Biotechnology and Pharmaceutical Commercialization Alliances: Their Structure and Implications for University Technology Transfer Offices

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ABSTRACT

Understanding biotechnology and pharmaceutical commercialization alliances in the context of several evolving business models has implications for university technology transfer offices (TTOs), as well as for public policymakers intending to promote biotechnology regionally. This chapter identifies the principal structural and economic elements of biotechnology and pharmaceutical commercialization alliances and the factors that influence partner selection for a particular alliance. The four characteristics of an alliance that generally define the allocation of value between an originator and a commercialization partner include stage of development, product supply, market opportunity, and scope. The chapter explains the types of economic terms typically found in biotechnology alliances and makes an empirical analysis of the economic terms from a sample of biotechnology alliances established between 1981 and 2000. Four specific alliances entered into at different stages of development are detailed as case studies. Several recommendations are provided for university TTOs, along with guidelines for drafting commercialization alliances.

1. INTRODUCTION

Since the 1940s, the pharmaceutical industry has largely followed a vertically integrated business model. This was the period when the first antibiotics were being introduced, leading to augmented manufacturing capabilities and, soon after, to the development of sales and marketing organizations. Over the next half century, the industry was sustained by the productivity of its medicinal chemists, who isolated natural products from microorganisms, plants, and animals, designed analogs and, sometimes, stumbled upon molecules with completely unexpected activity.

The emergence of biotechnology over the past several decades has transformed the drug business and ushered in a host of new participants and several novel business models. In the early 1980s, recombinant DNA and monoclonal antibody (mAb) technologies formed the basis of the first biotechnology business model, based on intellectual property (IP) relating to the isolation and/or production of novel compounds. Strong IP positions and difficult-to-master production methods would presumably allow biotechnology startups to initially partner with, and then compete against, established pharmaceutical companies. Assuming a series of novel products and increasingly favorable terms from partners, this model purported to be a blueprint for becoming a fully integrated pharmaceutical company, or FIPCO. Although most of the more than 100 biotechnology companies that went public prior to 1992 adopted this model, Amgen and Genentech are the only two companies from this era to have attained FIPCO characteristics to date.

By the early 1990s, two new biotechnology business models emerged. The first of these—a technology-platform model—was based on the

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use of novel techniques to discover new drugs and/or to increase the productivity of the drug discovery process. With a broad platform, a biotechnology company could perform fee-for-service research for multiple pharmaceutical partners while accumulating expertise to pursue programs for its own benefit. The earliest technology-platform companies developed novel assays for screening compounds. However, these screening companies depended on pharmaceutical partners for compounds to screen, and the terms were generally unattractive.

Other types of technology platforms soon emerged, including those using proprietary technologies to produce novel compounds from oligonucleotides (for example, antisense and gene therapy), lipids, carbohydrates, peptides, and combinatorial chemistry. With the sequencing of the human genome in the late 1990s, the technology-platform model broadened yet again to include companies that discover and validate novel drug targets. Joining them were companies making the instrumentation and software to handle the increased throughput of genomic materials, combinatorial libraries, and structural information.

These technology-platform companies had in common a fundamental reliance on corporate partners to pay for at least a portion of the platform's utilization and enhancement while adding to the biotech's infrastructure and expertise. Gilead Sciences and Vertex Pharmaceuticals are current examples of successful companies that have adopted the technology-platform business model.

A third business model to emerge in the early 1990s focused on diseases with significant unmet needs and specialized patient populations, such as cancer, dermatology, and neurodegenerative diseases. These companies sought to capture more of the value of innovative products by retaining commercial rights into clinical development—and potentially through to commercialization for selected market niches. Using this strategy, disease-focused companies attempted to create a balanced mix of discovery, development, and sometimes commercial-stage programs. However, the latter were typically less innovative products, used primarily to build a sales infrastructure and prepare the organization to eventually sell the more innovative products under development. Amylin and MedImmune are current examples of successful companies that have adopted the disease-focused business model.

By the mid-1990s, however, many of these disease-focused biotechnology companies had curtailed their drug-discovery programs owing to lack of investor interest. Similarly, technology-platform companies that had partnered their top drug-discovery programs to pharmaceutical companies came to view discovery research as an unattractive use of resources. With the consolidation of major pharmaceutical companies, these companies recognized that product-acquisition opportunities would emerge that were "flying below the radar" of ever larger drug companies. These companies turned their attention to in-licensing of approved and late-stage development compounds from pharmaceutical companies. Since most of these biotechnology companies focused on specialty markets that could be addressed with relatively small sales forces, such as cancer, anti-infectives, and dermatology, by the late 1990s investors came to view this group as a new business model, dubbed specialty pharma. Cephalon and Celgene are current examples of successful companies that have adopted the specialty-pharma business model.

The collective impact of these four biotechnology business models on the pharmaceutical industry has been to significantly enhance pharma's opportunity to obtain and divest compounds via licensing. This has eroded pharma's vertically integrated business model, to the point where most pharmaceutical companies now derive 25 to 50 percent of their product pipelines from external sources. In turn, pharmaceutical companies are the principal mode of commercialization for biotechnology products—of the 100 top-selling biotechnology drugs in 2005, 63 were partnered in development for at least some territories, as were eight of the ten top-selling biotechnology products in 2006.

Understanding biotechnology and pharmaceutical commercialization alliances in the context of these several evolving business models has implications for university technology transfer offices (TTOs), as well as for public policy-makers intending to promote biotechnology regionally.

First, under certain circumstances and with significant intellectual property and/or compounds to offer, TTOs may be in a position to play a role comparable to biotechnology companies as the licensor to a commercialization partner, whether that partner is a traditional pharmaceutical company, an emergent biotech, or a regional marketing company. Frequently, however, a TTO will be the upstream licensor of intellectual property and/or compounds that are bundled and developed by a biotechnology company before being sublicensed to a commercialization partner. In these instances, it may be important to understand, and perhaps influence, the likely terms of an eventual commercialization alliance in order to protect or augment the value contributed by the TTO's technology.

This chapter aims to identify the principal structural and economic elements of biotechnology and pharmaceutical commercialization alliances[1] and the factors that influence partner selection for a particular alliance. Section 2 describes four characteristics of an alliance that generally define the allocation of value between an originator and commercialization partner. Section 3 discusses the types of economic terms typically found in these alliances. Section 4 consists of an empirical analysis of the economic terms from a sample of biotechnology alliances established between 1981 and 2000. Section 5 describes four specific alliances entered into at different stages of development. Section 6 concludes with several recommendations to TTOs and guidelines for drafting commercialization alliances.

2. CHARACTERISTICS OF ALLIANCE-VALUE ALLOCATION

2.1 *Stages of development*

Drug development is broken into phases largely shaped by the regulatory requirements for new-drug approval. These are often referred to as discovery, lead, preclinical, investigational new drug (IND) filing, Phase I clinical trials, Phase II clinical trials, Phase III clinical trials, new drug application (NDA) filing, approval, and postapproval (Phase IV) clinical trials. Generally, the later in drug development an agreement is struck, the higher the share of consideration paid to the originator.[2] This industry practice reflects, in part, the cumulative investments of the parties to date, as well as the increased likelihood of getting the compound approved and on the market.

For example, as a compound successfully navigates various stages of drug development, there is less risk associated with the compound, and this increases the total value of the economic benefits that parties to an agreement will share. Other things being equal, a license negotiated later in a compound's development will bear a higher share of consideration paid to the originator than if the same license were negotiated earlier in the compound's development.

Conversely, a company in the early stages of developing a new compound faces substantial costs and risks as it invests in developing a new product that will probably fail. In order to have adequate incentive to take on those risks, the licensee of such a compound will demand a larger share of the expected sales or profits from the new product if it proves to be successful.

At the far end of the development spectrum, a company that has a fully developed product with a track record of increasing sales and substantial profit margins in one or more geographic markets faces relatively little risk as it attempts to expand the geographic reach of the product. All else being equal, the marketing partner of such a product will receive a much smaller share of the expected sales or profits from their efforts in expanding the geographic reach of the product.

In most instances, an originator has few nonreimbursable development obligations following the signing of a commercialization agreement at each stage of development. This reflects, in part, the commercialization partner's interest in controlling the pace and expenditures required for commercialization, as well as the originator's interest in retaining any prelaunch consideration paid for rights to the compound or technology. Exceptions occur, however, when the originator continues to have significant development obligations after signing. Such exceptions, generally associated with co-development or

distribution alliances, are discussed in Section 3.2 and typically would require that a higher share of consideration be paid to an originator.

2.2 *Product supply*

While many commercialization alliances simply provide a license to intellectual property and/or know-how associated with a compound or technology, some agreements additionally provide that the originator will undertake to supply all, or a portion, of a compound through commercialization. In such instances, the originator will incur greater costs and risks than in the absence of such supply obligations. As a result, alliances involving an obligation on the part of the originator to provide at least primary or bulk manufacturing of a compound through clinical development and commercial supply will typically increase the share of consideration paid to the originator.

2.3 *Market opportunity*

The gross margins of marketed pharmaceuticals have been high historically, often in the range of 75 to 95 percent. This is due to the benefits new products often bring compared to alternative treatments and the high costs and risks of development, combined with the significant regulatory and intellectual property barriers faced by new market entrants. With high gross margins and significant economies of scale in sales and distribution, top-selling pharmaceuticals (the so-called blockbusters) drive the overall profitability of major pharmaceutical companies. As a result, competition to access compounds with the greatest potential market size is intense. By contrast, compounds having relatively small market potential, such as those intended for niche markets, attract far less interest and less-favorable terms to the originator. Typically, therefore, the more attractive the market opportunity, the higher the share of consideration paid to the originator.

2.4 *Scope*

The scope of any particular commercialization alliance refers to a broad array of nonfinancial terms that either limit or broaden the rights conveyed under the agreement. Such terms might include whether the license granted is exclusive, semiexclusive, or nonexclusive, with greater exclusivity generally yielding a premium to the originator. Similarly, the larger and more economically attractive the territory, and the longer the duration of the alliance, the higher the share of consideration paid to the originator. This is because rights and any associated economic benefit would generally revert to the originator post-termination. Other things being equal, therefore, one would expect to see higher consideration paid to an originator for a long-term alliance than for one of limited duration entered into at the same time.

Should the alliance provide that one or more additional compounds or fields of use might be included as an option for the commercialization partner, such an element would also typically increase the share of consideration paid to the originator. Such an option potentially provides a broader pipeline to the commercialization partner, while minimizing this party's expenditure and development risk for the sustenance of such a pipeline. From the originator's viewpoint, granting a multicompound or multifield option to a commercialization partner would foreclose alternative arrangements, including forward integration by the originator itself, and so would normally require a premium as compared to a more limited scope.

3. TYPES OF ECONOMIC TERMS FOUND IN ALLIANCES

3.1 *Up-front payments*

Commercialization alliances typically will include an initial (so-called up-front) payment. The up-front payment may be due upon execution of the agreement and/or staged over a period of months or several years, but in the latter instance the payment obligation is noncancelable. This is not the case with development-milestone payments (see Section 3.3), wherein the payment obligation is contingent upon the achievement of predetermined events.

The up-front payment represents a "buy-in" by the commercialization partner, reflecting all or a portion of the originator's expense and risk in

bringing the compound or technology to its stage at signing. Discovery-stage deals may also entail an up-front payment, often described as a technology access fee.

For biotechnology companies, up-front payments are an important signal to investors that the partnered program is of high quality and that the commercialization alliance is being struck from a position of strength, rather than weakness. Such payments are generally nonrefundable, once paid, so their inclusion in an agreement will increase the risk-adjusted share of consideration paid to the originator.

3.2 *Reimbursement or apportionment of R&D costs after signing*

With respect to the research and development (R&D), manufacturing, and launch costs incurred during the course of bringing a pharmaceutical product to market after signing, commercialization alliances involving biotechnology companies are generally one of three types, although these types are sometimes blended or combined by product or territory.

Most biotechnology agreements are in the first category, wherein the commercialization partner takes over all costs after signing, including reimbursement of the originator's post-signing costs of continued R&D and manufacturing, as well as paying directly all other costs associated with the product's development, manufacture, regulatory approval, and launch. Such costs can be very substantial, and the risk of failure in development is largely borne by the commercialization partner.

Alliances that require reimbursement of the originator's R&D expenses after signing typically require that the originator provide a specified number of full-time equivalent scientists (FTEs) per year for one to five years, along with quarterly reimbursement at a maximum fixed rate per FTE. The originator is at risk for cost overruns, however. For example, if the FTE reimbursement rate is US$250,000 per FTE per year for ten FTEs, and the actual annual R&D expenditure by the originator is US$2.7 million, only US$2.5 million is reimbursed. Conversely, if the actual R&D expenditure by the originator is US$2.2 million, a credit of US$300,000 is carried forward to the next year's R&D reimbursement.

In the second category are alliances with regard to which both parties share costs (so-called co-development). In co-development alliances, up-front and milestone payments are generally used to adjust the parties' interests in the R&D program, and subsequent development and other costs are shared. In a typical co-development alliance, an originator may possess only a portion of the capability or resources to complete clinical development, commercial supply, and/or launch of a compound. Such alliances tend to have profit splits during the post-commercialization period, reflecting the parties' respective interests in the product. While the percentage or level of cost sharing varies by agreement, such alliances usually provide a mechanism whereby one party may reimburse excess costs incurred by the other, often at a premium.

With respect to the third category of alliances, the originator continues to incur all or substantially all development, manufacturing, and regulatory costs after signing, but the commercialization partner bears some or all launch costs and ongoing sales and marketing expense. Alliances of this third type are generally described as distribution agreements, if the originator relinquishes all sales and marketing responsibilities, or else co-promotion or co-marketing alliances, if both parties are involved in commercialization of the product.

Although a commercialization partner may commit substantial resources to a biotechnology alliance in the form of FTE reimbursements, such payments are not enriching to the originator, unlike up-front and development-milestone payments. Other things being equal, therefore, the share of consideration paid to an originator will be lowest for the type of alliance with respect to which all post-signing costs are borne by the commercialization partner, in the mid-range for co-development deals, and highest for distribution-type agreements. This industry practice reflects, in part, the total expected investments of the parties through product launch, as well as the proportion of risk borne by the commercialization partner that the compound will fail in development.

3.3 *Development-milestone payments*

Most biotechnology alliances involve contingent (so-called development milestone) payments that track the progression of the R&D program through the sequential stages of development achieved after signing of the agreement.

For an early-stage alliance, typical development milestones might be technical feasibility, patent issuance, lead compound designation, IND filing, start of Phase II clinical trials, start of Phase III clinical trials, NDA filing, and first regulatory approval. For a late-stage alliance, development milestones might track individual medical indications or market entry into major markets such as the United States, Japan, or the European Union.

Like up-front payments, development-milestone payments are generally nonrefundable once paid, so their inclusion in an alliance will increase the risk-adjusted share of consideration paid to the originator.

3.4 *Equity investments*

Approximately 15 to 20 percent of biotechnology alliances include one or more minority-equity investments by the commercialization partner in the biotechnology's equity as a component of the agreement. Such equity purchases usually involve newly issued shares, so the investment proceeds are available for use by the company. If the securities of the biotechnology company are publicly traded at the time of such an investment, the commercialization partner may purchase the shares for the fair market value (FMV) or may agree to pay a specified premium over FMV at the time of purchase. Shares purchased in nonpublic biotechnology companies, as part of an alliance, are typically purchased at a 20 to 50 percent premium over the FMV of shares sold in the most recent prior round of share issuance.

Unlike up-front and development-milestone payments, however, equity investments involve an exchange of capital for an ownership interest, so the extent of enrichment to the originator, if any, depends on the premium paid by the commercialization partner as compared to the FMV of the shares.

3.5 *Post-commercialization payments*

Post-commercialization payments usually consist of one or more of five types: (1) royalties on product sales paid by the commercialization partner to the originator; (2) payments for manufactured goods (so-called transfer prices) paid by the commercialization partner to the originator as supplier of bulk or final product; (3) one-time payments on achievement of post-commercialization milestones (so-called sales-threshold payments) paid by the commercialization partner to the originator; (4) a net profit allocation between the parties (so-called profit splits); or (5) marketing fees paid by the originator to the commercialization partner.

3.5.1 *Royalty rates*

The royalty rate paid by the commercialization partner to the product's originator commonly increases with greater product sales. For example, an alliance will specify a base royalty rate that will pertain to annual (or cumulative) product sales up to a certain sales level. Above this level, a higher royalty rate will apply until a second sales threshold is met, at which point a still higher rate will pertain, and so on, through three to five different *royalty tiers*. This practice is consistent with the industry's preference and competition for blockbusters over products for niche markets.

3.5.2 *Transfer prices*

Transfer prices for bulk or final product supplied by the originator to the commercialization partner are typically specified via one of three approaches: as cost plus a specified margin, as a specified price per unit, or as a percentage of the product's selling price. Since commercialization agreements are usually silent on the actual or anticipated cost of manufacture, it is difficult to ascertain the profit contribution from the transfer price. Of the three approaches, agreements that specify a transfer price as a percentage of the product's selling price are most informative, insofar as general industry practice is to attempt to price a new product such that the cost of manufacture is typically 5–10% of the product's selling price. This implies that a transfer price in excess of 10% of the product's

selling price is usually enriching to the extent of the excess.

3.5.3 *Sales-threshold payments*

Sales-threshold payments may be paid to a product's originator as one-time events. As with development-milestone payments, sales-threshold payments are typically nonrefundable.

3.5.4 *Profit splits*

Profit splits may vary by time period, or licensed region, and may or may not be inclusive of other types of payments specified by the alliance. In co-development deals, following the buy-in payments that adjust the parties' positions for preexisting risk taken and preexisting value created, profit splits tend to track the level of each party's clinical development expenditure after signing—for example, a party paying 40 percent of development costs would be entitled to 40 percent of net profits. In such agreements, the parties precisely define the development, manufacturing, regulatory, launch, and marketing expenditures that are deemed "allowable" for purposes of reaching or adjusting the agreed-upon profit split.

3.5.5 *Marketing fees*

Marketing fees paid by the product's originator to the commercialization partner generally apply only in the event that the originator is responsible for booking the sale of the product, as is sometimes the case in distribution and co-promotion alliances. Such fees are often termed royalties, except that the originator pays them to the marketing or co-promotion partner. In such agreements, there may be a static or moving level of sales (a so-called baseline) below which the commercialization partner is not compensated, reflecting the originator's capability to sell the product in the absence of the marketing party's assistance.

4. EMPIRICAL ANALYSIS OF THE ECONOMIC TERMS OF ALLIANCES

4.1 *Sample selection*

Biotechnology companies that are publicly traded on stock exchanges in the United States are required by the U.S. Securities and Exchange Commission (SEC) to file material documents. Biotechnology companies have historically interpreted this requirement conservatively and often file their contracts involving alliances with commercialization partners, as well as upstream licenses with universities and other technology providers.

Recombinant Capital's (Recap) Alliances Database contains copies of more than 20,000 research, development, license, supply, co-development, distribution, and similar alliances established since 1973. Recap analysts collected these agreements from SEC filings, predominantly by biotechnology companies, as material disclosures. In aggregate, Recap's analysts have tracked the SEC filings of approximately 1,400 companies, the vast majority of which consist of biotechnology companies engaged in pharmaceutical discovery and development.

Companies can and usually do request confidential treatment for sensitive business information in these alliances, including royalty rates and other payments, but such grants of confidentiality are time limited. Recap's analysts first collect these SEC-filed agreements and then attempt to secure unredacted copies through use of Freedom of Information Act (FOIA) requests made to the SEC.

Figure 1 shows the number of alliances selected for inclusion in a sample of development-stage R&D alliances entered into between 1981 and 2000 by the 20 most active biotechnology and pharmaceutical commercialization partners. The "Top 20" commercialization partners were selected on the basis of their total number of biotechnology alliances over the past three decades, including alliances established by commercialization partners subsequently acquired by one of the Top 20. For example, Novartis has in aggregate more than 700 biotechnology alliances, including those entered into by Ciba-Geigy and Sandoz. Thirty-two Novartis alliances are included in the sample. These are all of the unredacted, development-stage R&D alliances involving Novartis as the commercialization partner in Recap's Alliances Database as of February 2006. A similar process was followed for the other 19 most active com-

mercialization partners of biotechnology R&D programs, resulting in a final sample of 259 unredacted development-stage R&D alliances.

4.2 *Prelaunch payments*

Figures 2 and 3 show the average and median prelaunch payments, respectively, for biotechnology alliances established by the Top 20 commercialization partners between 1981 and 2000. The alliances are grouped by the stage of development at signing, where *mid stage* refers to alliances signed at the preclinical or Phase I clinical trials stages, and *late stage* refers to alliances signed at the stages of Phase II or III clinical trials or NDA filing.

The data in Figures 2 and 3 supports the observation that the later in drug development an agreement is struck, the higher the amount of consideration paid to the originator. For example, median prelaunch payments to originators of mid stage alliances were US$21.8 million, but US$30.7 million for late-stage deals. While median prelaunch payments for discovery-stage alliances exceed those for lead-stage deals, the largest component of such discovery-stage payments are for R&D reimbursement, and so are not enriching to the originator.

4.3 *Royalty and other post-commercialization payments*

Figures 4 and 5 show the average and median effective royalty rates (that is, rates adjusted for royalty tiers) and maximum royalty rates (which include consideration from transfer prices), respectively. This data also supports the observation that the later in drug development an agreement is struck, the higher the amount of consideration paid to the originator. For example, the data shows that the median effective royalty rate promised to a product's originator in the event of annual sales of US$500 million was seven percent for discovery-stage alliances, eight percent for lead stage, 9.6 percent for middle stage and 15 percent for late stage. Likewise, on average, the effective royalty rate increases with greater annual sales of the product.

When transfer prices and the maximum royalty rate are combined, the analysis shows that the median compensation to a product's originator increases to eight percent for discovery-stage alliances, 10 percent for lead stage, 15 percent for middle stage and 20 percent for late stage. However, none of these average or median post-commercialization payments includes the effect of the 44 alliances that involve profit splits, since this form of consideration is not directly comparable to royalties.

5. ILLUSTRATIVE INSTANCES OF ALLIANCES AT SEVERAL STAGES

5.1 *Discovery-stage alliance*

In May 1997, Eli Lilly and MegaBios (later merged to become Valentis) signed a worldwide alliance to develop gene-therapy products to treat cancer. At the time of commencement, MegaBios had a technology platform for gene therapy, but no lead compounds had yet been developed in the field of cancer.

As shown in Figure 6, the technology originator, MegaBios, received no up-front payment, but Lilly committed to US$7 million in FTE and manufacturing-process payments over two years. Lilly was responsible for all other development, clinical, manufacturing, and regulatory expenses. Development-milestone payments totaled US$27.5 million, consisting principally of amounts associated with the clinical development of compounds to treat ovarian and breast cancer. Lilly purchased US$3 million of MegaBios' equity at signing. In the post-commercialization period, Lilly committed to paying tiered royalties to MegaBios, increasing with annual net sales from six to 13 percent. Such royalties would be due for either the life of any issued patents, or the seven-year-period following product launch, whichever was longer, on a country-by-country basis, after which Lilly would retain a paid-up license.

5.2 *Lead-stage alliance*

In December 2000, Novartis and Celgene signed a worldwide alliance to develop treatments for osteoporosis. At the time of commencement,

Celgene had several lead compounds based on selective estrogen-receptor modulators (SERMs).

As shown in Figure 7, the compound originator, Celgene, received a US$10 million up-front payment, plus US$4 million in FTE payments over two years. Novartis was responsible for all development, clinical, manufacturing, and regulatory expenses. Development-milestone payments totaled US$30 million. There was no equity investment. In the post-commercialization period, Novartis committed to paying to Celgene tiered royalties that increased with annual net sales from ten to 12 percent. Such royalties would be due for either the life of any issued patents or the ten-year–period following product launch, whichever was longer, on a country-by-country basis, after which Novartis would retain a paid-up license.

5.3 *Midstage alliance*

In November 1997, Eli Lilly and Ligand Pharmaceuticals signed a co-development, license, and co-promotion alliance for worldwide rights to RXR retinoids for the treatment of diabetes. At the time the parties entered into the alliance, several of Ligand's RXR compounds were undergoing preclinical testing.

As shown in Figure 8, the compound originator, Ligand, received a US$12.5 million up-front payment. There were US$49 million in FTE payments over five years, and Lilly was responsible for all development, clinical, manufacturing, and regulatory expenses. Development-milestone payments totaled US$73 million, divided among six separate types of compounds and ranging from US$6.5 million to US$14 million per compound. There was no equity investment. In the post-commercialization period, Lilly committed to pay tiered royalties to Ligand, increasing with annual net sales and varying by type of compound from five to 12 percent of net sales. Such royalties would be due for either the life of any issued patents or the ten-year–period following product launch, whichever was longer, on a country-by-country basis, after which Lilly would retain a paid-up license.

5.4 *Late-stage alliance*

In December 1993, Burroughs Wellcome (later acquired by GlaxoSmithKline) and Centocor (later acquired by Johnson & Johnson) signed a co-development, license, distribution, and supply alliance for rights outside of Asia to Panorex, a monoclonal antibody for use as adjuvant therapy for the treatment of colon and colorectal cancers. When the parties entered into the alliance, Panorex was undergoing Phase III clinical trials.

As shown in Figure 9, the compound originator, Centocor, received US$19 million in up-front payments, US$10 million on signing, plus an additional US$9 million when the territory was expanded to include Asia in 1994. There were no FTE payments, and Centocor was responsible for the completion of Phase III trials. Development-milestone payments totaled US$47.5 million. Wellcome purchased US$23.5 million of Centocor's equity—US$20 million on signing plus an additional US$3.5 million when the territory was expanded. In the postcommercialization period, Centocor committed to paying a transfer price of 50 percent on the first US$200 million in annual net sales, then 40 percent on the next US$200 million, then 35 percent on net sales greater than US$400 million. The term of the agreement would be for the duration of product supply by Centocor.

6. RECOMMENDATIONS AND CONCLUSIONS

Although lacking vendor booths or trading floors, a robust marketplace exists for the exchange of discoveries, intellectual property, and services related to the development and commercialization of products in the life sciences. After several decades of trial and error, biotechnology and pharmaceutical companies have settled upon the principal structural and economic elements in the identification, creation, and sharing of value in this marketplace.

As the authors have noted in previous publications,[3] the economic stakes of university TTOs, primarily in the United States and Great Britain, as upstream licensors and enablers in this marketplace are also well established.

New entrants to this marketplace, especially university TTOs representing institutions in territories other than the United States, Great Britain and, to a lesser extent, Canada, Germany, and France, have an opportunity to join this marketplace with knowledge of its inner workings. At a minimum, new entrants should be in a position to undertake programs of technology or compound development with the knowledge that downstream events that would be likely to be perceived as value creating. Conversely, should these institutions be able to assemble significant intellectual property and/or compounds to offer, such TTOs may choose to supplant biotechnology companies and take it upon themselves to deal directly with prospective commercialization partners, be they traditional pharmaceutical companies or regional marketing firms.

This chapter has attempted to identify the principal structural and economic elements of biotechnology alliances and the factors that influence their selection. In the interest of brevity, only the most important structural terms have been discussed. Other provisions that are usually addressed in these alliances are noted in Box 1. ■

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1 Since this chapter is principally concerned with development-stage biotechnology R&D programs, the term *alliance* is used to describe generally the relationship between the parties. Such relationships typically involve a license and/or sublicense, as well as other rights and responsibilities of the parties. Except where specifically noted, the terms alliance, agreement, deal, partnership and license are used interchangeably in this chapter.

2 In this chapter the term *originator* refers to one who licenses (a licensor) a compound or technology to a commercialization partner. When the originator is a biotechnology company, the conveyed intellectual property may include one or more sublicenses of university-derived intellectual property.

3 Edwards M, F Murray and R Yu. 2003. *Value creation and sharing among universities, biotechnology and pharma. Nat. Biotechnol.* 21: 618–24. Also Edwards M, F Murray and R Yu. 2006. *Gold in the ivory tower: equity rewards of outlicensing. Nat. Biotechnol.* 24: 509–15.

Box 1: Guidelines for Drafting Licensing Deals

I. Research & Development:

A. Scope of Agreement
- Effective date
- Nature of the collaboration
- Field of research
- Method of joint development
- Identify key research terms

B. Research Period
- Term of sponsored research program (if any)
- Note possible extensions

C. Reimbursement Basis or Cost Sharing
- R&D payments (amount and type)
- FTE (full time equivalent) reimbursement rates

D. Upfront Payment
- Payment(s) upon signing (or calendar based)
- Technology access fees
- Credit given for option payments received prior to signing?

E. Benchmark Amounts
- Pre-commercial milestones (i.e., IND, NDA)
- Sales-based milestones
- Creditable against royalties? Credit limitations

F. Technology Acquisition Fees
Applicable for asset purchases & assignments

G. Payment Schedule
i.e., quarterly

H. Budgets
- Approved in advance?
- Are budgets appended to agreement?

I. Reimbursement Start Date
- Typically on signing

J. Regulatory Filings
- Who controls and pays for regulatory filings?
- Do responsibilities vary by stage, territory or product?

K. Specific Capital Requirements
- Capital equipment paid for by licensee
- If special equipment is purchased, who keeps it upon termination?
- Transfer of materials

L. Patent Ownership
- Know how, patents, IP, material ownership
- Who owns the patent rights?
- Joint inventions

M. Patent Filing Costs
Who pays filing, prosecution, maintenance costs?

N. Patent Defense Costs
- Who has first right to sue third-party infringers?
- Who pays for the patent defense costs?
- Allocation of recovery from such action

O. Third-Party Patents
- Who has first right to respond to 3rd party suits for infringement?
- If royalties due to third-party, typically 50% of such payments are creditable against 50% of amounts due to licensor

P. Non-compete Provision
Each party can or cannot compete in the Field

Q. Publications
- Approval procedure
- Licensee may request delay for patent prosecution

R. Core Technology
- Who owns core technologies?
- Visiting scientists, retained rights, etc.

S. Cancellation Amounts
- Any amount due in the event of termination?
- May include wind-down of sponsored R&D

T. Termination
Termination rights include (i) mutual, (ii) licensor, (iii) licensee.

(Continued on Next Page)

Box 1 (continued)

U. Product Reversion
- Who keeps product rights after termination?
- Royalties due to the non-terminating party?

V. Change in Control
- Typically "not assignable without the prior written consent of the other party"
- Are co-promotion and/or supply rights lost in the event of change in control?

W. Options/Other
- Additional research options (i.e., added fields, products)
- Right of first refusal (ROFR) to other research

II. Product License

A. License Holder/Type
- License grant(s), including make, have made
- Exclusive, nonexclusive or semiexclusive (note limitations)
- Commercialization rights (right to sublicense?)
- Is know-how included?

B. Product Field of Use
- Define product field of use
- Does IP have utility beyond scope of license?

C. Territory Splits
- Define territory; what are major markets?
- Are there territory options for inclusion/exclusion?

D. Royalty Rate
- Royalty rates and/or profit splits
- Adjustments under certain conditions (type of IP protection, gross margins, competition)
- Note limitations to royalty offsets for third party patents and/or credits for prior payments

E. Right to Sublicense
- Is prior consent required?
- Impact on royalty rates
- Pass-through payments to upstream licensor

F. Term/Patent Life
- How long does license agreement last?
- Term of royalty obligations ("life of license") ("continue until the last to expire patent....")
- What happens to exclusivity upon expiration of royalty obligations?
- Note any rights of licensee to sell product after expiration (subject to royalty?)

G. License Maintenance and Diligence
- Annual license maintanence fees and/or minimum royalties
- Due diligence (e.g., IND, Phase I, NDA filing by certain dates, "use reasonable efforts to develop," etc.)
- Terminate or non-exclusive for non-performance

H. Royalty Accounting
- Define "net sales" or equivalent
- Other defined terms for royalty calculations?
- Audit provisions
- Late-payment fees, penalties, interest

I. Patent-Royalty Tie-In
- Are royalty rates tied to the granting of patents?
- Step-down rates for know-how only
- Treatment of pending patents by country if product launched prior to patent issuance

J. Options/Other
- Co-promotion rights, if any
- Commercialization options for related products

(Continued on Next Page)

Box 1 (continued)

III. Manufacturing & Supply:

A. Right Holder/Type
- Who has the right to manufacture?
- ID on packaging
- What about second source or back-up supply?

B. Bulk/Dosage Form
- Bulk or final form
- Does this change by stage of development or scale?

C. Territory
Supply territory

D. Reimbursement Basis
- Define basis of payment (e.g., fixed price per unit, manufacturing cost plus markup, percentage of net sales)
- If transfer price, inclusive/exclusive of royalty?

E. Process Development Terms
- Terms with respect to manufacturing process development
- Who is responsible for manufacturing program?
- Timing of orders and delivery commitments
- Ownership of production equipment

F. Clinical Use Manufacturing
- Who supplies compound for clinical trials?
- Reimbursement basis for clinical supplies

G. Shipment Terms
- FOB (freight on board) place of shipment
- Standard cost for bulk?
- Terms for replacement of non-spec shipments

H. Financing
- Is licensee providing financial arrangements for Licensor to meet supply obligations?

I. Escape Clause
- If Licensor cannot satisfy supply requirements, right of licensee to make or have made such quantities
- Trigger event(s) of default
- Temporary or permanent?
- Product/territory specific?

J. Product Liability
- Indemnification, including standard and limitations
- Insurance requirements

K. Options/Other
- Supply options
- Options to repurchase product

IV. Collaboration Management:

A. Representation
- Governance of program
- Committees established between the parties
- Make-up of committee, mandates

B. Quorum
Any specific quorum?

C. Basis of Actions
Unanimous vote or majority rule?

D. Meetings
How often does the committee meet?

E. Disagreements
- Dispute resolution (escalation procedure)
- Arbitration or mediation and applicable rules
- Appeal?

F. Buyout/Windup
- Applicable for JV arrangements
- Purchase option(s) in the event of termination/ expiration of the JV

G. Options/Other
- Any other terms relating to the governance of collaboration

Box 1 (continued)

V. Equity Investment:

A. Type of Security
Number and type of shares purchased

B. Pricing
Price paid

C. Board Seat
- Board seats granted?
- Specific individual or named by party when relinquished

D. Research Tie-Ins
If proceeds must be used for R&D

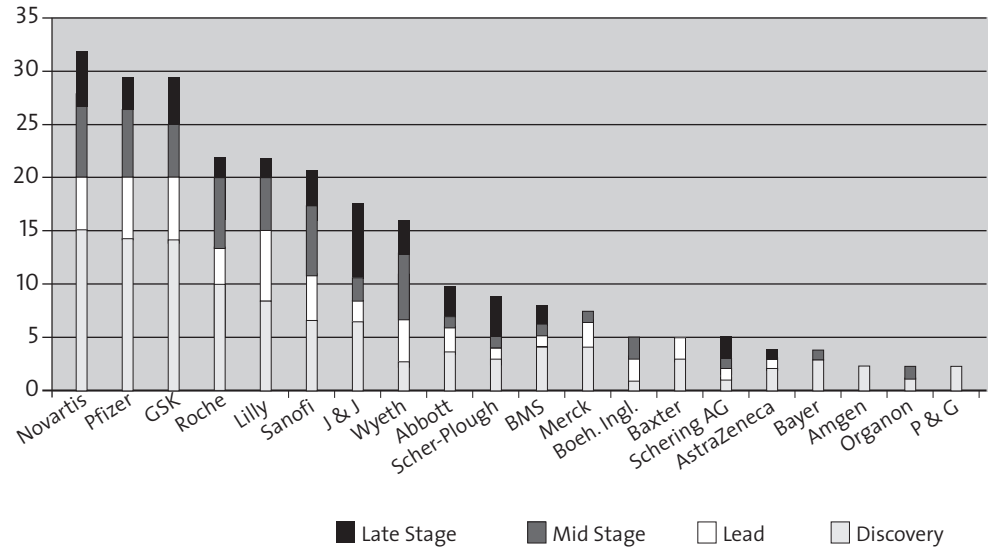
E. Options & Rights
- Additional equity purchases
- Convertible loans
- Rights/obligations of purchaser:
  - registration rights
  - anti-dilution protection
  - sales restrictions
  - standstill
  - market standoff
  - right of first refusal

VI. Signatories:

A. For University or Biotech Co. (R&D Co.)
Name, title, company

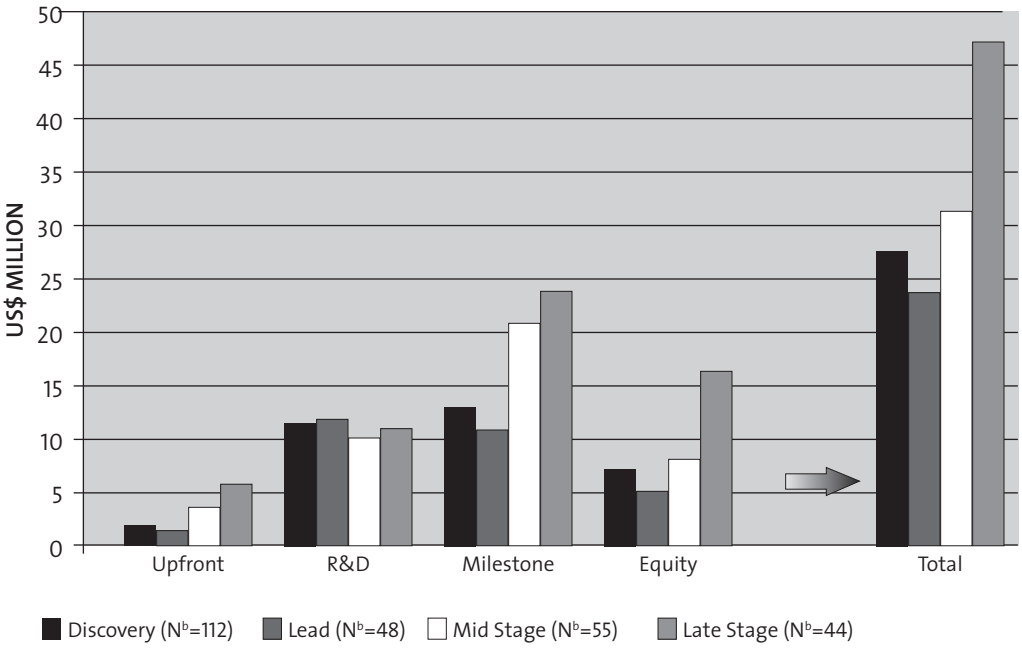
B. For Biotech or Drug Co. (Client Co.)
Name, title, company

Figure 1: Unredacted Biotech Alliances of the Top 20 Pharmas (259 Alliances Signed between 1981 and 2000, by Stage at Signing)



Source: Recombinant Capital www.recap.com

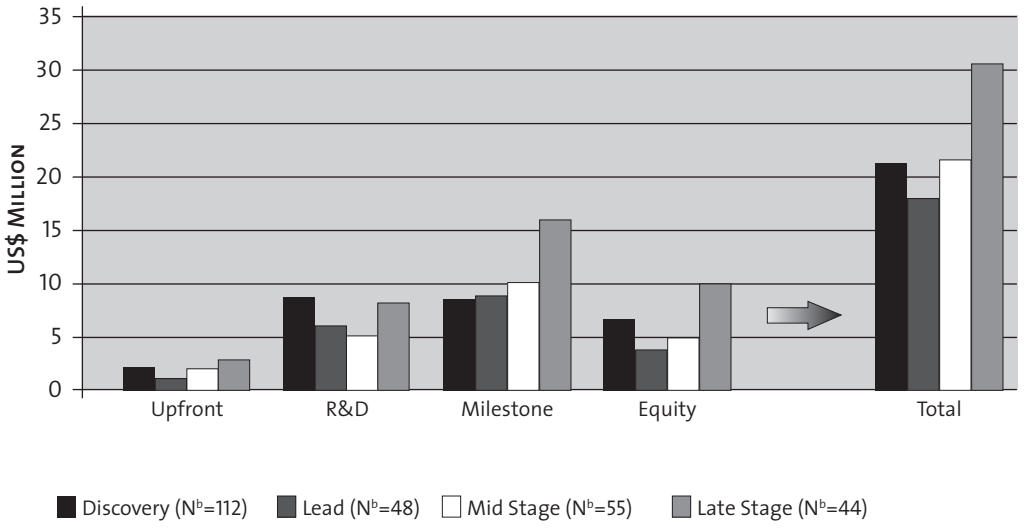
Figure 2: Average Top-20 Prelaunch Payments[a] (between 1981 and 2000, by Stage at Signing of Alliance)



a Average nonzero payments, by type
b Number of alliances

Source: Recombinant Capital www.recap.com

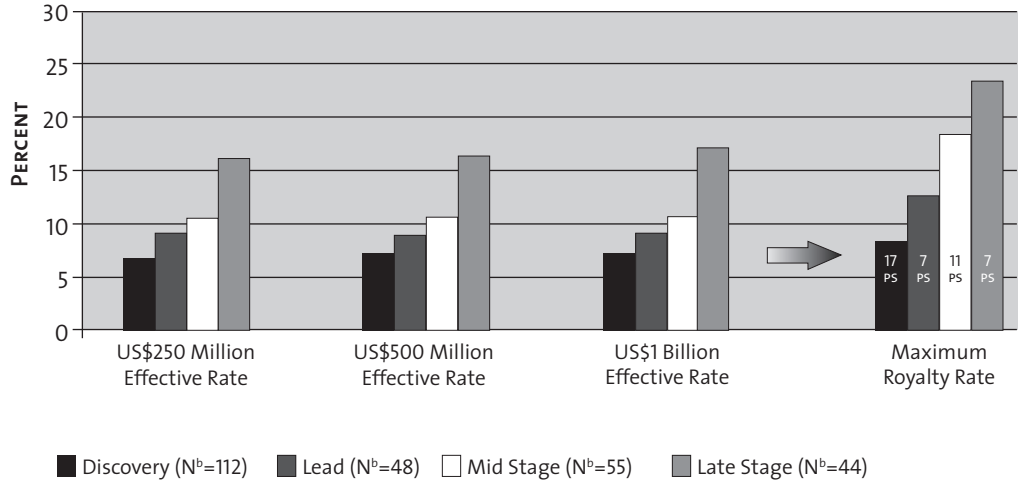
Figure 3: Median Top-20 Prelaunch Payments[a] (between 1981 and 2000, by Stage at Signing of Alliance)



a Median nonzero payments, by type
b Number of alliances

Source: Recombinant Capital www.recap.com.

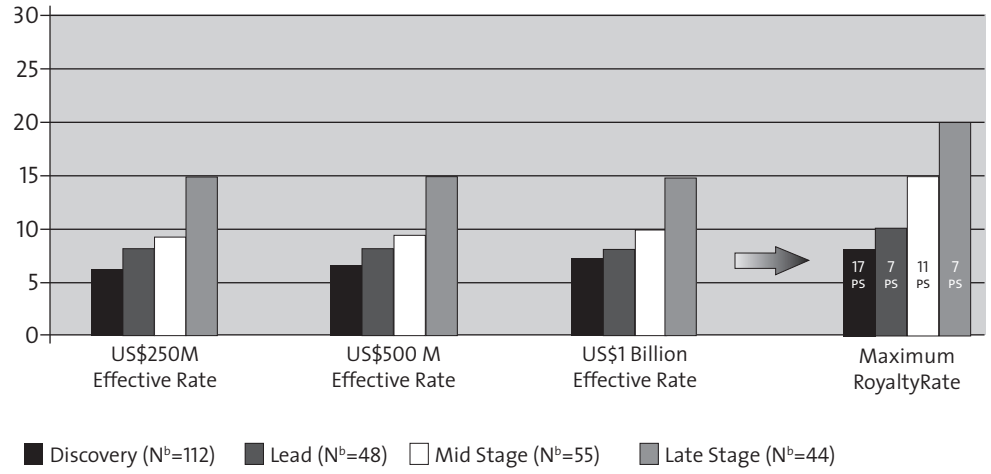
Figure 4: Average Royalty Payments by the Top-20 Pharmas (between 1981 and 2000, by Stage at Signing of Alliance)



a Maximum royalty includes transfer prices but not profit splits
b Number of alliances

Source: Recombinant Capital www.recap.com.

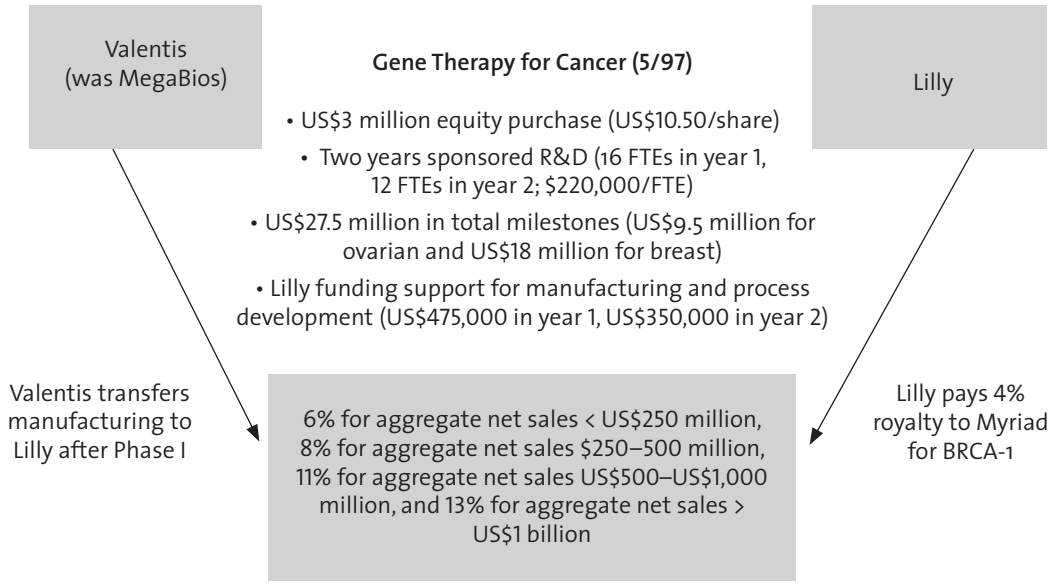
Figure 5: Median Royalty Payments by the Top-20 Pharmas (between 1981 and 2000, by Stage at Signing of Alliance)



a Maximum royalty includes transfer prices but not profit splits
b Number of alliances

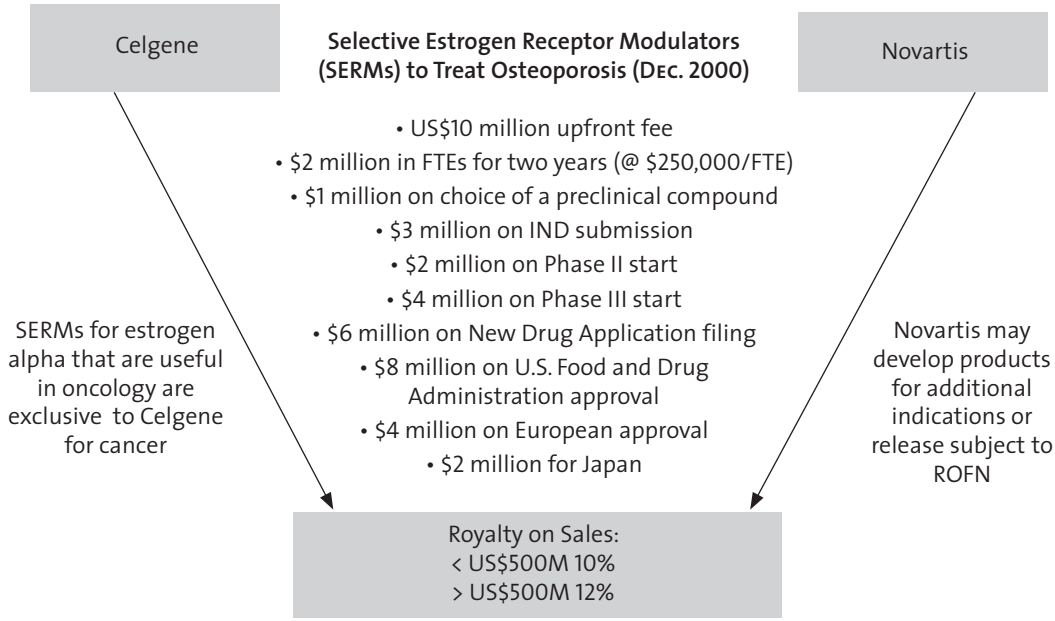
Source: Recombinant Capital www.recap.com.

Figure 6: An Illustrative Discovery-Stage Alliance



Source: Recombinant Capital www.recap.com.

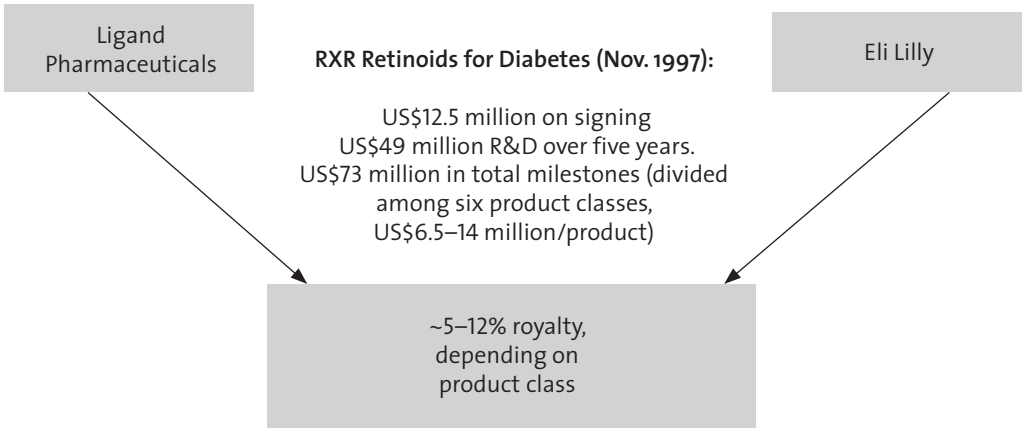
Figure 7: An Illustrative Lead-Stage Alliance (all figures in U.S. dollars)



Celgene has the right to partner SERMs for estrogen alpha for cardiovascular indications based on activity in its cardiovascular assay.

Source: Recombinant Capital www.recap.com.

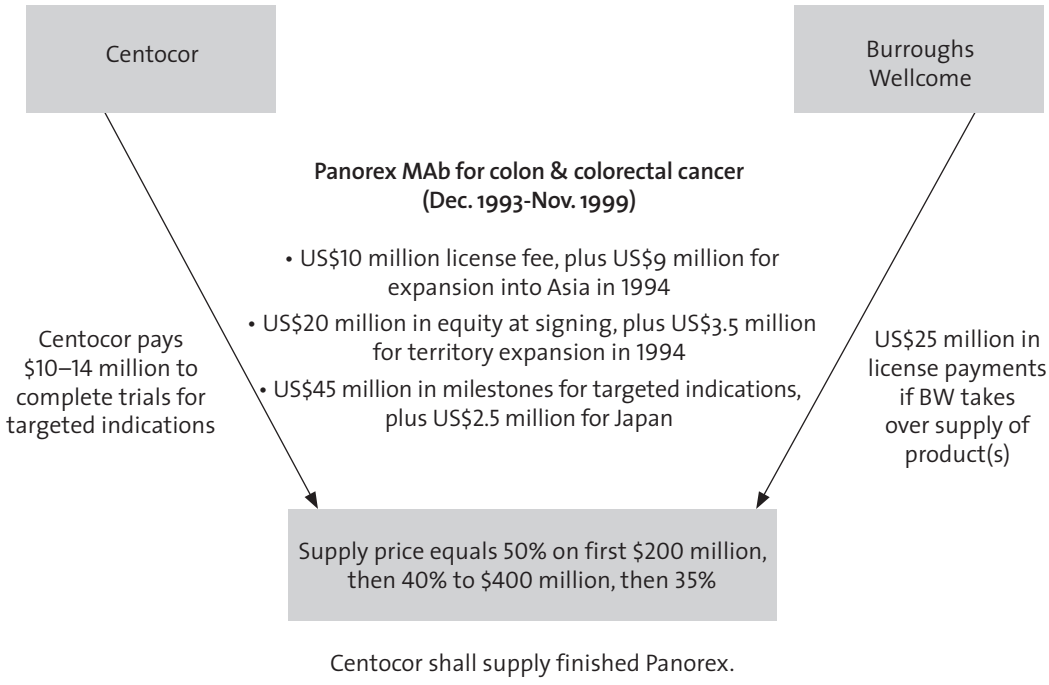
Figure 8: An Illustrative Mid-Stage Alliance



Ligand has the option to co-develop SERM oncology product, by paying 33% of development costs after Phase II, and for one-third higher royalty on cancer sales.

Source: Recombinant Capital www.recap.com.

Figure 9: An Illustrative, Late-Stage Alliance



Source: Recombinant Capital www.recap.com.