

State of the Art In Biotechnology Alliances

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Structuring effective alliances requires strategic thinking, not simply developing a capstone or firming.

As in no other industry, biotechnology companies thrive on collaboration. For most young companies, taking a new pharmaceutical product from discovery to market, particularly in the first time, is too great of an undertaking to accomplish alone. Institutional pharmaceutical companies have the necessary resources, but they recognize that the biotechnology industry is increasingly more profitable in new drug discovery. The result is that, over time, their own, those industries are joining forces to increase the efficiency of bringing new drugs to market.

Biotech and pharmaceutical companies have always formed alliances. As the industry has matured, however, it has become more sophisticated in how it structures those alliances. In the early days, biotech companies principally focused on acquiring cash and reliability. But, as the focus comes to realize biotechnology's significance and that a great portion of new drug discoveries will come from biotech companies, both biotech companies and their pharmaceutical-company counterparts are becoming more creative in structuring alliances to optimize the partnership value they add. In many cases, the result is less cash up front for the biotech company and a greater share of responsibility and profits, in what some call "50/50 deals" or "true alliances."

OVERVIEW OF ALLIANCE STRATEGIES

Today, the biotech industry is rethinking its business and reaching for new models. It is realizing that,

with the purchasing power for pharmaceuticals likely to become concentrated in a much smaller number of buyers and with increased competition and pressures to reduce costs, there will likely be an overcapacity of pharmaceutical sales forces. As a result, companies are starting to see that the objective of becoming a "fully integrated biopharmaceutical company" may not be optimal. Rather, many are re-evaluating, on the particular strategic value they can add, and designing their business models to best leverage that value component. This reevaluating reflects itself largely in their alliances with pharmaceutical companies.

One of the most intriguing aspects of strategic collaborations is that no two are alike. At most, they share a common framework—a series of "variables" for which one sets the values. First, there are the "strategic" variables that allocate markets and operations between the parties. Second, there are "financial" variables that define the expense and compensation aspects of the relationship. Third, is the "choice of entity" which defines whether the alliance will be directly between the partners or through a separate joint venture company.

How a company positions these variables in its alliances will define its business model for years to come. The key for both parties is to think strategically about where they want to be, focus on that strategy, and design the relationship accordingly.

Strategic Variables

The principal strategic variables are those that define each partner's markets and operations, geographic territories, field of use, manufacturing rights, degree of exclusivity and right to control clinical development. These five aspects of a particular business will be allocated in every alliance.

Geographic Territory. One of the classic alliance strategies is to allocate markets geographically, granting each partner exclusive rights in one or more of the major markets. Because most biotech companies wish to retain the United States, this typically involves licensing Japanese biotech to the pharmaceutical partner.

Regional alliances are highly synergistic. The pharmaceutical company requires a product with less time, expense and risk than it might otherwise incur, and the biotech company gains access to a territory without having to build its own infrastructure there.

Beyond training significant markets for itself, and ensuring the funding necessary to exploit those markets, the biotech company may well receive clinical and preclinical data that reduce its need to undertake studies and/or reduce the risk of funding those studies. In fact, dividing responsibility for clinical trials reduces the cost and risk of the project for both companies. Further, each company gains the other's strategic influence in any successful alliance—learning from its partner what the partner does best.

In addition, many times the type of partner that will accept a regional territory may itself have products for which it will need a partner outside its own territory. Even if there is no regional exchange of products in the initial agreement, one may later arise as the relationship develops. Thus, a bilateral exchange of products results, and the synergy multiplies.

Ultimately, the pharmaceutical business is increasingly a global one, and leading pharmaceutical companies increasingly insist on world

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wide rights. Opportunities for regional alliances will remain, but probably will involve smaller players. As a result, biotech companies will likely find themselves granting worldwide marketing rights. That means they will have to concentrate more on the other strategic variables to carve out markets and/or operations in their own.

Field of Use. Dividing markets by fields of use is a functional principle of strategic alliances; that is, granting to the partner exclusive rights to a product or technology for a defined purpose or application, while the biotech company retains the product or technology for other uses. Doing so allows the biotech company to grant exclusive markets to its partner, yet leverage the alliance into a business of its own.

Of all the strategic variables, the field of use probably affords the greatest degree of flexibility and, therefore, room for creativity. Much of this flexibility will depend, however, on the particular technology and markets involved. If the product at hand is a transnational path for research, for example, there will not be much opportunity for field-of-use licensing. For particularly where the subject of the collaboration is a broad platform technology, there may be many different ways to define fields of use.

■ Defining ■

Defining the field of use is a good example of how focusing on the underlying strategy may lead to a different kind of structure. When Genia Pharmaceuticals structured its alliance with Marion-Merrill Dow for Genia's Avaine product, its underlying strategy was to develop a small sales base targeting the hospital market.

With that in mind, the partners defined MMD's field of use as oral formulations of Avaine, so that Genia retained for itself the intravenous formulations that would be used only in hospitals. Thus, even though Genia gave up worldwide rights to the oral formulations, it retained a significant market for itself — exactly Genia's strategy.

Licensing by field of use can be risky, however, for the pharmaceu-

tical company, the field must be broad enough that it has the right to reasonably exploit the technology. For the biotech company, the field must be narrow enough not to prevent it from doing what it wants to do or from licensing other fields. In any case, the technologies involved often are in their infancy and all of their applications may not be fully understood. It is therefore critical that both partners gather as much input as possible in order to verify that the field of use definition does not have unintended results.

For field licensing to work, the field must define products that are truly distinct. Otherwise customers will advantage the partner's products, and the partners will end up competing in each other's markets.

Defining the field of use in terms of disease indications, for example, may well be a recipe for dispute. If the dosage and formulations are the same, doctors may prescribe the product without regard to the authorized indications. Amgen and Ortho learned that lesson the hard way in their eventual dispute over erythropoietin.

Manufacturing Rights. Regardless of whether the biotech company gives up worldwide marketing rights, it can retain a very significant part of the business by retaining the right to manufacture some or all of the partner's product requirements. Particularly where management does not have a manufacturing background, biotech companies often fail to appreciate both the difficulty and importance of manufacturing.

The advantages of manufacturing are both obvious and not so obvious. First, if the biotech company runs its profits on the transfer price of the product, it will show operating earnings rather than royalties. Operating income, at least for now, is valued by the investment community much more highly than a comparable level of royalty income.

Second, there is no substitute for the assistance that a young biotech company will gain from its partner in scaling up and ramping the launch of its first product. With potential first year product sales of \$100-200 million or more, the marketing partner will go to great

lengths to ensure that the manufacture ramp-up runs smoothly.

Third, when manufacturing may be an important aspect of the technology field, retaining manufacturing rights is a way for the biotech company to build its technology base.

And fourth, but by no means last in importance, manufacturing products for a partner opens manufacturing overhead.

Given the redundancy of distribution channels likely to exist in the future, building a business based upon manufacturing and licensing makes a great deal of sense. That strategy paid off for drug delivery companies like Amn, and may be the model of the future for biopharmaceutical companies as well. In contrast, this model allows to the biotech company drug discovery and manufacturing, while the pharmaceutical companies focus on distribution and, perhaps, clinical development.

Industry. Traditionally, biotechnology companies have relied primarily on the first three strategic variables — geographic territories, fields of use, and manufacturing rights — to retain markets and operations for themselves. In recent years, however, they have increasingly retained some degree of co-manufacturing as a way to leverage their business.

Co-promotion has been one of the most popular themes in structuring alliances over the last five years. Retaining the right to co-promote allows a biotech company to build a sales base without taking on the full responsibility, and cost, of marketing a product itself. It is also another way for the biotech company to earn operating revenues and profits, rather than royalties. For its part, the pharmaceutical company gains access to a highly targeted, entrepreneurial sales force to supplement its own, at a fraction of the cost of hiring additional sales personnel.

At the same time, retaining co-promotion rights will probably require the biotech company to fund, or at least reimburse, a significant portion of the development costs. Considering again whether building a sales force is the right strategy,

one might question the wisdom of negotiating for co-promotion rights. Ultimately, however, the value of co-promotion rights will depend on the particular market, technology and strategy involved.

Beyond co-promotion, it is rare to see an alliance based on non-exclusive rights for each partner. Yet, in certain circumstances, a non-exclusive alliance may well be appropriate. When the collaboration focuses on enabling technologies, so that each partner can build its own proprietary position by "adding" to the platform, sharing costs in exchange for nonexclusive rights makes strategic sense. This type of opportunity is often missed, however, because executives fail to consider challenging the established positions of exclusive rights.

Right to Control Clinical Development. Recently, there have been a few transactions in which the biotech company retained the right to control clinical development of a product in the partner's territory. Until a few years ago, clinical development was almost sacrosanct — pharmaceutical companies have a great deal of experience in regulatory affairs and were therefore largely unwilling to delegate that expertise to a young biotech company. Immunologic went a long way toward changing that thinking in its alliance with Marion Merrell Dow for its Alzheimer's drug vaccine. Immunologic wanted to leverage its business in clinical development, as well as marketing, at a point, in addition to retaining co-promotion rights. Immunologic negotiated for the right to control clinical development in the United States. Beyond that, however, the arrangement was structured in a way to use the existing infrastructure each company already had in place, rather than each partner creating its own. This is yet another example of how thinking strategically about an alliance may result in a different kind of relationship.

Thus, while the right to control clinical development was probably not on the table in the past, today it may well be. Recognizing that right parallels in many respects the benefits of manufacturing rights, and in addition, allows the biotech company to begin establishing a rela-

tionship with the health regulatory agencies and to better control the pace of development.

FINANCIAL VARIABLES

As with the strategic variables, there are many ways to structure the financial terms of an alliance. In general, though, the financial terms fall within five categories: "promoter" payments, royalties, share of profits, licensee pricing and equity.

Promoter Payments. Several types of payments typically are made to the biotech partner prior to the commercial introduction of a product. These include license fees, development funding, and milestone payments.

The central issue in promoter payments is determining the appropriate amounts. For development funding, this is usually relatively straightforward: the amount is derived from the anticipated man-years the biotech company will devote to a given project, and the negotiation is over the rate of reimbursement. There may be issues about exceeding the budget, but the rationale is fairly clear.

• Hedge Against Risk •

When it comes to setting license fees and milestone payments, however, the justification becomes less clear. Ultimately, these promoter payments should reflect the net present value of the product, appropriately adjusted for risk. However, setting the aggregate amount is significantly more intuitive than, for example, establishing a royalty rate, and total payments vary widely from transaction to transaction. In any event, the trend is clearly upward. Courage, Ltd. recently topped its own agreement to pay Pro Design Labs up to some \$80 million in pre-market payments when it agreed to pay Cell to up to \$110 million in pre-market fees.

As the total promoter payments increase, these payments are increasingly allocated to milestone payments. Pharmaceutical companies are willing to pay handsomely for successful products, but they are looking for ways to reduce their risks. Thus, milestone payments,

although potentially higher than fixed license fees, can be a win-win scenario for both partners. The biotechnology company increases its upside, and the pharmaceutical company reduces its risk.

As a further hedge against risk, some pharmaceutical companies are looking to be made whole in various ways. At a simple level, they may ask to recoup their promoter payments against future royalty or profit payments. More significantly, in at least a few cases pharmaceutical companies have gained rights to additional products if the first product fails. Such recoupment and additional product rights probably are justifiable, however, only when a substantial premium has been paid for a late-stage product. For early-stage collaborations, the promoter payments and royalties themselves should take into account the risk of failure.

Share of Profits. One of the most profound trends in biotechnology alliances in recent years has been the movement toward profit sharing rather than royalties. The industry alliance that signaled this trend was Amgen Pharmaceuticals' 1991 alliance with Glaxo Holdings. In that transaction, Amgen negotiated for a sharing of responsibility, jointly funding its own work, in exchange for a share of the profits and an option to co-promote the product.

In 1991, when biotech companies could rarely finance themselves in the public markets, that strategy was much easier to appreciate. Not even though the public equity markets have been less than inspired since then, biotech companies continue to enter alliances in which they agree to fund a portion of the development in exchange for a share of the profits.

It can anticipate that pharmaceutical companies will be lower in the future — not only as a result of health care reform, but also because more technologies will compete against each other — one might question whether a 12 or 15% royalty on gross revenues would not be better than a 50% share of net profits profits.

The perception of Bill Street and most industry executives, however, is that operating profits attract in-

vestees to a greater extent than royalties. Although industry leaders are beginning to question this perception, for now the view prevails. Consequently, the trend toward "50-50" profit sharing is likely to continue. In any event, biotech companies will continue to negotiate for a substantial part of the overall profits, and because of the importance to pharmaceutical companies of maintaining a product pipeline, they likely will succeed.

Royalties. Unlike premarket payments, the industry has generally settled on an accepted range of royalties for various types of products. In a typical alliance for development of a drug with significant preclinical data, royalties will range between 8% and 12%, with an outside range of 5% to 10%. These percentages are based on the expectation of typical pharmaceutical margins, however, and ultimately the royalty in any particular case should reflect a reasonable split of the anticipated profits based upon the stage of development, funding by the licensee, degree of risk, level of contribution of the licensed subject matter, patent protection and the like.

Which like defining fields of use, structuring royalty payments can be tricky. This is, again, because royalty provisions must anticipate the future. How the product will be distributed, whether it will be sold in combination with other products for a single price, whether there will be royalties payable to third parties, and other similar factors may unexpectedly change the appropriate-ness of a given royalty rate.

The royalty rate typically assumes, for example, that the partner will distribute the product itself rather than taking into account the possibility of sales at a lower price through distributors or additional marketing partners. If this assumption proves faulty, a biotechnology company that expected a "10%" royalty might end up with 8% or 5% of the ultimate wholesale price, or only 5% royalties based on their original intentions. One therefore must identify the assumptions underlying the royalty rate in advance, and provide for adjustment if those assumptions prove in-

correct.

Transfer Pricing. If a biotechnology company has retained manufacturing rights, it may wish to build its results into negotiated transfer pricing for the products rather than a royalty. This effectively transforms royalty income into operating profit (and may avoid withheld taxes as well). Generally, there are three mechanisms for transfer pricing: percentage of resale price, "cost-plus" and a fixed-dollar price.

Pricing based on a percentage of the resale price is probably the best solution. Generally, this percentage ranges between 15% and 40% of the resale price of the product (but the manufacturer should negotiate a maximum fixed-dollar return price, so that in any event it is guaranteed to cover its costs and earn a minimum gross margin). In addition, the pricing provisions must address many of the same contingencies as royalties, such as shifting through distributors.

Cost-plus pricing, which involves a fixed markup over manufacturing cost, is often used but is probably the least satisfying alternative. It provides no incentive for the manufacturer to reduce costs and, since margins will be disclosed, it generally will not lead to the type of return that the manufacturer would like to earn. Establishing a fixed price is often not possible, since the costs to manufacture are not known. If a fixed price is established, however, the agreement should provide an escalator to protect against cost increases.

Equity. The last financial variable in equity investment by the pharmaceutical partner, liquidity is an important one for the pharmaceutical company to hedge its bets on the present by spreading its investment across the biotechnology company's entire business. In addition, financing development through equity may allow the pharmaceutical company to avoid having to expense that portion of the R&D funding.

For both partners, equity helps create a truly "win-win" environment. There is no question that a significant equity stake in the biotechnology company induces the tendency toward an "us-versus-them" perspective. Moreover, if the

biotechnology company goes public within a few years of the agreement, the partner may have an opportunity to recoup its R&D funding, and share a profit, well before there is a product.

The rule-of-thumb is that a strategic partner should pay a 20% premium over what a "financial" investor would pay for the same equity stake. As with most "value-at-risk" scenarios, however, this is probably not the case in often as it is in Coe's recent alliance with Protein Design Labs and CellPro, for example, the premium Coe's paid was in the 10% range.

CHARACTER OF ENTITY

Another important trend in biotech alliances has been toward the establishment of true joint venture companies, that is, separate partnership or corporate entities that are jointly owned by the partners. In reality, the result often is a hybrid between a true joint venture and a direct alliance — the partners form a joint venture company but retain for themselves certain rights or responsibilities, such as manufacturing or marketing.

The trend toward joint venture companies is no doubt an extension of the trend toward sharing of costs and profits by companies in direct "50-50" alliances. A joint venture structure is often used, however, when no strategic reasons support the creation of a separate company and, in fact, significant strategic reasons exist for not doing so.

Executives often fail to anticipate the many subtle difficulties of a joint venture structure. In a direct alliance, the partners are usually content to delegate to the other partner particular areas of expertise. In joint ventures, however, the tendency is for both partners to seek control over such decisions, leading to issues of deadlock and delay. Significant issues also arise from transferring employees into the joint venture company. What will their equity compensation be? Will the transfer create divided loyalties? Will they take on a "second-class" status? In addition, once employees are transferred, unperformed funding obligations will often follow, and if

the joint venture is not profitable, a partner may not be able to control the losses flowing through to its own P&L.

A separate joint-venture company does make sense in certain situations. For example, it may be an excellent way to enter a particular market, such as Japan, where a jointly owned company may help establish a direct presence. Similarly, if a green technology or product is not directly within the companies' strategic plans,

a joint-venture company may well be a way to split all their operations. In any event, companies should consider carefully whether a joint-venture structure is optimal. Unless there is a strong reason to set up a separate company, they should probably avoid such a structure.

CONCLUSION

Structuring alliances is reckoning time for defining a company's busi-

ness model and strategy. As a result, it is critical to think strategically — to focus on what one wants to be five-to-seven years into the relationship. That type of approach by companies like Harley, Cirrus and Intrepid — as well as their partners — to how alliance structures have evolved, no doubt they will continue to evolve, as companies define new business models and use the flexibility allowed by these basic licensing variables.