this author have ruled? The key issue was

whether the applicant was entitled to the benefit of his filing date. Under *Hawkins*, this boils down to whether it was evident from the specification that the invention was fully capable of being reduced to practice by the applicant—not to whether the specification enabled others to practice the invention. The claim in *Lundak* was to a cell line, per se. To reduce such a claim to practice, *Lundak* had to actually isolate the cell line. There was no reason to doubt, based on what was presumably a detailed description of the isolation procedure and a detailed taxonomic study of the isolated myeloma, that he had in fact actually reduced the claimed cell line to practice. The supply of samples to the other professors acted to corroborate this reduction to practice. (And in interference practice, there is no requirement that the corroborator be "impartial and objective," since fellow employees of the same assignee may corroborate.) A deposit with the ATCC might have been a weightier corroboration because of the ATCC's disinterested relationship to the invention, but that is all.

The CAFC, on appeal,[62.14] reiterated the "three-function" analysis of 35 U.S.C. §112 first aired by its predecessor court. To comply with 35 U.S.C. §112, there must be assurance that:

(a) At the time the application for patent is *filed*, it is fully capable of being reduced to practice;
(b) During the *pendency* of the application, the Examiner will be able to evaluate whether the claimed invention is new, useful and nonobvious, and whether, at the time of issuance, its specification would be enabling; and
(c) At *issuance*, one of ordinary skill will be able to make and use the claimed invention.

This analysis first surfaced in Judge Baldwin's concurring opinion in *Argoudelis*,[62.15] but was tacitly adopted in Judge Lane's majority opinion in *Feldman v. Aunstrup*.

Point (c) was moot in *Lundak* since a deposit satisfactory to the PTO was made during the pendency of the application. With respect to point (b), the CAFC saw no "controlling dis-

[62.14] In re Lundak, 773 F.2d 1216 (Fed. Cir 1985).
[62.15] 434 F.2d 1390, 1394 (CCPA 1970).

tinction" between the PTO's access to Aunstrep's deposit in the Netherlands and to Lundak's cell line at the University of California. The request would be made to the inventor under 35 U.S.C. §114, and it was immaterial whether it was filed directly by the applicant or indirectly by his agent, the depository.

Point (a) was the stickler. Here, unfortunately, the CAFC did not squarely address the issue of whether Lundak's cell line was "fully capable of being reduced to practice." Possibly, the CAFC felt that the PTO had tacitly admitted that the cell line was actually reduced to practice prior to filing. Certainly, there was evidence that the cell culture *existed* on the filing date, even though it was not generally *available.*

Specifically, Lundak had petitioned the Commissioner to change his filing date from March 26, 1981 to April 2, 1981. The petition was denied since the application appeared to be complete "for the purpose of having a filing date accorded thereto."

The discussion therefore shifted to whether either (1) the subsequent deposit per se or (2) the subsequent reference to the deposit was "new matter" under *In re Glass.*

Rather than distinguishing *In re Glass,* the CAFC proceeded to hold that the filing was a constructive reduction to practice, and that the insertion of the deposit number was not new matter, by what must unfortunately be viewed as *non sequiturs.*

In discussing *Hawkins,* the CAFC observes that the applicant had made an "attempt to add the information" required. This, however, would seem relevant to point (c), not to point (a). But it is clear that the CAFC did not intend to drop test (a) from its §112 analysis, since in a prior sentence Judge Newman identifies "not enabling *as filed"* with "not fully capable of being reduced to practice."

In discussing *Argoudelis* and *Feldman,* the CAFC said that in those cases the requirements for "constructive reduction to practice" were met. However, in those cases, the strains were in the hands of independent instructions at the time of filing.

More logically, the CAFC could have said that proof that the organism was in existence at the time of filing is proof of actual reduction to practice (not merely "capability") and justifies

according a filing date to an application describing the organism and its orgin.

In any event, the CAFC held that "it is not material whether a sample of Lundak's cell line resided in his hands or in the hands of an independent depository as of his filing date." Not surprisingly, it further concluded that the depository data was not "new matter."

This author feels vindicated by the *In re Lundak* decision, since in 1982 he urged (in this book) that one should not abandon hope if a deposit plan went astray. Now, however, there is a need to point out some of the dangers of deliberately deferring deposit. One is that it may be necessary to prove that the organism eventually deposited is of the same strain or cell line as that in the applicant's possession on filing.

This problem was pointed out by the two concurring opinions in *Ex parte Lundak*. Thus, McKelvey said that "appellant's evidence is not sufficient to prove that the cell line in his possession on March 26, 1981 is the cell line which was deposited in the ATCC." Rzucidlo was more specific:

> No chain of possession of the instant cell line between the filing date of this application and the receipt of the cell line at ATCC has been established. No declaration evidence has been submitted from someone at ATCC attesting to the maintenance of the instant cell line at locations other than appellant's laboratory, the instant record contains only the assertions of Dr. Lundak's corroboratory declarations . . . [and] should be presented.

The PTO is likely to seek answers to the following questions:

(a) Did the applicant possess the claimed strain at the time of filing?
(b) Did the applicant maintain the claimed strain until the time of deposit?
(c) Did the applicant deposit the very strain which was in his possession at filing?

First, however, we must ask whether the mere failure to make a deposit puts the onus on the applicant to submit proof of the facts above. It is up to the Examiner, for example, to

make out a *prima facie* case of inoperativeness before the applicant need prove that his claimed invention will work. It could be argued that if the specification contained a description, in the past tense, of the isolation and cultivation of the new organism, that no *prima facie* case of nonenablement would exist. Here, I would bear in mind the CAFC's impatience with the PTO's fear of "sham" applications.

Second, we must determine whether the proof on these points must satisfy the stringent requirements of interference proceedings (particularly the corroboration requirement) or the lesser standard applicable to Rule 131 affidavits. My view is that corroboration is uncalled for unless an interference is declared. However, Examiner-In-Chief Rzucidlo is clearly of a different mind, given his call for obtaining corroborating declarations from the other laboratories.

It is clearly dangerous for an applicant to rely solely on a single culture in a single facility. If that culture were contaminated or killed the chain of custody would be broken. The moral is, "buy another refrigerator." Moreover, it is desirable that the culture be in the custody of a non-inventor, who may then act as a corroborating witness.

In a related vein, it is essential that identifying characteristics of the novel organism be ascertained. Otherwise, it will be impossible to ascertain the common identity of the organism deposited. Because of contamination and mutation, proof of continued custody is not ironclad evidence of common identity.

Another problem is that some foreign patent offices might refuse to accord priority to a U.S. application relating to a novel organism if the organism had not been deposited before the filing date. See §5.02[18].

Given these difficulties, are there any reasons for deliberately delaying deposit? One is cost. A deposit with ATCC would run about $1,000. This is substantial relative to the usual costs of preparing and filing a U.S. application. It would be very helpful to be able to defer deposit until allowable subject matter is indicated.

A second reason is control. The applicant will want to police

the use of his novel organism. Under *Roche v. Bolar*,[62.16] experimental use of an organism, if directed toward commercialization, is an act of infringement, unless it comes within the special "FDA" dispensation of 35 U.S.C. §271 (e) (1). While the Budapest Treaty provides for giving the patentee notice of each request for subcultures, a competitor might request a subculture through a "tame" professor, making the request appear innocuous.

Imagine what an uproar would occur if Congress were to enact an amendment to the patent law which required that the owner of a patent on a cyclotron not merely disclose the design drawings and operational data for his apparatus, but also give the apparatus itself to anyone that wanted it. But that is the practical effect of the deposit "requirement," since the public may receive the organism itself, not merely the written description of the organism. Indeed, the true analogy would be to require the cyclotron patentee to provide a "turnkey" plant for *manufacturing* cyclotrons to each requester, since each subculture may be cultivated and grown indefinitely.

The ramifications of *Lundak* were probed in *Ex parte Old*,[62.17] decided December 12, 1985. The assignee Sloan-Kettering, had filed a Declaration asserting (1) that the assignee had maintained certain hybridoma cell lines from before the date of filing; (2) that access would be provided during pendency to anyone deserving access to the application; (3) that upon grant the cell lines would be transferred to ATCC and made irrevocably available to the public, without restriction, for the life of the U.S. patent; and (4) that prior to transfer to the ATCC, Sloan-Kettering would replace any non-viable deposit with the same line from its second bank (Sloan-Kettering preserved its hybridoma cell lines in 10-20 ampules frozen in two independent liquid nitrogen banks).

It is not surprising that Sloan-Kettering sought to avoid immediate deposit of all of the recited cell lines with the ATCC, since *seventeen* cell lines were involved. The Board held that "no more can be asked for applicants," commenting that

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62.16 Roche Products Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir. 1984).

62.17 Ex Parte Old, 229 USPQ 197 (BPAI 1986).

Sloan-Kettering was "an institution of renown and integrity" and that the ATCC was a "recognized depository."

[12] A Deposit in Any Corporate or Academic Collection, With Appropriate Guarantees, Might Be Effective

On March 15, 1983, in his capacity as Chairman of the APLA Chemical Practice Committee, Albert Halluin wrote Rene Tegtmeyer, then Assistant Commissioner for Patents, expressing:

> . . . concern that some patent examiners are permitting applicants to use their own depository for cultures or plasmids referenced in a U.S. patent application. The problems with such a practice are obvious in the case of foreign patentees, deceased patentees or where the patent owner has gone out of business. Such a practice does not give the public assurance about continued public availability and permanency of cultures or plasmids during the life of a U.S. patent.

The test under *Metcalfe*, of course, is one of "reasonable" availability, and the quoted passage begs the question of what assurances are reasonable. Presumably, the manufacturers of proprietary trademarked materials may be foreign, may die, or may go out of business, so all of these problems are familiar ones that we live with in the case of trademarked products.

With trademarked products, however, the patent applicant has no way of controlling or assuring the continued availability of the material. If he knew how to make it, he would not need to refer to it by its trademark at all, but would simply describe the manufacturing process. With organisms, the patent applicant has greater control. He can reproduce the organism so as to provide an indefinite number of subcultures. Thus, requirements which are unreasonable in terms of assuring the continued availability of nonliving materials obtainable only from others may be reasonable in the case of living materials actually in the hands of the patentee.

Still, it is appropriate to ask whether patent applicants need

insulate the public from the applicants' business risks. The only reason for requiring a public deposit and ignoring a private deposit is that a private depositary institution is likelier to go out of business.

Ex parte Lundak hinted at a second reason: that when the applicant is his own depository, being unbound by contract to maintain the culture or supply it to others, he could refuse to supply the culture after the patent issued. I am not impressed with this reasoning. An applicant who behaved in that manner would be begging for a judicial declaration of the unenforceability of his patent.

Deposit in a company collection, if effective, could well be preferable to deposit with ARS, ATCC *et al.* The cost of complying with the deposit requirement would be low, since companies engaged in fermentation research maintain collections of their own. Requests for subcultures would be immediately known to the depositor, without the payment of a special notification fee. Organisms with peculiar maintenance requirements could be maintained under the watchful scrutiny of the researchers most familiar with their needs. Special precautions could be taken for organisms of great commercial value.

The CAFC, in reversing the Board, pointed out that the deposit was no real safeguard against sham applications. It pointed out how it would be "subverted by the dishonest, while being unnecessary to the honest."

At a bare minimum, to satisfy 35 U.S.C. §112, the applicant must state that: (1) a culture of the organism will be maintained during the pendency of the application and, should a patent issue, for the life of the patent; (2) during pendency, subcultures must be made available to persons having "access" under Rule 12; and (3) after issuance, they will be available to all properly identified requesters.

It may be to the advantage of the company to organize its culture collection as a separate not-for-profit corporation and sign a contract with the collection, to set up a trust to manage and finance the collection, to post bond that it will comply with the terms set forth above, or at least to submit to the PTO affidavits from the inventor and the curator of its culture collection which state that those terms can and will be met. The

curator's affidavit might also indicate how long the culture collection has been maintained, the size of the collection, the number of requests for subcultures received and complied with, and whether any patent cultures have been lost. Other information might also be recited to convince the PTO that the culture collection is a responsible business entity providing reasonable assurance that after the patent issues, any person skilled in the art will be enabled to make and use the invention.

The company collection should cross-reference its strains by deposit number, scientific name, patent number, patent application number, and inventor's name, to ensure that the strain remains "available."

Testimonial evidence is likely to play an important role in winning acceptance of a private depository by the PTO or the courts. Thus, in *Feldman v. Aunstrup*, Dr. de Vries, an official of CBS, "testified in detail on the high standards and careful means of preservation employed at CBS to assure permanent viability of cultures. Dr. Clifford W. Jesseltine [of NRRL] testified . . . 'We've had exchanges with CBS, and we believe it to be a very reliable culture collection.' "[63] This testimonial evidence can be presented in the form of affidavits attached to the applicant's response to a § 112 rejection.

The applicant should also collect and submit literature articles which note that the researcher obtained his test culture from the private depository. Thus, Kaken Chemical Co. might point out that a recent IJSB article reported a study of an *Actinoplanes armeniacus* strain obtained from Kaken, KCC

(*Text continued on page 5-29*)

[63] 517 F.2d 1351, 1353 (CCPA 1975).

A-0070.[64] This evidence, which shows that persons skilled in the art regarded the cultures in the collection as available and reliable, might be supplemented by the collection's records of requests for samples, and the filing of these requests. It would also be of interest to show that "outsiders" actually placed deposits with the collection. (These various users of the collection could, of course, provide testimonials.)

If the applicant has published any articles about his new strain, the articles should give the name and address of the culture collection and the accession number of the strain, and specifically state that subcultures are available upon request.

As a final precaution, the legal instrument formalizing the collection might state that, in the event of dissolution of the collection, the cultures therein will be donated to (1) ARS, (2) ATCC, or (3) any other collection requesting them, with notice given in publications like ASM News.

In *Ex parte Argoudelis,* the Board remarked, in dictum, "If an applicant urged that he or she or his assignee had specimens of necessary starting materials in their safe (or refrigerator) at their deposition, this would hardly be considered to meet the statutory requirement for an enabling written disclosure. We do not see any difference in the case of an agent holding something at the order of his principal.[65] The Board's decision that Argoudelis' conditionally available deposit with NRRL did not satisfy the "enablement" requirement was overruled by the CCPA (*In re Argoudelis*).[66] By the Board's own logic, if the applicant notified the public that subcultures of a deposit in his own "safe" or "refrigerator" were to be freely available once the patent issued, and if the applicant took reasonable measures to assure the "permanency" of the deposit, the enablement requirement is satisfied.

In *Merck and Co., Inc. v. Chase Chemical Co.*[67] discussed in § 5.02[3], *supra,* an unrestricted deposit with the stock culture collection of Rutgers University, made prior to the filing date,

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[64] Wellington and Williams, Transfer of *Actinoplanes armeniacus* Kalakoutskii and Kusnetsov to *Streptomyces,* 31(1) Int'l J. Systematic Bacteriol. 77 (1981).

[65] 157 U.S.P.Q. 437, 441 (POBA 1966) (on petition for reconsideration).

[66] 434 F.2d 1390, 1392-93 (CCPA 1970).

[67] 155 U.S.P.Q. 159 (D.N.J. 1967).

was deemed to make the organism available to the public, and to "enable" the practice of the invention described in the application. Coupled with the holding of *In re Argoudelis* that general availability is required only on the date of issuance; *Merck* stands for the proposition that a deposit in a university culture collection may be enabling. The possibility of extending this proposition to cover a corporate culture collection is suggested, however, obliquely, in *Ex parte Argoudelis*, just prior to its citation of the *Merck* decision:

> If the applicant can show that . . . the organisms involved were known and available to persons skilled in the art then the question of sufficiency of disclosure of the type here involved would not arise. This is a question of fact, subject to proof by evidence. Applicants may have recourse to any competent evidence to show this fact with or without having made any deposit. Of course making a certain character of deposit in a stock culture collection prior to filing the application would greatly simplify the burden of proof.[68]

The Board made it clear that it was indifferent as to whether deposits were made in U.S., foreign, governmental or academic collections.

> [T]he particular stock culture collection utilized by appellants is an agency in the Department of Agriculture. . . .[A]ppellants do not take the position that being a government agency is per se material, but that . . . making deposits in any suitable depository would be sufficient. To contend otherwise would involve considerable anomalies, since such collections are maintained by various universities here and abroad and also by agencies of various foreign governments, and no distinction could be made.[69]

Even if a company does not choose to rely on its own collection, there seems to be no insurmountable legal obstacle preventing it from negotiating a "tailor-made" deposit agreement, with desirable provisions regarding ownership,

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[68] 157 U.S.P.Q. at 442 (1967).
[69] Id., 443.

care, viability testing, fees, notification, with a university. This prospect will undoubtedly lead to a more competitive atmosphere among the many culture collections.

One caveat must be made: these comments regarding corporate and academic collections apply only to U.S. patent applications which do not ask for Budapest Treaty treatment.

[13] The "Permanent Availability" Test Is Moderated By a "Rule of Reason"

The argument could be made that the applicant for patent must assure the availability of his culture even after the patent expires, as the patent laws contemplate that the invention will then fall fully into the public domain. This argument, taken to absurd extremes, could bring down any patent, as was pointed in a case involving a starting material identified by a trademark:

> [I]t is always possible that the practice of a given patented invention may become impossible because an essential material (or even apparatus) becomes unavailable due to a lack of raw materials, public disaster, or other occurrence not within the control of the patentee, and this possibility exists whether or not the "essential material" was identified in the patent only by trademark.[70]

In *In re Metcalfe* (1969), the resins utilized as starting materials in the various examples were identified by trademark and manufacturer in the application, and a pamphlet was available at the time the application was filed which set forth the physical properties of at least one of these resins.[71] The solicitor argued that the manufacturer might change the ingredients of the product sold under the referenced trademark, or even discontinue the product entirely, and that the worker

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[70] In re Metcalfe, 410 F.2d 1378 1382 (CCPA 1969).
[71] Id., 1380.

in the art might not be able to duplicate the former product.[72] The CCPA pointed out

> (1) There is always the possibility that sometime after the issuance of a patent, the disclosure which was initially enabling may become "unenabling" and (2) whether a given disclosure which identifies a material to be employed in the practice of the claimed invention is "enabling" within the meaning of 35 U.S.C. §112, must be decided by a rule of reason applied to the facts of the case.[73]

The analogy between trademarked products and culture deposits was recognized by the CCPA in *In re Argoudelis* (1970).

> The only rational ground for concern on the part of the Patent Office appears to be for the permanent availability of the deposited microorganism. The deposits are not a part of the patent application, and the Patent Office exercises no control over them. This concern may be jusitifed in some situations. A similar problem was involved in In re Metcalfe. . . . We conclude that the possibility that the disclosure may someday become enabling is even more speculative than in *Metcalfe*, and hence does not render the disclosure insufficient under §112.[74]

The analogy with *Metcalfe* is not complete, as a depositor of microorganisms is normally able to replace a culture lost by a culture collection, while the applicant normally cannot replace a trademarked product discontinued by its manufacturer. Nonetheless, the CCPA has clearly indicated that it is unlikely to sustain a § 112 rejection on the basis of the speculative unavailability of a required organism.

Since the CCPA still allowed that the PTO's concern might be justified in some situations, it is desirable that the applicant structure his case to parallel the facts of *Argoudelis* and *Metcalfe*. *Argoudelis* suggests that the applicant should have a

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[72] Id., 1381-82.
[73] Id., 1382.
[74] 434 F.2d at 1393-94.

contractual agreement, with a technically reliable depository, providing for public access after issuance. The applicant should also be prepared to rebut any suggestion that the cultures will undergo physical changes which will render them unusable. *Metcalfe* suggests that the applicant should provide taxonomic information on the organism, just as Metcalfe's Example 1 identified the resin as a "long oil linseed oil modified alkyd resin," and implicitly relied on the pamphlet description of its viscosity, color, acid number, specific gravity, etc.[75] *Metcalfe* also suggests that the applicant may utilize several different depositories, just as Metcalfe identified "three different materials from three different manufacturers.[76]

Metcalfe was followed by the CCPA in *In re Coleman* (1973), involving a §112 rejection of a claim supported by a list of several adhesives identified "solely by trademark or tradename and manufacturer."

> [T]here have been no challenges to the asserted usefulness of adhesives which possess the characteristics described in appellant's specification or the materials identified by trademark or trade name to channel the inquiry. The implicit allegation that those skilled in the art could not ascertain suitable adhesives without exhaustive investigation is, to us, unreasonable and unrealistic in this case. In short, we find ourselves confronted with no adequate justification for denying appellant patent protection of the scope sought. . . .
>
> We find no real likelihood at all, or even most, of either the specific materials disclosed being removed from the market or the trademarks or trade names being applied to significantly different products such as to render the present disclosure nonenabling. The risk may be present, but it is small, and occurrence of the event of nonenablement is too remote and speculative to support a rejection under the first paragraph of §112.[77]

Just as *Coleman* indicated that *Metcalfe* "should not be regarded as setting inviolate bounds for permissible and imper-

[75] 410 F.2d at 1380.
[76] Id., 1382.
[77] 176 U.S.P.Q. 522, 524 (CCPA 1973).

missible use of trademark or tradename designations,"[78] *Feldman* warned against "elevation of the specific facts presented in *Argoudelis* to the status of a rule of law.[79]

[14] Depositor Should Assure the Viability and Availability of the Culture at Least Until the Patent Expires

Two questions were left unanswered by *Argoudelis:* (1) must the depositor contract for the maintenance of the deposit beyond the date of expiration of the patent; and (2) what happens if the strain, against all odds, *in fact* becomes unavailable.

If the depositor is proceeding under the Budapest Treaty, the deposit must be maintained for thirty years from the date of deposition. If the depositor is proceeding under domestic law only, it is probably a reasonable compromise between safety and expense to contract for maintenance at least until the patent expiration date, and possibly for an additional six years (the statute of limitations period).

While *Metcalfe* nominally suggests that there is no obligation to assure availability beyond stating a *present source* for the starting material, it did not squarely consider whether a greater burden should be imposed on a patent applicant who is himself a source of the starting material. Moreover, should patent infringement litigation occur, the accused might raise the defense that he could not ascertain whether he was infringing if the strain were unavailable. The patentee would doubtless wish to avoid laying a foundation for this defense.

On the other hand, the patent disclosure, like the works of "Ozymandas, King of Kings," will one day crumble into dust. The patent life provides ample time for interested parties to request subcultures. The patentee need not set up a trust to ensure the availability of the culture even after his business expires! However, one might reasonably suggest that the patentee should—if he still has the culture—provide subcultures to requestors even after expiration.

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[78] Id.

[79] 517 F.2d at 1355.

A similar answer might be given to the second question. The Budapest Treaty—and a number of depository agreements—specifically obligate the depositor to replace nonviable deposits during the specified deposit period. Under domestic law, replacement would avoid possible defenses to an infringement action. It may be that the effect of a failure to replace will be measured by a "rule of reason," considering the number of requests received, the time the deposit was viable, the reason the patentee failed to replace the culture, etc., but it would be foolish to risk the validity or enforceability of a patent by voluntarily refusing to replace a nonviable deposit during the term of the patent.

The MPEP §608.01(p) language regarding "permanent availability" did create some problems for the legal and scientific community; some examiners insisted that depositories be asked by contract to maintain deposits in perpetuity.[79.1] Mrs. Bobbie Brandon of the ATCC has noted that the ATCC would not sign such a contract, and advised patent applicants to make their deposits under the more definite and more reasonable storage duration requirements of the Budapest Treaty.

In *Ex parte Lundak*, an eighteen-member panel of the PTO Board of Appeals affirmed a 112 rejection of an application involving a deposited cell line, in part because the contractual obligation of ATCC to maintain the cell line would have expired before (April, 2001) the earliest possible expiration date of the patent (2002). The applicant had contracted with the ATCC to maintain the collection for twenty years from the date of deposit, which was in April, 1981. The Board held that the *Metcalfe* "rule of reason" required that the cell line be maintained for "at least a reasonable time after expiration of the patent rights." The Board suggested that the Budapest Treaty style deposit contract (thirty years or five years after last subculture request, whichever is later) "should almost invariably ensure public availability after expiration, and indeed

[79.1] *See* B. Brandon, "National and International Deposit Requirements for Microbiological and Genetic Engineering Inventions," p. 3, available from American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852.

maintenance for as long as the public expresses the slightest interest in it."

Certainly, the *Metcalfe* case[79.2] does not require maintenance in perpetuity. The storage requirement proposed by the Board, that of maintenance for a "reasonable time after expiration of the patent," does have a considerable logical appeal. However, it is likely that examiners will require applicants to agree to the more onerous storage requirements of the Budapest Treaty because of the favorable reference to it at the end of the majority opinion. Such a requirement would not be justified by the *Metcalfe* "rule of reason," since in most cases the Budapest Treaty deposit period would elapse many years after the expiration date of the patent (the average pendency period is about thirty months and the patent term is seventeen years), and since *Metcalfe* itself does not require the availability of the "essential material" for the full term of the patent.

The McKelvey concurrence did not address the storage duration issue. The Rzucidlo concurrence did, expressing its agreement with the majority in a footnote.

In a request for reconsideration of the Board's opinion in *Lundak,* appellant explained that the deposit contract had been modified to comply with Budapest Treaty requirements. The Board held, on October 31, 1984, that this modification mooted the storage duration issue.

Presently, the PTO is requiring applicants to undertake to provide the culture for the Budapest Treaty period *or* for the life of the patent, whichever expires later. While the Budapest Treaty period is longer than a patent term, it runs from the date of deposit, not the date of grant, and the long pendencies of many biotechnology patent applications and/or a patent term extension under the 1984 Act could result in the Budapest Treaty period expiring while the patent is still in force.

An applicant can initially make a deposit under a restrictive contract that does not assure public availability until expiration. When the examiner rejects the application under §112, the applicant may argue that the deposit was unnecessary because the organism was genetically engineered from publicly available starting materials and, if this argument is accepted,

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[79.2] 410 F.2d 1378, 1382 (CCPA 1969); discussed at §5.02 [13].

delete the reference to the deposit from his application. (It thus will not appear in the published patent, though it could be found by an inspection of the file wrapper.) If, on the other hand, the rejection is maintained, applicant simply modifies his contract with the depository.[79.3] This approach is safer than simply filing without depositing first.

In *Ex parte Lundak,* the Board recognized that deposited strains, "even when afforded the greatest care, ... die, mutate or otherwise become worthless." The Board did not suggest that the patent then becomes invalid, or that the patentee must quickly replace the nonviable deposit. Rather, it stated that the continued maintenance of the deposit then "becomes a very long and expensive condition which may yield little or no benefit to the public when the culture maintained is of no commercial or scientific interest."

[15] Depositor Should Endeavor to Prevent or Mitigate Mishaps that Might Render a Strain "Unavailable"

There are a number of ways in which a deposit may cease to be usable by the public in practicing a patented invention. The deposited culture may become contaminated. Attempts to preserve it may fail. The culture containers may be mislabeled. The classification of the organism within the collection may differ from the classification given to it in the patent. The culture collection itself may be destroyed, or abandoned for lack of funds.

Dr. Stevenson of the American Type Culture Collection, in a letter to the American Society of Microbiology, spoke of some of the problems ATCC has experience with biological research materials:

> The very nature of biological models, living systems being inherent in them, implies that change constantly occurs, and whether this be a genetic drift, contamination, parasitism, dedifferentiation or malignant transformation, they are phenomena to be expected and guarded against.

[79.3] I thank Patrick Kelly for suggesting I consider this tack.

Inbred animals, cell cultures, and microorganisms of every variety have all been shown to have these events associated with their use, and two major strategies have been used to minimize the problems.

These are cryopreservation to suspend living processes and change and frequent recharacterization to detect drift or contamination.

Laying down of seed stock, backcrossing of animals, and recourse to authenticated collections of type species are recognized practical means to achieve these ends.

When descriptions of research materials contain no reference to the source, history, authentication, methods of propagation, procedures for detection of contamination, or conservation of the utilized germ plasm, a reader is left in serious doubt whether the experiments are reproducible.

In attempts to serve the needs of the scientific community, we have often asked for and received purported pure cultures or microorganisms and cell lines only to find mixed cultures or ones completely different from their putative species of origin.

. . .

This letter is a plea to use the publication review process to encourage and insist upon explication of biological research materials thereby improving the reproducibility of results, the enhancement of comparability between work of laboratories, and the reliability of the literature.[80]

The traditional method of preserving bacteria is regular "subculture." As a preservation technique, "subculturing" risks include mislabeling, contamination ("This is all too frequent however much care is taken, and many tubes regularly subcultured become contaminated, especially by Bacillus spp."), inoculation with the wrong organism, and loss of the culture. ("This is frequent with delicate organisms.[81])

Newer methods include drying, freezing, and freeze-drying. None of those methods can be considered universally successful. Pseudomonas, for example, are not preserved well by drying; Neisseria, by freezing; or halobacteria, by freeze-drying. Loss of freeze-dried strains of Bacillus megaterium, Bacteroides melaninogenicum, Clostridium chauvoei, and Neisseria gonorrhoeae, have been reported in the literature.[82]

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[80] 47 ASM News 43 (February 1981).

[81] S. P. Lapage et al., Culture Collections and the Preservation of Bacteria, in 3A Methods in Microbiology 135, 163 et seq. (1970).

[82] Id.

C. W. Hesseltine and W. C. Haynes stated in 1973, "We have encountered many cultures reputedly pure but which carried a second microorganism never separated from the original culture at the time of isolation."[83] They also warn that "certain species of mites [which] feed on fungus species [can] carry various mold spores on them"; that "some strains of bacteria and actinomycetes carry phage in one form or another," that "culture rundown frequently occurs in some of the species of *Penicillium* and *Aspergillus,*" and that sometimes "inadequately trained people just do not know how to transfer subcultures so as to avoid contamination." They add that "one prominent microbiologist has estimated that from one-third to one-half of all the work published on bacterial physiology has been done with contaminated cultures or with the wrong species." These comments should be given heed if the organism must be preserved by subculturing.

Tuovinen and Nicholas reviewed the patent protection of thiobacilli. They commented that "the culture collections do not usually check on the proposed classification, identity, and properties of the cultures. . . . There appears to be no control over the possible changes in the deposited culture resulting from new information on their identity and characteristics or from mutations taking place during storage.[84]

The "viability problem" should not be exaggerated, of course. In the *Tabuchi* case, mycologist Dr. John B. Boutien testified as follows:

> Q86. Have you had experience in ordering and receiving organisms from the American Type Culture Collection?
>
> A. Yes, I have purchased cultures since probably 1948 or 1950.
>
> Q87. In your personal experience, have the organisms which

[83] C.W. Hasseltine and W. C. Haynes, Sources and Management of Micro-Organisms for the Development of a Fermentation Industry, in Thoma, Industrial Microbiology 23, 40-43 (1977).

[84] Tuovinen and Nicholas, Patent Protection for Microorganisms with Special Reference to Ferrous-Iron and Sulfur Oxidizing Bacteria, 17 Biotech. & Bioengineering 1853 (1975).

you have ordered proven, in fact, to be the organism as described by the American Type Culture Collection?

A. Insofar as I can recall, every one was exactly what the American Type Culture Collection claimed it to be.[85]

NRRL estimates that "substantially less than 1 percent of the thousands of lyophilized preparations tested over the past thirty years have proven to be nonviable.[86] However, two NRRL employees have expressed the thought, "(I)n case of accidentally contaminated cultures, legal questions as to whether the depositor or the curator was responsible could be raised."[87]

As industrial microbiologists deposit more and more organisms which are poorly studied, and often fastidious, such as extreme thermophiles, or otherwise difficult to handle, such as patnogens, the risk of losing a culture will increase.[88] Multiple deposits are likely to be used to prevent legal problems from arising.

Another problem is that it is not always possible to find a particular patent strain in the catalog. Thus, in a study of 584 ATCC deposits, 479 strains were listed under their correct name, 58 were incorrectly listed (but located by means of the numerical listing in the ATCC catalog, which the CMI and NCYC catalogues do not provide), and 47 were not listed.[89]

Bannister and Oppenheim suggest that the unreliability of culture collection catalogues means that a searcher wanting to investigate a particular culture further may have problems finding out if a given microorganism can be obtained or if it has been mentioned in a patent.[90]

Nor can any culture collection be assured of an eternal lease of life. During the 1930s, in 1948 and again in 1971, the ATCC

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[85] 194 U.S.P.Q. at 526. The ATCC stores cultures under liquid nitrogen.

[86] Pridham and Hesseltine, Culture Collections and Patent Depositions, 19 Advances in Applied Microbiol. 1, 17 (1975).

[87] Id., 8.

[88] Id., 8-9, 15.

[89] Bannister and Oppenheim, Information About Microorganisms Contained in Patent Specifications, 19 J. Chem.-Inf. Comput. Sci. 123, 124 (No. 3, 1979).

[90] Id., 125.

experienced financial crises.[91] (Of course, the holdings of a disbanded collection are likely to be salvaged by other collections.) Finally, a natural disaster may destroy a collection.

What if a viable deposit becomes nonviable prior to issuance of the patent? The outcome arguably might depend on whether it could be proven that the culture was viable when deposited. The argument would be that under *Argoudelis,* the deposit of viable organisms was sufficient "to entitle [the applicant] to the benefits of a filing date" [434 F.2d at 1393]. Consequently, a § 102(g) bar would not be interposed automatically.

What if the nonviable deposit was not replaced prior to issuance? If, *on the day of the issuance,* the deposit was "nonviable," then under the second branch of the CCPA analysis, the patentee has not taught how to make or use the invention and his patent is invalid under § 112. Under domestic U.S. patent law, it may, however, be possible to make a new deposit and revive the patent through reissue. The questions would then be: (1) does the newly deposited organism match the old one, or is the reference to the "new" deposit an addiction of "new matter"; (2) was the deterioration of the deposit a result of the negligent or intentional acts of omissions of the depositor; and (3) when was the second deposit made? It should be evident that the depositor's taxonomic description of the originally deposited organism will be determinative of whether the new deposit constitutes "new matter." In addition, the Budapest Treaty gives depositors a right to replace a nonviable deposit.

The patentee is advised to deposit his organism with more than one culture collection, if possible, and to indicate in the application that the strain will be freely available from its *own* culture collection. This will decrease the risks of a viability problem becoming critical. The patentee may also wish to obtain viability statements from the culture collection, if possible, on both the date of deposit and on the date the culture becomes publicly available.

With the Budapest Treaty in effect, it is expected that the PTO will join WIPO in insisting that a viability statement be

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[91] W. A. Clark and D. H. Geary, The Story of the American Type Culture Collection—Its History and Development (1899-1923), 17 Advances in Applied Microbiology 295 (1974).

obtained from the depository before the application is filed. This requirement would be based on Rule 10 of the treaty. The APLA notified its membership that "(t)o prevent bars from occurring sufficient time for viability testing prior to filing must be allowed."[92]

[16] Deposits Under the Budapest Treaty On the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure

The Budapest Treaty came into force in the United States on August 19, 1980. The heart of the Budapest Treaty is Article 3. The Contracting States—Austria, Bulgaria, Denmark, Finland, France, the Federal Republic of Germany, Hungary, Italy, Netherlands, Norway, Senegal, Spain, Sweden, Luxembourg, Switzerland, the United Kingdom, the United States, and the USSR—agreed to recognize for the purposes of patent procedure "the deposit of a microorganism with any international depository authority." (IDA) These IDAs are created pursuant to Article 7 and must conform to the requirements of Article 7. An IDA need not be a governmental institution, provided it is located on the territory of a Contracting State which is willing to assure the viability, purity, availability, and permanence of the cultures on deposit. An institution may become an international depository authority be virtue of the unilateral declaration of a Contracting State. At the request of any Contracting State, the *Assembly* may change the status of an "authority" by a majority of two-thirds of the votes cast. (*See* Article 8.) One-half of the Contracting States is a quorum in the Assembly.

U.S. patent practitioners must be familiar with the terms of the Budapest Treaty and Regulations thereunder, for Article 3(2) provides that:

> As far as matters regulated in this Treaty and the Regulations are concerned, no Contracting State may require compliance

[92] APLA Bulletin, Jan.-Feb. 1981, at 29-30.

with requirements different from or additional to those which are provided in this Treaty and the Regulations.

It is unclear whether this article applies to the requirements of any Contracting State with regard to any IDA deposit, or only to deposits relied on for priority purposes.

Rule 6.1 discusses the requirement for the *original deposit* of the microorganism. This deposit is to be accompanied by a written statement bearing the signature of the depositor and containing:

(1) An indication that the deposit is made under the Treaty;
(2) The name and address of the depositor;
(3) Details of the conditions necessary for the cultivation of the microorganism, for its storage and for testing its viability and also, where a mixture of microorganisms is deposited, decriptions of the components of the mixture and at least one of the methods permitting the checking of their presence;
(4) An identification reference (number, symbols, etc.) given by the depositor to the microorganism;
(5) An indication of the properties of the microorganism which the international depository authority cannot be expected to foresee but which are dangerous to health or the environment, particularly in the case of new microorganisms.

Rule 6.1 does not explain whether the depositor, in states which follow the U.S. "applicant-inventor" rule, is the inventor or the assignee. Have both sign.

Rule 6.1 does not require that the statement include "the scientific description and/or proposed taxonomic designation of the deposited microorganism," but strongly recommends that this information be furnished. This recommendation should be followed.

Several features of Rule 6.1 raise interesting legal questions. First, what is the effect of failing to comply with Rule 6.1? Can the culture collection refuse the deposit, and, if so, does the depositor still have the right to rely on the date of tender? If it accepts the deposit, does the depositor lose the right to rely

on Article 3, thus becoming obligated to prove that the culture collection is an acceptable repository under MPEP 608.01(P)? Or is Rule 6.1, thanks to the American ratification of the Budapest Treaty, incorporated into the requirements of § 112, thus warranting a § 112 rejection for noncompliance with Rule 6.1?

Another question is raised by subparagraph (5). If this provision is violated, how would it affect the outcome of a negligence suit brought by persons damaged by the depository's inadvertent release of the organism? Concepts such as joint negligence, proximate cause, and negligence per se are pertinent.

Other requirements with which depositors must comply include those dealing with the form and quantity of the deposit (Rule 6.3), fees (Rule 12), and official language (Rule 3.1(b)(v)).

Under Rule 7, the IDA issues the depositor a receipt for the deposit in question.

Under Rule 10, the IDA has an *obligation* to test the viability of the microorganism deposited with it:

(1) Promptly after any deposit referred to in Rule 6 or any transfer referred to in Rule 5.1;
(2) At reasonable intervals, depending on the kind of microorganism and its possible storage conditions, or at any time, if necessary for technical reasons;
(3) At any time, on the request of the depositor.

Note that this is a requirement to test for viability, not contamination. (*Query* whether the failure to test, or negligent testing, may be actionable.)

Under 9.1, the IDA must store the microorganism "with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request [for a sample] and, in any case, for a period of at least thirty years after the date of the deposit. (Note that this greatly exceeds the term of the patent grant.) (*Query* whether negligent storage may be actionable.)

Samples are furnished pursuant to Rule 11 to interested Industrial Property Offices (Rule 11.1), to the Depositor (Rule 11.2(r)), to authorized parties (Rule 11.2(ii)), and to parties legally entitled to access (Rule 11.3—compare 37 C.F.R. §1.11),

as certified by an industrial property office. (If the certified party has the right prior to publication, the certification must state as much and cite the applicable legal authority.)

Neither samples, nor other information concerning deposits, are otherwise furnished. If a sample is furnished to another party, the IDA will notify the depositor, supplying a copy of the request (Rule 11(g)). (Unfortunately, notification is made *after* the fact.) Persons entitled to samples are also entitled to know the submitted scientific description (Rule 7.6) and to receive a statement regarding the viability of the sample (Rule 10.2(iii)).

Provision is made for amending the scientific description or taxonomic designation of the microorganism (Rule 8).

When the deposited organism is no longer viable or when local law prevents the furnishing of samples by the IDA, the IDA notifies the depositor, who, under Article 4(a), has the *right* (not the obligation, apparently) to make a new deposit of the microorganism which was originally deposited. The new deposit is treated as if it were made on the date of the original deposit where "all the preceding statements concerning the viability of the originally deposited microorganism indicated that the microorganism was viable and where the new deposit was made within three months" of the notice (Article 4(d) and (e)). (The statement which must be furnished with a new deposit is set forth in Rule 6.2.) According to Article 4(c):

> Any new deposit shall be accompanied by a statement signed by the depositor alleging that the newly deposited microorganism is the same as that originally deposited. If the allegation of the depositor is contested, the burden of proof shall be governed by the applicable law.

The term "same" should be interpreted as meaning "having substantially the same morphology and bioactivity." To avoid uncertain litigation, retain a freeze-dried culture of the original microorganism.

The PTO has prepared a memorandum which sets forth, briefly, the requirements which have to be met by International Depository Authorities (999 O.G. 2). As of January, 1984, there were thirteen International Depository Authorities, of

which three were located in the United States. (See Appendix 2.02[8].)

[17] Deposit Under the Patent Cooperation Treaty

Patent Cooperation Treaty Rule 13 bis discusses the manner in which the "international application" should refer to the depositing of a microorganism in a culture collection. If the applicant complies with this rule, the reference "shall be considered as satisfying the requirements of the national law of each designated state." Failure to comply with the Rule leaves the applicant at the mercy of the national laws in question, but "is not of consequence in any designated state which does not require a deposit."

Under PCT Rule 13 bis.3, the reference should at least indicate:

(1) The name and address of the depository institution with which the deposit was made;
(2) The date of deposit of the microorganism with that institution;
(3) The accession number given to the deposit by that institution.

Additional information can be required by a "national office" if it gives proper notice under PCT Rule 13 bis.7. To the best of this author's knowledge, the United States has not invoked this exception even though MPEP 608.01(P) requires a "taxonomic description" while PCT Rule 13 bis (MPEP 1832.01) does not. This oversight will probably be corrected after the PTO becomes more familiar with PCT practice. (A grace period of two months from publication of the correction would be allowed for filing international applications, with the U.S. as a designated state, under the present rule.)

If *any* of the indications referred to in Rule 13 bis.3(a) are omitted from the international application as filed but are supplied within sixteen months after the priority date, "the indication shall be considered by any designated Office to have been furnished in time" (Rule 13 bis.4).

Once again, the PCT Rule is in conflict with U.S. practice, which requires that the deposit reference be complete in "the specification as filed" (MPEP 608.01(P)). There is a mechanism by which the sixteen-month PCT grace period may be reduced or eliminated, but the PTO, to the best of this author's knowledge, has not activated it.

PCT Rule 13 bis also discusses the furnishing of samples. The provision is not very clear, but it seems to place strict limitations on the furnishing of samples prior to "international publication." This seem to conflict with the requirements of 37 C.F.R. §1.14 as interpreted by MPEP 608.01(P). The PTO probably will construe designation of the United States by the applicant as being, by operation of 37 C.F.R. §1.14, an authorization to furnish samples to those having "access" under 37 C.F.R. §1.11.

[18] Deposits Under the European Patent Treaty

Microorganisms are patentable under the European Patent Convention, Article 53(b). [*See Guidelines for Examination,* Chapter II, paragraph 6 and Chapter IV, subparagraph 3.5.] The deposit requirements under the European Patent Convention were set forth in Rule 26. Rule 28 was amended, effective June 1, 1980, and a supplementary Rule 28a was also promulgated. The discussion following is directed to the 1980 rules.

Rule 28 of the EPT differs from PCT Rule 13 bis in a number of respects. First, the *filing date* of the European application is the date by which the culture must be deposited with a recognized culture collection, though a (normally) sixteen-month grace period is allowed for stating the depository institution's accession number. Second, the *filed* application must provide "such relevant information as is available to the applicant on the characteristics of the microorganism." Third, the deposited culture is available upon request "to any person from the date of publication of the European Patent Application and to any person having the right to inspect the files under the provisions of Article 128, paragraph 2, prior to that

date." Fourth, the culture is made available to the requester only if the latter undertakes

> [N]ot to make the deposited culture or any culture derived therefrom available to any third party before the application has been refused or withdrawn or is deemed to be withdrawn, or, if a patent is granted, before the expiry of the patent in the designated state in which it last expires;
>
> [T]o use the deposited culture or any culture derived therefrom for experimental purposes only, until such time as the patent application is refused or withdrawn or is deemed to be withdrawn, or up to the date of publication of the mention of the grant of the European patent. This provision shall not apply insofar as the requester is using the culture under a compulsory license. The term "compulsory license" shall be construed as including ex officio licenses and the right to use patented inventions in the public interest.

Until the date on which the technical preparations for publication of the application are deemed to have been completed, the applicant may limit the issuance of samples to an "expert" nominated by the requester and recognized as an expert by the European Patent Office, or to any person approved of by both the requester and the applicant. This limitation is valid until the publication of the mention of the grant of the European Patent, or until the application is refused or withdrawn. The U.K. Institute for Biology had advised the European Patent Organization to delay public access to a deposited culture until the date of grant but to employ an independent expert to verify the applicant's claims of viability and operability, while the application is pending.[93]

It must be emphasized that once the descriptive reference is communicated to the EPO, applicant has given an irrevocable consent to the deposited culture being made available to the public in accordance with the Rule. Thus, if the application is subsequently abandoned, the culture becomes publicly available.

EPT Rule 28a deals with the nonviable deposit problem. It

[93] J. R. Norris, The Microbiologist and the First European Patent Convention Process Biochemistry, 29, 31 (June 1977).

provides a grace period of *three months* for the depositor to furnish a new deposit, accompanied by a statement alleging that the newly deposited microorganism is the "same" as that originally deposited. (The test for "sameness" will probably be based on the definition of a "derived culture"—"one which still exhibits those characteristics of the deposited culture which are essential to carrying out the invention.") EPT Rule 28a is harsher than the Budapest Treaty, and "the provisions of the latter shall prevail in case of conflict" (EPT Rule 28a(5)).

The U.K. Institute of Biology told the European Patent Organization that "often microorganisms which have been specifically developed by processes of mutation and selection are not easy to maintain in a viable state or in a condition that will retain their desirable characteristics," and that responsibility for proper handling and release of cultures should be borne by the European Patent Office, not by individual culture collections.[94] The European Patent Office has not, however, accepted this responsiblity.

[19] PTO Draft Guidelines on Deposits

In May 1986, Patent Examining Group 120 publicly distributed "draft guidelines for depositing biological materials for patent purposes."[94.1] These declare "the requirements of 35 U.S.C. §112 are considered to be satisfied in circumstances [which] require a sample of the biological material where the biological material required is known and readily available to the public or a deposit of the biological material is made in accordance with the procedures and conditions specified below."

Subsequently, in June 1987, the P.T.O. promulgated an advance notice of proposed rulemaking.[94.2] This proposed new rules 1.200-1.208 on deposit of biological materials.

Initially, the Examiner determines whether a deposit is needed, or if one was made, if it is acceptable for patent pur-

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[94] Id.

[94.1] *See* PTCJ (BNA) (May 22, 1986).

[94.2] 52 Fed. Reg. 34080.

pose. If 35 U.S.C. 112 is not satisfied, the affected claims would be rejected, with an explanation of why a deposit is needed. The Applicant must respond by making a new deposit, explaining why the existing deposit (or giving written assurance that an acceptable deposit will be made on or before payment of the issue fee), establishes that the biological material is known or readily available to the public, or arguing that deposit is unnecessary for compliance with 35 U.S.C. 112. Based on a written assurance of deposit, a Notice of Allowance can be issued with a requirement that deposit be made within three months. See proposed 37 C.F.R. 1.208.

"Biological material need not be deposited if it is known and readily available to the public or can be made or isolated in a reproducible manner from known and readily available material." (Proposed 37 C.F.R. 1.201(b)).

The draft guidelines suggested that, in determining whether the conditions are met, the PTO will look to listings in commercial catalogues, references in printed publications, testimonials as to availability from other researchers, and evidence that the biological material is abundantly available in nature. Since the PTO calls these "representative indicia," this list is not exhaustive.

While the PTO did not rule out inferring "ready availability" even when the patent owner would retain control over commercial availability, the draft guidelines pointed out that the patent owner might have a motivation to eliminate or restrict access to the biological material when the patent expired or when a decision was made not to enforce it. Thus, availability through suppliers not under control of the prospective patentee would be less controversial.

The draft guidelines did not address the issue of price. That is, they did not address whether a biological material available at a prohibitive price is "readily available." By referring to availability through "commercial suppliers," they did imply that it is acceptable to make some charge for the subculture.

Subsequently, in the preamble of the ANPR, the PTO explained that it "will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has unrestricted access to the material." Price will be considered

to affect "availability." On the other hand, "the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assign shall not by itself justify a finding of non-availability, absent reason to believe that access to the biological material would later be improperly restricted."

The PTO had yet to comment on the measures by which an applicant could rebut the unfavorable implications of retained control, for example: (1) posting bond to the effect that the material would be retained in their catalogue for a specified, reasonable period, and/or (2) making a restricted deposit with a recognized depository, committing it to be opened if they ceased supplying the material commercially.

The PTO might further also consider the "track record" of a company. If a company were known to have abruptly discontinued selling a referenced cell-line in the past, the PTO could look askance at its future claims of "ready availability."

In discussing references in printed publications, the draft guidelines suggested that the number of publications, the number of authors, the span of years covered, the situs (foreign or domestic) of the publication, and whether the published article requires peer review are all relevant. The number of publications and authors would seem less significant than the number of distinct laboratories or research groups represented. Ten publications by the same ten authors would not be as indicative of wide dissemination as three publications by single authors at different universities.

The allusion to the situs of the publication is troubling if it means that foreign publications are suspect. Certainly, a foreign citation of material developed in the U.S. indicates greater, not lesser, availability. If the foreign publication describes use of material developed abroad, there is still no reason to doubt that the material could *eventually* be brought into the United States; the amount of "red tape" may be greater, of course.

In the preamble to the 1987 ANPR, the PTO stated that there "was no intent to discriminate between domestic and/or foreign applicants or publications." Instead, its concern was that "publications in a single country . . . would suggest more limited distribution. . . ."

It is difficult to perceive the relevance of "peer review," though that is preferred (Proposed 37 C.F.R. 1.202(a)). The reviewers do not check whether the biological material is available. What is more important is the publication's policy on availability. Some journals refuse articles on new antibodies if the antibodies are not made available to researchers.

Now let us examine the formal deposit route.

Deposits need not be made in an International Depository Authority under the Budapest Treaty. The draft guidelines permitted deposit in any "permanent depository not under the control of the depositor of the patent owner which meets the requirements of an IDA (except that it would not be required to store microorganisms) as determined by the PTO."

The guidelines do not define "permanent" or "control," or explain how the PTO's requirements for a depository might differ from those under the Budapest Treaty. The parenthetical exception was probably written with the seed depository in Fort Collins in mind.

Newly proposed 1.202(b) says that a deposit may be made in any depository "recognized to be suitable by the Office." Six conditions are set forth, and these are clearly based on the requirements for international Depository Authorities under the Budapest Treaty.

The *Argoudelis* requirements as to access are unchanged. By implications, requiring identification of the ultimate recipient or enjoining the further transfer of the material is prohibited under proposed Rule 1.207. The draft guidelines stated that asking the depository to identify sample recipients is permissible, but this identification cannot be a "precondition to release." Restrictions "required by law or regulation for safety, public health or similar reasons" are also permissible under proposed 1.201(b).

This passage represents a retreat from the position taken by the PTO in the "NCYC" case. There, the PTO emphasized the "all" in the "all restrictions" language of *Argoudelis*. Now, the PTO admits to at least a health and safety exception.

The Budapest Treaty recognizes that the export and import of deposits (Article 5) or samples (Article 4(a) (ii)) may be prevented or restricted by health authorities. An IDA may refuse to accept dangerous organisms (Rule 3 (b) (iii)), and a depositor

is obligated to inform the IDA of the dangerous properties of its microorganism (Rule 6(a)(v)). Finally, the container in which the sample is furnished must be accompanied by an indication of those dangerous properties (Rule 11.4(f)).

It does *not,* however, authorize an IDA to refuse to provide a sample to a domestic requester on health or environmental grounds. This was an unfortunate oversight, and the PTO is to be commended for realizing that a depositor should not risk his patent rights because a depository institution, *in obedience to law,* refuses to furnish a sample to a particular requester.

Still, one wonders whether both the PTO and the Budapest Treaty Assembly need to address product liability issues. Sometimes, it is prudent to go beyond what the law requires in handling dangerous materials in order to reduce one's product liability exposure. The PTO guideline speaks only to what is required by law. However, the P.T.O. refused to accept restrictions for national security reasons or to comply with product liability insurance requirements.

The guidelines need to be revised to clarify the information about the recipient which the depository may be asked to obtain prior to release. BT Rule 11.4(e)(1) clearly requires that a request for sample provide the "name and address of the requesting party." It is not clear whether "sample recipients" referred to in the guidelines are the actual requesting parties or the "ultimate recipients."

Nothing in the draft document sets forth any time period within which the depository must be notified of the patent grant, but the PTO generally suggests that notice is due "promptly after the patent issues." Clearly, the duty of notification is being imposed on the patentee. There is no indication that the PTO intends to communicate lists of accession number to IDAs as provided for by BT Rule 11(b).

Another requirement is that the specification identify the deposit by deposit number and the name and address of the depository. It must also provide a taxonomic description. (Proposed 1.208(d).) In accordance with *Lundak,* this reference need not appear in the application as filed; the information may be inserted at any time on or before the date the issue fee is paid.

The PTO also intends to require a Viability Statement. (Pro-

posed 1.206.) While such statements were not required under past U.S. practice, IDAs under the Budapest Treaty have an obligation to test viability. The PTO guidelines do not require testing by the depository, as long as the test is performed on a subculture provided by the depository to applicant or a third party. The guidelines unnecessarily require that the subculture be "promptly returned" to applicant for testing; if it is viable today it was viable a year ago, too.

The availability of the deposit must be assured for the *greater* of (1) the Budapest Treaty period (thirty years minimum and five years past the most recent request) or (2) the enforceable life of the patent. (Proposed 1.205.)

When deposit is made after filing, a verified statement will be required from a person in a position to corroborate the fact that biological material described in the application as filed is the same as the deposited material. (Proposed 1.203(b).) The PTO comments that the statement should indicate that the material was viable and capable of reproduction as of the filing date.

The draft guidelines suggested that when an applicant relied upon a deposit of another, redeposit might be necessary. The proposed rules recede from that requirement. The PTO recognized that redeposit might be deemed an act of conversion, and observed that the prior deposit would carry a rebuttable presumption that the deposited material was known and readily available to the public.

The proposed rules require an applicant *or patentee* to take remedial action if a biological material ceases to be available.

Specifically, a new deposit must be made within three months of receiving notification of the inability of the depository to furnish samples of the original deposit. The Office must be notified of the replacement and the reason for it, and it must be given assurance that "the replacement deposit is to the best of the depositor's knowledge identical to the original deposit." The PTO advises that a contaminated, but viable original deposit cannot be replaced under the proposed rule. "In the event that a deposit is replaced, the PTO will apply a rebuttable presumption of an identity between the original and the replaced sample where the patent making reference to the deposit is relied upon during any PTO proceeding." The

guidelines suggest that a patentee seek a certificate of correction if a deposit must be made under a new accession number.

The propriety of the PTO's reference to the duties of a patentee (except, of course, in a reissue situation) is certainly doubtful.

Under the Budapest Treaty, Article 4, an applicant has a right, but not a duty, to replace a nonviable deposit within three months notice of the problem. The PTO guidelines impose a duty, but do not set forth any explicit diligence requirement.

It should be noted that with respect to (1) the required deposit period, (2) the requirement of a viability statement, and (3) the requirement of remedial action by a patentee, the guidelines go beyond what has been mandated by the courts.

With respect to applications claiming priority under 35 U.S.C. 119, the comments on the proposed rules state that "it must also be emphasized that applications may not be granted priority in applications filed in countries foreign to the United States if they fail to make a deposit in a permanent depository acceptable to that foreign country before the filing date of the application in the United States." It is assumed that the PTO is referring to whether a foreign patent office will accept a claim of priority from a U.S. application.

The draft guidelines reminded foreign applicants that their applications cannot claim the benefit of any foreign application which does not satisfy the guidelines, if applicable, even if it satisfies the disclosure requirements of the home country.

§ 5.03 The Selection of a Culture Depository for Enablement Purposes

Since the protection of the majority of microbiological inventions will require the use of the patent depository services of a culture collection, it appears appropriate to discuss the history of the culture collections and deposited cultures, and the major considerations to be weighed before making a deposit in a particular collection.

[1] History of Culture Collections

"The first known type culture collection, the Kral collection, was established in Prague around 1900."[95] Among the major collections today are the American Type Culture Collection (Rockville, Maryland), Northern Utilization Research and Development Division, USDA (Peoria, Illinois), Quartermaster Research and Development Center, U.S. Army (Natick, Massachusetts), the Institute Pasteur (Paris, France), Institute for Fermentation (Osaka, Japan), National Collection of Industrial Bacteria (Aberdeen, Scotland) and the Centraal bureau voor Schimmelcultures (Baarn, Netherlands). The World Director of Collections of Cultures of Microorganisms lists many more collections. The table on the following page shows the worldwide distribution of culture deposits.

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[95] Pelczar, Reid and Chan, *Microbiology* 143 (4th ed. 1977).

DISTRIBUTION OF CULTURES IN CULTURE COLLECTIONS[96]

	Algae	Bacteria	Filamentous Fungi	Protozoa	Tissue Cultures	Viruses Animal	Viruses Bacterial	Plant	Yeast
Africa (11)	19	1917	340	812		226		1	51
Asia (30)	468	14589	11748	30	30	597	412		5117
Australia/ New Zealand 39	39	6902	7464	2	2	226	239	52	325
Eastern Europe/ USSR (38)	1058	22208	7115	25	10	817	221		5000
Western Europe (100)	3926	76084	29284	345		667	304		15551
Latin America (23)	12	8168	1803	1	10	110	26		2573
Middle East (13)		8502	85	7		40	54		107
North America (67)	232	106524	52327	57	120	1295	565	173	10202

[96] Id.

Collections differ greatly in terms of the organisms they accept, the preservation techniques they employ, the tests they perform, their schemes for indexing and cataloguing their accessions, the fees they charge, and the speed with which they process requests for samples.

UNESCO sponsors an International Center for Information on and Distribution of Type Cultures (Lausanne, Switzerland), which can help attorneys locate a particular culture.[97] Attorneys should certainly obtain the catalogues of the major collections in their country and in other countries in which they frequently file microbiological patent applications. A U.S. government publication is available which explains the acronyms used to designate these collections.[98]

The first deposition of a culture for patent purposes occurred in August 1949, when American Cyanamid deposited cultures of strain Lederle A-377 of *Streptomyces aureofaciens* Duggar with the NRRL collection.[99]

[2] The American Type Culture Collection

The American Type Culture Collection began as the Bacteriological Collection and Bureau for the Distribution of Bacterial Cultures of the American Museum of Natural History in New York. It was founded in 1911 by the curator, Mr. Winslow, and published its first catalogue, listing 350 strains, in 1913. The collection, which was incorporated as a nonprofit scientific institution in 1925, moved frequently as the collection outgrew its old quarters. It began charging for cultures in 1930, exacting the payment of one dollar per culture. In 1973, about half of its financial support came from fees, and half from grants and contracts. The ATCC currently maintains cultures of 27,000 strains of bacteria, fungi, protozoa, algae, plant and animal viruses, and animal cell lines.

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[97] At 19 Avenue Cesar Roux, Lausanne, Switzerland.

[98] T. G. Pridham, *Micro-Organism Culture Collections: Acronyms and Abbreviations,* ARS/USDA Publ. ARC-NC-17 (June 1974).

[99] T. G. Pridham and C. W. Hesseltine, Culture Collections and Patent Depositions, 19 Advances in Applied Microbiology 1, 3 (1975).

The ATCC accepts deposits for patent purposes. If the deposit is in connection with a U.S. application only, the depositor is allowed to pay for the deposit on an annual basis. The initial fee is $145, and the depositor then pays $100 each year until the U.S. patent issues. This fee structure covers the maintenance of the deposit for the life of the U.S. patent.

If the deposit is in connection with the European Patent Office or national patent offices outside the United States, a one-time fee of $570 per strain must be paid. This fee covers maintenance of the deposit for thirty years.

Payment of an additional $300 fee ensures that ATCC will notify the depositor of the identity of any persons requesting samples of the strain for a thirty-year period.

Upon request, ATCC will restrict the distribution of subcultures of a patent deposit pending issuance of the pertinent patent. ATCC will not restrict distribution after a pertinent U.S. patent issues. The depositor is responsible for notifying ATCC of the issuance of the U.S. patent.

If a patent application is abandoned, upon notification the ATCC will return the culture to the depositor. After a patent is granted, cultures of the strain in question will be catalogued, preserved and distributed, along with information relating to it, for at least the life of the patent, without additional charge to the depositor. The ATCC catalogue lists strains by their scientific name, and indicates patent deposits by the appellation "patent strain." The ATCC catalogue also includes a numerical index and an incomplete list of strains with special applications. The majority of the ATCC strains are preserved by freeze-drying, but other preservation facilities are available. ATCC's fees for providing subcultures to commercial firms and non-profit institutions are $54.50 and $34.00, respectively, per item. The recipient assumes all risks and responsibility in connection with their receipt, handling, storage and use, but ATCC will replace a culture received in a non-viable, impure or atypical condition if notified within a stated period.

[3] The Agricultural Research Service Collection (ARS or NRRL)

The ARS Collection began as the culture collection of the U.S. Department of Agriculture's Northern Regional Research Laboratories in Peoria, Illinois. The NRRL's Fermentation Division, served by this collection, was established during World War II, and significantly contributed to the development of penicillin. The first "patent deposit" in the U.S. was with the NRRL collection. The ARS collection, as it is now known, is still a part of USDA, and its policies are still subservient to USDA's mission and philosophy.

Like the ATCC, the ARS will allow depositors to restrict dissemination of a patent strain until a U.S. patent is issued. However, it will *not* return deposits should the application be abandoned, since it takes the view that these deposits are "public property." It is not entirely clear from the ARS contract whether it would distribute to the public, upon request, subcultures of a deposit that is the subject of an abandoned application. Since the ARS does not "issue a catalogue or list," it is unlikely that a strain would be requested unless the requestor knew, from other sources, the depositor's number or the ARS (NRRL) number for the strain. It should be noted that the depositor's wishes with regard to distribution may be deemed subordinate to Department of Agriculture policy. Nonetheless, "it has been an ARS Culture Collection policy that its own researchers would not have a particular strain [deposited in connection with patent applications] available for research work until not only the patent issued, but after three requests for the strain had been filed after issuance of the patent."

A second distinction is that the ARS refuses to accept deposits of plasmids, fastidious microorganisms, mixed cultures, viruses, "plant pests," and anaerobic or microaerophilic strains of *Actinomyces*.

§ 5.04 Possible Alternatives to "Deposit" in the Case of Genetically Engineered Or Fully Genotyped Organisms

[1] Fully Genotyped Organisms

Theoretically speaking, since the entire genome of an organism is a precise recipe for the construction of duplicate organisms, and since gene synthesizers are now on the market, it should be possible to describe a novel microorganism and the manner and process of making it merely by stating its genotype, base pair by base pair.

In an early article on the Plant Patent Act, Robert C. Cook suggested that "type" specimens of new plant varieties be cultivated to serve as a "living embodiment of what was patented" and thus to serve as an "accurate basis of comparison in the event of infringement suits." He noted, however, the possibility that genetic studies would obviate the need for a type specimen:

> As the genetics of a larger number of plant species becomes more completely known, the relations of the genes and the chromosomes will doubtless be used in describing new varieties. This could be done under the existing statute. Maize is the only plant in which even provisional chromosome maps have yet been made, but in time others will follow, and the use of such descriptions in a patent will place the patenting of plants on a status very similar to that of the patenting of chemical compounds.[100]

The CCPA held in a plant patent case that the description of a novel plant variety in a catalogue did not raise a statutory bar to the issuance of a plant patent on the variety as the description alone did not enable others to reproduce that variety. It declined, however, to rule that such description could be "totally ignored" indefinitely.

> Current studies to "break the chromosome code" may also add to the knowledge of plant breeders so they may someday secure

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[100] R. C. Cook, Applying the Plant Patent Law, 13 J.P.O.S. 22, 24 (1931).

possession of a plant invention by a description in a printed publication. . . .[101]

In a similar vein, Waddell Biggart suggests that "future developments may provide additional knowledge of microorganisms, their life processes and genetic makeup so that the drafting of a U.S. patent application specification on a microorganism-related invention" would be similar to preparing an application for a chemical invention, and "the necessity for deposition may well be practically eliminated.[102]

[2] Genetically Engineered Organisms[103]

One of the issues confronting applicants is whether to deposit. There is a natural reluctance to deposit the "production organism" since this provides a headstart to competitors who obtain a subculture. A professor may make the formal request, to avoid awakening the patentee's suspicions, and then secretly transfer the organism to the rival company.

At the 1981 Battelle Conference, Leo Malossi suggested that it might not be necessary to deposit a culture of a genetically engineered organism in order to satisfy 35 U.S.C. §112, if the parent strains were already on deposit, and "step-by-step directions for the construction of the new strains were set forth in considerable detail in the specification." Mr. Malossi advised that it be established "*On the record* that one of ordinary skill in the art had actually reproduced the [desired] host-vector system from organisms available to the public using the techniques in the specification and that useful quantities of the

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[101] In re LeGrice, 133 U.S.P.Q. 365, 374 n.7 (CCPA 1962).

[102] W. A. Biggart, *Patentability, Disclosure Requirements, Claiming and Infringement of Microorganism-Related Inventions,* at 2-124, *in* PRG, Genetically Engineered Microorganisms and Cells (1981).

[103] The term here includes both strains created by induced conjugation of normally incompatible, natural plasmids, and strains created by transforming a host organism by means of a composite plasmid.

peptide of interest were produced by the completed host-vector system.[104]

Ex parte Goeddel[104.1] related to the enablement of claims to bacterially derived, mature human leukocyte interferon. The opinion unfortunately does not say very much about the scope of the disclosure, and the patent has not yet issued, but the corresponding European patent application is illuminating. No deposit was made by Genentech, but it referenced ATCC deposits of two host strains of *E. coli.*[104.2] Genentech cloned its quasi-synthetic interferon gene into the commonly available transfer vector pBR322. Genentech never deposited an interferon genebearing plasmid, but the sequence of the insert was set forth in Figure 3 Genentech also made use of Miozzari's plasmid pGMI (as a source of the *trp* promoter), Rodriguez' plasmid pBRHI (as a source of the promoter-less *tet* gene) and Goeddel's pHGH 107 (also as a source of the *tet* gene). A new microorganism was produced—a genetically engineered strain of *E. coli* which expressed the leukocyte interferon gene and the *tet* marker gene. This organism was then used to produce interferon.[104.3]

The Examiner was of the opinion that the "new microorganism used to produce the products of the instant claims" should have been deposited. The Board disagreed. "One skilled in the art palpably would have no difficulty in following appellants' instructions in order to realize the claimed product starting with known precursors." The Board admonished the Examiner that deposit was not mandatory, only permissive.

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[104] L. Malossi, *Protecting the Genetic Engineering Invention,* in 3 Proceedings of the BMI Genetic Engineering Conference (April 8, 1981) 13, 14-15 (Keenberg, ed. 1981).

[104.1] 5 U.S.P.Q.2d 1449 (BPAI 1987).

[104.2] EP Appl. 43,980 at 10.

[104.3] Id. at 19, 20, 22.

§ 5.05 The "Written Description" of Microorganisms, Plasmids, and Fermentation Products, and of Eukaryotic Cell, Tissue and Organ Cultures

[1] Description of Organisms

[a] Deposit Is Desirable if Organism Is Poorly Characterized

It is very important that the patent specification, when filed, contains a statement referring to the deposit of the organism, identified by the deposit number, name, and address, of the depository, as suggested by MPEP 608.01(p). While the MPEP does not have force of law, it follows the argument in *Argoudelis* that the specification must indicate when filed that the applicant is willing and able to make the specification enabling upon issuance. Even if only cursory taxonomic information regarding the organism is known at filing, the deposit reference allows the applicant to introduce the taxonomic description by amendment without introducing "new matter."

[b] Arguably, a Culture Deposit Is Itself a "Description" of the Organism

While the MPEP encourages examiners to require that a taxonomic description be included in the specification, it could be argued that the deposit of the organism (and its later release to the public) *completely* satisfies the enablement requirement.

In *Ex parte Davidson*, the Board reversed a § 112 rejection of a claim for

> A process for the 11-beta-hydroxylation of a steroid compound having a methylene group at the 11-position, which comprises contacting said steroid compound with a material selected from the class consisting of a living culture of the microorganism pycnosporium sp. QM703 and the myceluem of said microorganism.[105]

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[105] 118 U.S.P.Q. 520 (POBA 1957).

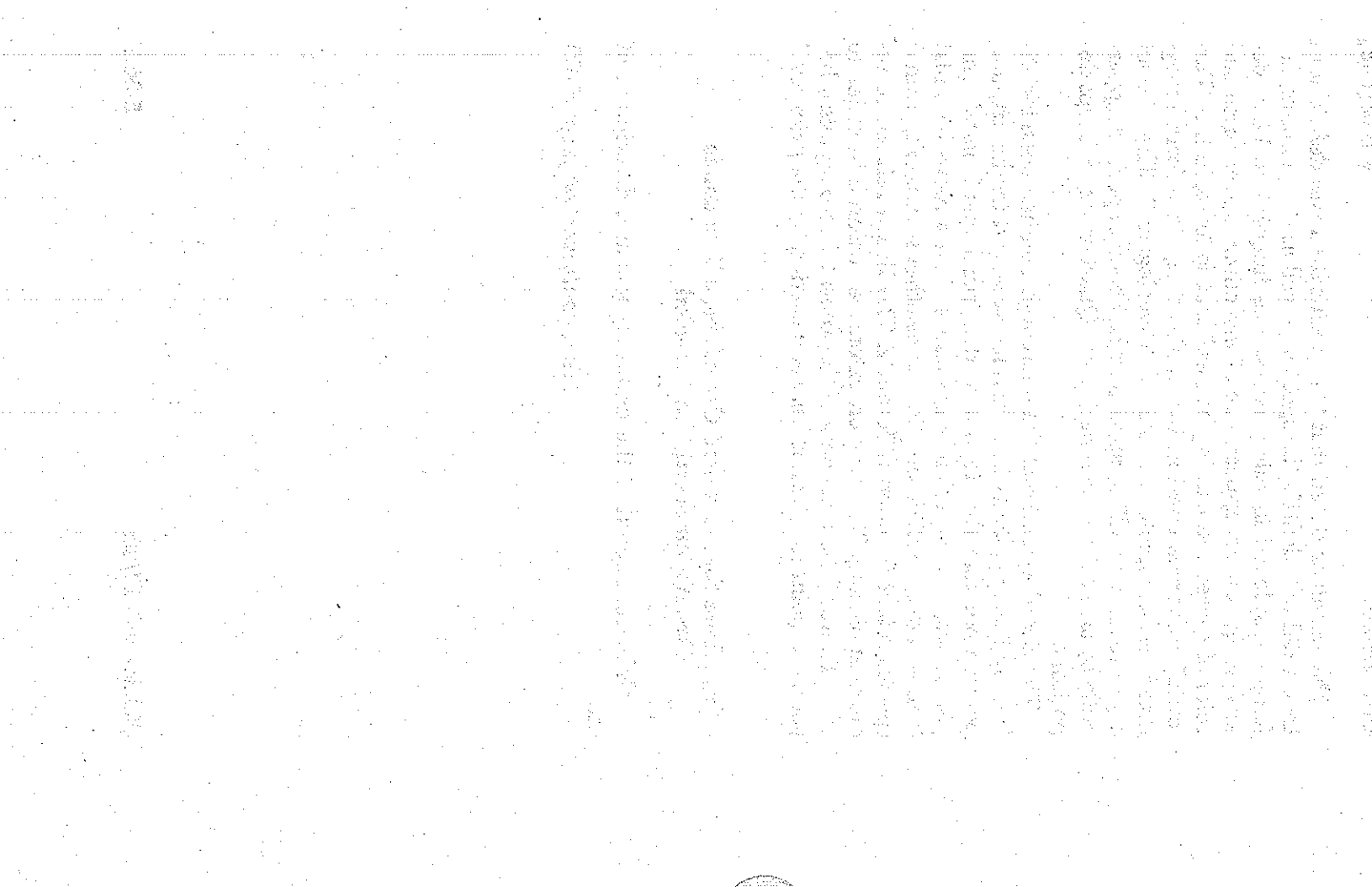
The examiner stated that the specification was deficient in that it did not identify the species as well as the genus of the fungus employed in this process. The fungus had been described by source, appearance of mycelium, appearance and color of spores and fruiting bodies," and so forth, in the "Farlowia" reference cited in the application, "in a form recognized as complete by skilled mycologists." The "exact organism employed" by applicants had been deposited (apparently by an earlier researcher) in the Quartermaster Corps depository.

The Board agreed that the microorganism had been identified by the appellants in a manner accepted in the art, and pointed out that the deposit of the "particular isolate" employed was a *more* reliable disclosure than a mere binomial (genus-and-species) description, since other strains of the same species might function differently. The Board refused to require applicants "to carry on extensive research in order to carry forward the taxonomy of the known microorganism beyond the point to which it has been carried by the prior art."

[c] Even for Deposited Organisms, a Taxonomic Description Should Be Provided

While the deposit of the organism acts as a description of the

(*Text continued on page 5-57*)



organism's morphological characteristics, and thereby satisfies § 112, omission of the taxonomic description is inadvisable. MPEP 608.01(q); EPT Rule 28(1)(b).

One reason is that the taxonomic description gives the courts a foundation on which to support a "doctrine of equivalents" argument, with the taxonomic description used as a test of equivalency. A second reason is that it is a safeguard should the strain become "unavailable." A third reason is that the courts might consider it a necessary ingredient of an "enabling" disclosure.

In *CPC International, Inc. v. Standard Brands.*[106] the court held Marshall's "Enzymatic Process" claims 2-4 invalid. Claims 2, 3, and 4 of Marshall's CIP application had "listed Pseudomonas hydrophilia as an appropriate micro-organism for obtaining the desired enzyme preparation [containing xylose isomerase]." The organisms used by Marshall had indeed been referred to in a 1954 technical article as *P. hydrophilia,* but in 1960 Canadian researchers determined that the strains so referred to in fact belonged to the species *Aerobacter cloacae.* Claims 2, 3, and 4 therefore did not cover the operative strains. CPC applied for a reissue patent, but the reissue application was rejected on the ground that it contained "new matter." CPC abandoned the reissue application, and the Court recognized that the three claims were defective.

[d] Taxonomic Classification of Organisms Is Difficult at Best

Patent literature descriptions of microorganisms are often confusing.[107]

> Much confusion has arisen in the patent literature because of the various descriptions of microorganisms. Many of the descriptions have omitted characteristics which are now consid-

[106] 184 U.S.P.Q. 332, 335, 337 (D. Del. 1974).

[107] Whittenberg, Microbiological Patents in International Litigation, 13 Advances in Applied Microbiology 383, 387 (1969).

ered stable and critical for proper classification. Others have placed undue emphasis on unstable and variable characteristics.

A major problem in the description of microorganisms is the subjective character of certain of the taxonomic tests in current use:

> The color of the aerial mycelium to be classified within preestablished color categories has been recognized, for the same strain, by 36 experiments as being gray 48 times, white 39 times, yellow 2, orange 1, pink 9, red 2, brown 6, on a substrate common to all investigators. This observation is in no way an isolated instance! As far as the structure of the sporophores is concerned, one strain has been evaluated 58 times as spira, 8 times as rectus, 14 as rectus-flexibilis, 10 as rectinaculum-apertum, 7 as monoverticillatus-spira, 2 as biverticillatus-spira. Of 25 strains, 14 were considered by all the experimenters to present all the possible forms of sporophore listed above.[108]

L. G. Silvestri and D. Gottlieb reported in 1964 that "recent research has shown that taxonomic keys of the streptomycetes . . . are inadequate. Even trained investigators are unable to identify species from them.[109]

[e] Compendium of Recommendations Regarding the Taxonomic Description of Patent Strains

According to J. V. Whittenberg, in 1962, the "Nordic Patent Authorities" published instructions for the description of "unknown" microorganisms calling for:

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[108] Baldacci, The Classification of Actinomycetes in Relation to their Antibiotic Activity, in 3 Advances in Applied Microbiology 257, 259 (1961).

[109] Silvestri and Gottlieb, Taxonomy and Legal Aspects of Industrially Important Micro Organisms, in 1 Global Impacts App. Microbiol. 109, 112 (1964).

(1) The name of the organism and, if so required, the designation in a public collection of cultures, and if possible also date and place of the isolation.

(2) Description of growth referred to a definite substate, with a detailed description of the microscopic properties and characteristics and the microscopic morphology (including the shape and size of the spores, the morphology of the spore formation, the modes of ramification, and hyphal width of the mycelium).

(3) Growth properties (the morphology of the colonies, and information as to colors and, possibly, separated pigment) in at least ten standard substrates.

(4) Physiological properties referred to growth in substrates containing milk, nitrate, gelatine, starch, tyrosine, and, possibly, cellulose.

(5) The capability of the organism to produce hydrogen sulfide (melanin pigment) on organic or inorganic substrate.

(6) The capability of the organism to utilize a number of carbon sources.

(7) Reference to the most related species which is/are mentioned in Bergy's Manual of Determinative Bacteriology (1975) together with particulars as to how the said organism may be distinguished from the known organisms.

(8) Possible supplementary particulars regarding individual properties, for example, the production of antibiotics.

(9) In connection with the description of the physical and chemical properties of the antibiotic substance, a table on the quantitative special effects of the product shall be given as well as a table wherein, by + or −, the activity of the antibiotic substance against gram-positive and gram-negative bacteria, fungi, and yeasts is stated and, if possible, also the activity against protozae, viruses, and rickettsiae, if such information is available.[110]

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[110] J. V. Whittenberg, Microbiological Patents in International Litigation, 13 Advances in Applied Microbiology 383, 389-390 (1969).

In 1963, the Subcommittee on Taxonomy of the Actinomycetes of the International Committee on Bacteriological Nomenclature published certain "Recommendations for Descriptions of some Actinomycetales Appearing in Patent Applications":

1. That patent offices accept microorganisms for process patents which fit any of the taxa in Rules 6, 7, 8 of the International Code of Nomenclature of Bacteria and Viruses;
2. That the following minimum of criteria should be used in a description for a patent:
   A. Morphological observations
      a. Morphology of spore-bearing hyphae: Simple or verticillate; whether straight, flexuous, loops (open spirals), or spirals (closed spirals). Included in the description of the sporophore should be a reproduction of a picture or drawing of these structures.
      b. Number of spores whether single, pairs, number of spores from 3 to 10, and more than 10 forming a chain.
      c. Presence of globular sporangia as in Actinoplanaceae.
      d. Presence of flagellated spores, as in Actinoplanes.
      e. Ability to form aerial mycelium.
      f. Formation of conodiophores and conidia on substrate and/or aerial mycelium.
      g. Tendency of the mycelium to fragment.
      h. Morphology of spore surface observed under the electron microscope.
      i. Occurence of sclerotia.
   B. Color: Description of any significant color. Chemically defined media on petri dishes should be used, and age of cultures, temperature, and medium be stated.

Record color of surface of well-sporulated aerial mycelium, also the reverse and surface of vegetative mycelium.

Record any diffusible pigment: other helpful observations would be the pH-effect on color and the general nature of the pigment.

C. Physiological characters:
   a. Melanin production studied on Pepton-Iron Agar and/or Organic Medium of Gauze.
   b. Utilization of the following carbohydrates:
      Control without carbohydrates
      d-Glucose (as positive control)
      l-Arabinose
      Sucrose
      d-Xylose
      i-Inositol
      d-Mannitol
      d-Fructose
D. Temperature: The ability to grow at 50°C should be determined.
E. Microaerophilic growth.[111]

A good example of a description of a strain which emphasizes morphological characteristics is U.S. Patent No. 2,398,-837. The recent Argoudelis patent (4,259,450) emphasizes cultural characteristics. Future patent specifications will, eventually utilize numerical and molecular taxonomic descriptions.

[f] The Specification Should Discuss Any Recognized Taxonomic Problems

Taxonomic problems should be addressed in the specification. Thus Frankenfeld, U.S. Patent No. 3,347,688 [1967] states

While the above bacteria (ATCC No. 14987) have been classi-

[111] 13 Int'l Bull. Bacteriol. Nomenclature & Taxonomy, 169-170 (July 15, 1963).

fied as *"Micrococcus cerificans"* by Dr. Kallio, more recent experimental information acquired in the laboratories of the present inventors indicate that a more proper designation would be *Arthrobacter ureafaciens* [citing test results].

Similarly, in Sebek's U.S. Patent No. 2,877,161 [1959] on reduction of steroids by trichomonads, he notes that Kudo places the family Trichomonadidae in the order Polymastigma, while Morgan puts it in the order Trichomonadida.

As Whittenburg has stated[112]

> It will also be appreciated that many microorganisms now having valid specific rank and which were first disclosed in patent applications will perhaps have descriptions in the patent literature which differ in some respects from their descriptions in the scientific literature. The descriptions of microorganisms first disclosed around 1950, of course, reflect the systems then used to classify them. In many instances later descriptions of the microorganisms in the scientific literature will include characteristics not employed at the time of the writing of the original descriptions or developed later as, for example, the morphology of spore surface observed under the electron microscope.

[2] Description of Plasmids

When a plasmid is used as a cloning vehicle, it is desirable to specify its molecular weight, genetic markers, and restriction sites in the specification. The "markers" are used to identify which organisms have been transformed by the plasmid, usually on the basis of their resistance to a specific antibiotic. The restriction sites are the sites affected by the commonly used restriction enzymes (if a particular plasmid is cleaved by a particular enzyme at only one point, that point is a "single" restriction site).

In Manis, U.S. Patent No. 4,273,285 [1981], Upjohn provides the restriction endonuclease cleavage map for pUC6, with restriction site coordinates given in Kilobase units. The source of the plasmid (a biotype of *S. vellosus)* is described in detail.

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[112] Whittenberg, *supra* note 110 at 387.

Upjohn also states the molecular weight of pUC6 and the average number of copies per cell. Finally, it notes that the development complied with NIH guidelines.

There is an authoritative article on nomenclature for bacterial plasmids. (In the Manis patent designation, "p" denotes plasmid, "UC," the naming laboratory, and "6" is its reference number in that laboratory's collection.) The article[113] also discusses phenotype and genotype notations. Other discussions of plasmid nomenclature appear in the Chakrabarty patents.[114]

It does not appear that a nucleotide-by-nucleotide disclosure of a novel plasmid will normally be required.

[3] Fermentation Products

Preferably, a structural formula for the product is disclosed. If not, the physical and chemical properties of the compound, such as its melting point, boiling point, color, gross structure, solubility, reactivity, IR, UV, NMR, and mass spectra, and elemental composition are disclosed. Typically, the biological activity data for the product, and the means used to purify and characterize the product, are also discussed. Significant derivatives might also be referred to.

[4] Cell, Tissue and Organ Cultures

It is desirable that these applications conform to the recommendations of the Tissue Culture Association.[115]

According to the recommendations of the Committees on Nomenclature of the Tissue Culture Association, a *primary cell culture* is one "started from cells, tissues or organs taken directly from an organism." The primary cell culture is started from an "explant," an excised fragment of a tissue or an organ. If a cell culture is desired, the cells of the explant are deliber-

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[113] Novick, et al., Uniform Nomenclature for Bacterial Plasmids: A Proposal, 40 Bacteriol. Revs. 168 (1976).

[114] *E.g.*, U.S. Patent No. 4,259,444.

[115] *See generally* Paul, *Cell and Tissue Cultures* (4th ed. 1970).

ately *disaggregated,* or separated. In an organ culture, deliberate measures are taken to prevent cell disaggregation, which otherwise occurs naturally (to some degree). To *subculture* a culture is to transplant some of the cells into another culture vessel. The *split ratio* is the number of subcultures into which a culture is divided. When a primary cell culture is subcultured, it becomes a cell line. *Subculture number* is the number of transplantations, and the time between successive transplantations is the *subculture interval.* The terms *passage* and *subculture* are synonymous.

During the first few subcultivations, the cultured cells exhibit the properties of normal cells. Later, they go through a crisis period, after which they either die or emerge with radically different properties (a process known as *cell alteration).* Genetically speaking, cells which are normally *diploid* (two sets of chromosomes) become *heterodiploid* (a different number of sets, a/k/a *heteroploid).* The term *karyotype* refers to a description of the chromosomes of a cell. A *heterodiploid* cell typically lacks "contact inhibition," and often loses its specialized functions. Once a *cell line* displays the potential for unlimited subculturation (*i.e.,* cancerous growth), it is called *established.*

Arbitrarily, the TCA considers a cell line to be one in which at least 75 percent of the cells have the same karyotype as the cells of the diploid source species.

Established cells in culture are typically fibroblast-like (spindle-shaped) or epithelial-like (polygon-shaped). They often have a different metabolism than the parent "normal" cells do. They are often grown in *suspension* rather than on a surface. According to Dr. Paul, a cell line generally is not characterized as established "unless it has been subcultured at least seventy times at intervals of three days between subculture."

A *cell strain* is a culture derived from a cell line by selecting for cells having specific properties or "markers." *Substrains* may also be defined. A *clone* is a population of cells derived from a single cell by cell division. This population will not remain. A *cloned strain or line* is one descended from a clone. The *cell generation time* is the time between successive cell division.

Cultures may be maintained either *in vitro* or *in vivo* (in a

living organism). *In vitro* techniques require the *explantation* (removal) of tissue from a source to a petri dish, flask, or test tube. In a *plasma clot culture,* the explanted tissue is placed in a drop of plasma, together with embryo extract, and the medium is allowed to clot. In a *Maitland culture,* minced tissue is placed in suspension in a culture medium. The literature distinguishes between *monolayer* (surface) and *suspension* (three-dimensional) cultures. Cells may also be transplanted into a living medium, such as an embryo, into a genetically similar host, or into a nonvascular area (*e.g.,* the anterior chamber of the eye) of a dissimilar host. *Ascites tumors* are transplantable tumors which may be made to grow as a suspension of free cells within the peritoneal cavity, and which often may also be cultured *in vitro.*

A problem in cell culturing is adventitious contamination. Viral contamination presents hazards to both the handlers and the recipients of the cultures, and also interferes with the use of the cultures in experimental work. Monkey kidney cell cultures are particularly prone to contamination by dangerous organisms, such as Marburg Agent (green monkey fever) and the SV40 virus. If this is a major problem with the class of cell cultures in question, the patent attorney may find it advisable to describe the measures taken to prevent contamination, such as vaccination of the source animals, sterilization, and aseptic handling of the cultures, and the antibiotic treatment protocol as well as the measures employed to test for contamination. In addition to viral contamination, bacteria, fungi, algae, mycoplasmas, and other cell lines (cross-contamination) may contaminate a culture. Contamination by dissimilar organisms is often apparent to the eye.

Balanced salt solutions (BSS) are used as short-term culture media. Most long term culture media contain *sera* obtained from living sources, either in untreated or inactivated form. *Defined media* include a large number of known chemical constitutents which, in combination, are expected to provide most, if not all, of the requirements for growth. The patent application should indicate a preferred medium, but the patent claims should not unduly be limited to the use of a particular medium (save in a *dependent* claim). One scientific authority makes an observation that may have pertinency to

the issue of the nonobviousness of a particular medium: "A percentage of sera are always toxic but autologous sera may be just as toxic as heterologous ones and the rule is that a serum is either toxic or non-toxic irrespective of its origin."

Cell lines should be characterized as fully as possible, *i.e.*, by both immunological testing and by karyotyping. Cell lines should also be tested for oncogenicity.

Even in the case of "cloned cell lines," it is important not to claim a "homogeneous" or "pure" culture:

> [C]hromosome mutations may introduce new cell types into the culture. Thus, prolonged cultivations may result in the emergence of cultures with quite different properties from those of the original cell lines. There is also the danger of . . . accidental contamination. . . .

When first describing a cell line, it is desirable that the application state:

1. Whether the tissue of origin was normal or neoplastic and, if neoplastic, whether benign or malignant;
2. Whether the tissue was adult or embryonic;
3. The animal species of origin;
4. The organ of origin;
5. The cell type (if known);
6. The designation (in the form of a series of not more than four letters indicating the laboratory of origin, followed by a series of numbers indicating the line, *e.g.*, NCL 123.

In characterizing the cell line it is desirable that the application discuss:

1. History;
2. Subculture number;
3. Culture medium;
4. Growth characteristics;
5. Absolute plating efficiency;
6. Morphology;
7. Frequency of cells with various chromosome numbers in a culture;

8. Karyotype(s) characteristics of the stem line(s);
9. Whether sterility tests for mycoplasmas, bacteria, and fungi have been done;
10. Whether the species of origin of the culture has been confirmed and the procedures by which this was done;
11. Virus susceptibility of a culture at a given subculture number.

A description of a cell strain should include the procedure of isolation, the morphological, biochemical, and genetic characteristics of the cells, the number of subcultures, the length of time since isolation, and a description of the cell line or primary cell culture from which it was isolated.

One final comment on nomenclature is that the term "transformation," as applied to prokaryotes such as bacteria, refers to the genetic recombination brought about by the introduction of purified DNA into a bacterium, while eukaryotic transformation is the alteration of a normal eukaryotic cell into a cancerous cell, with or without the introduction of exogenous DNA.

§ 5.06 "How-to-Make" Disclosures

[1] Organisms Isolated From Nature

In patents containing claims to fermentation methods employing newly isolated organisms, or to cultures of newly isolated organisms, it is desirable to set forth the geographic locale and microhabitat in which it was found, the techniques used to isolate, culture, and select the desired organisms, and the phenotypic characteristics for which the organism was selected. When the techniques employed are routine, such as replica plating, a brief description is all that is called for; where the technique is novel (such as culturation on a special substrate), more detail may be needed to educate the person skilled in the art.

[2] Organisms Obtained By Mutation and Selection

Many fermentation processes utilize organisms descended from mutants of naturally occurring strains. Patents claiming these processes, or the mutant strains themselves, present specific disclosure problems. A variety of radiological and chemical mutagens are utilized to induce genetic changes in exposed organisms. Preferably, the geneology of the organism in question should be traced. For each step in which a chemical mutagen is employed, the mutagen, the concentration employed, the temperature, the length of exposure, and other relevant parameters ought be disclosed. If radiation is used, the nature, intensity and duration of the radiation should be disclosed. If intermediate strains have been deposited in public culture collections the deposits should be identified. If, as is frequently the case, selection on special substrates, or by unusual physical conditions, is used in conjunction with mutagenic treatment, the selection techniques employed may be disclosed.

[3] Genetically Engineered Organisms

When the organism was transformed by a recombinant plasmid not already known to those skilled in the art, the construction of the recombinant plasmid should be described, step-by-step, sources of difficult-to-find starting materials or reagents should be identified with specific disclosure of materials, equipment, laboratory procedure, and process conditions; and the selection technique used to isolate the transformed organism disclosed. To the extent that they are known, the site of the cleavage, the sequence incorporated into the plasmid at that site, and the phenotypic characteristics imparted by the new plasmid might be revealed. When a plasmid is transferred to a host organism, the conditions necessary to assure transfer, the means employed (such as UV radiation) to stabilize normally incompatible plasmids in the host cell, the techniques used to select and culture the "engineered" cells, and the testing performed to confirm the distinctness, uniformity, and stability of the new strain should be disclosed.

[4] Is a Deposit a Complete "How-to-Make" Disclosure?

It might be argued that reexamination of soil samples and repetition of mutagenic techniques cannot guarantee that a particular strain will be obtained, while a subculture of a deposited strain is almost certain to provide a means for making more cells of that strain. Nonetheless, patent specifications have grown, not shrunk. One reason may be reluctance to rely on a deposit that could, conceivably, become "unavailable." A second reason is that the PTO is not equipped to examine culture deposits. Finally, the taxonomic description may be a necessary part of the "description" requirement, as distinct from the "enablement" requirement.

[5] Vaccines

In *Ex parte Szabo,* the Board recited some of the parameters which it felt the inventor of an anticancer vaccine should set forth in his specification:

> [T]he Examiner has pointed out many ambiguities and generalities in the specification which fails to set forth the specific conditions, proportions, and expedience required to obtain a hitherto unavailable anti-cancer vaccine. Not only are the details of the injection to produce the tumor, the amount of formaldehyde used in producing the vaccine, and the precise amount and kind of tumor tissue produced and employed, not specifically defined but the number of serial passages, the isolation and identification of the malign tumor, and complete details of conversion into the vaccine are lacking. Since the specific tumor is not defined, it cannot be determined what type of tumor the vaccine is to protect against. This rejection will, therefore, be sustained.[116]

On the other hand, in *Bankowski,* the CCPA held that claims are not "indefinite" because they "fail to specify a definite number of serial passages before attenuation occurs,"

[116] 136 U.S.P.Q. at 305.

when the tests for attenuation are "standardized and well known."[117]

§ 5.07 "How-to-Use" Disclosures

Article I, section 8, clause viii of the U.S. Constitution permits the issuance of patents only on "discoveries" which "promote the progress of the Useful Arts." 35 U.S.C. §101 states that an invention must be "useful" to be patentable. 35 U.S.C. §112 requires the *disclosure* of the "manner and process"of using the invention. These distinct but interwoven statutory requirements will be applied to typical biotechnology inventions in this section.

In *Hybritech, Inc. v. Monoclonal Antibodies,*[117.1] Judge Conti concluded that the specification taught the desired result—a sandwich assay using a monoclonal antibody—but not how to reach it. Conti summarized the teaching as, "you screen till you get two antibodies that work in an assay."

[1] Pathogenic Organisms

Only a "useful" invention is patentable. In 1817, Justice Story, riding the circuit in Massachusetts, instructed a jury that

> By useful invention, in the statute, is meant such a one as may be applied to some beneficial use in society, in contradistinction to an invention, which is injurious to the morals, the health, or the good order of society. . . . The law . . . does not look to the degree of utility; it simply requires, that it shall be capable of use, and that the use is such as sound morals and policy do not discountenance or prohibit.[118]

The Story test has been used to justify the denial of relief for

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[117] 138 U.S.P.Q. at 77.

[117.1] 227 USPQ 215 (N.D. Cal. 1985), rev'd, — USPQ — (Sept. 19, 1986).

[118] Bedfort v. Hunt, 1 Mason, 302, 3 Fed. Cas. 37 (No. 1217) (C.C.D. Mass. 1817).

patents on gambling machines[119] and "cure-all" devices.[120]

The Supreme Court has suggested that an invention which is unduly hazardous might not be considered "useful."

> Cases arise, also, even where the means described will accomplish the described result, when it cannot be held that the invention is useful if it appears that the operator, in using the

(*Text continued on page 5-71*)

[119] Reliance Novelty Co. v. Dworzek, 80 Fed. 902 (N.D. Cal. 1897).
[120] Mahler v. Animarium Co., 111 Fed. 530 (8th Cir. 1901).