BY ELISABETH PENA

BIOTECH:

LIFE-CYCLE management

Traditional pharmaceutical companies are well-versed in developing **life-cycle management strategies** for their branded products. But according to some industry analysts, **the biotech industry is not as well-prepared** — for myriad reasons.

Patent Expiration Dates for Key Biologic Products

Total sales susceptible to generic competition by the end of 2005 = $13.5 billion

Brand (generic)	Company	2001 Sales ($ in millions)
2001		
Cerezyme/Ceredase (alglucerase)	Genzyme	$570
2002		
Novolin (human insulin)	Novo Nordisk	$1,829
Humulin (human insulin)	Eli Lilly	$1,061
Intron A (interferon alpha-2b)	Schering-Plough	$700 e
2003		
Avonex (interferon beta-1a)	Biogen	$972
Humatrope (somatropin)	Eli Lilly	$311 e
Nutropin (somatropin)	Genentech	$250
2004		
Epogen (epoetin alpha)	Amgen/Johnson & Johnson/ Sankyo	$5,772
2005		
Activase (alteplase)	Genentech/Boehringer Ingelheim/ Mitsubishi/Kyowa Hakko Kogyo	$276
Protropin (somatrem)	Genentech	$250
2006		
Neupogen (filgrastim)	Amgen/Roche	$1,533

Notes: Estimated sales of Genentech's Activase are $130 million;"e" denotes Datamonitor estimate.
Source: Datamonitor, New York. For more information, visit datamonitor.com.

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Biotechnology medicines generally are highly complex and feature large molecular mixtures derived from living organisms. In contrast, chemical drugs typically consist of smaller, synthesized, and chemically defined molecules. While the safety and effectiveness of a chemical drug can be established by the specification of its active ingredient, the safety and effectiveness of a biotech product can be impacted by the manner in which it is made, as well as by detailed in-process and final characterization.

Given the complexities surrounding the production of biotech drugs, many thought that the high-cost and high-science of biotech products would protect them from generic competition. But, according to Datamonitor, with more than half of the therapeutic proteins market — valued at $27 billion in 2001 — open to competition from generic alternatives by 2005, the appeal of more than $13.5 billion in biotechnology-based products will be a powerful lure for manufacturers of "biogenerics" to enter the market.

Despite the potential of the market, the uptake of biogenerics is expected to be slow because of the high cost of producing these therapeutics and the lengthy process of establishing an approval pathway. The approval process for biogenerics is expected to be established by 2006, and by 2010, industry analysts say a number of biogeneric companies will be in operation.

One of the biggest issues confronting the biogenerics industry, which may or may not emerge, is the huge regulatory uncertainty. **WE DO NOT KNOW WHAT THE FDA IS GOING TO WANT AND THAT MAKES IT VERY RISKY TO BE ENTERING THIS AREA.**

Dr. Tillman Gerngross

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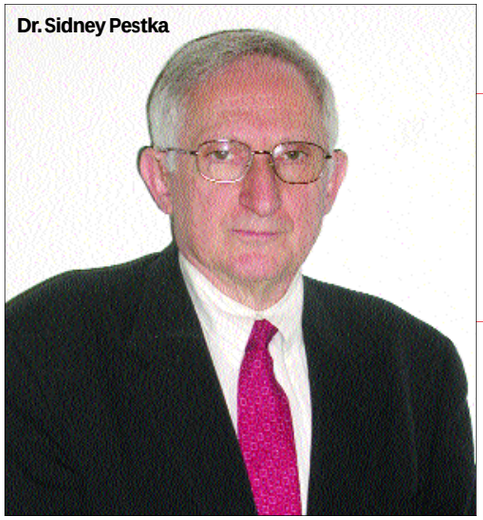

Dr. Sidney Pestka

GENERIC PRODUCTS THAT ARE ESSENTIALLY IDENTICAL WILL EVENTUALLY BE ALLOWED once regulatory agencies can be assured they meet proper safety and efficacy requirements.

The REGULATORY Horizon

LAMBLE. We do not definitely know if and when an abbreviated pathway is going to be introduced but Datamonitor expects it to be by 2006, in which case $13.5 billion of the 2001 market for therapeutic proteins is at risk to biogeneric competition. That shows how big the market for biogenerics is with almost 50% of the market for therapeutic proteins potentially set for generic competition.

PESTKA. The regulatory agencies have established standards for biotherapeutics and the timing of a clear pathway to approval may be around 2006. Once these standards are met, generic products likely will be approved. But generic companies will likely need to reach a higher standard than the original standard for approval.

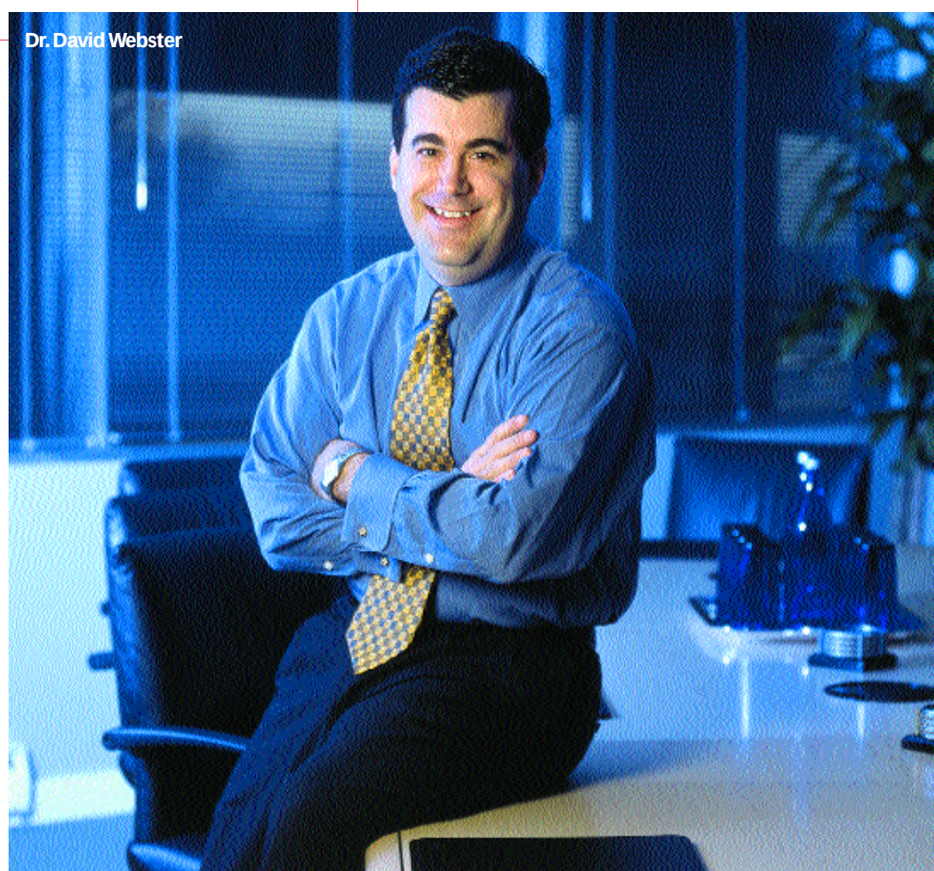
There are a number of hurdles that remain that make the speedy approval of **BIOGENERICS UNLIKELY TO HAPPEN IN THE NEXT THREE TO FOUR YEARS**.

PHILLIPS. The scientific and legal factors regarding this issue are very complex, and it is difficult to predict when the final requirements will be determined. There is clear agreement among scientists and regulators in the European Union, and increasingly so in the United States, that follow-on biologics will need to be tested more extensively than conventional generic products.

WOOD. It is important to note that biogenerics are in a grey zone with respect to current generic laws and regulations in the United States and in Europe. This is in part because some currently marketed recombinant proteins are registered as biologicals, while others are registered as pharmaceuticals. The difference in registration leads to different regulatory pathways initially and to different generic approval processes later on, which in the United States involve different laws and regulatory agencies. Furthermore, whatever the category of initial registration, there are difficulties applying currently existing terminologies and procedures for biologicals or for pharmaceuticals to these "biopharmaceuticals." We will soon be entering a period of complex legislative "clarification" with respect to these issues.

SEARCY. I don't believe that the regulatory process can be the same for biotech drugs as for chemically derived drugs. The safety and effectiveness of a chemical drug can be established by the specification of its active ingredient. But, the safety and effectiveness of a biotech drug may be affected by the manner in which it is made and processed, which may not be evident when examining a detailed in-process and final product characterization. Small differences from the originator in manufacturing, for example, may change the drug in a way that could impact safety or immunogenicity. This is likely a bigger issue for proteins than peptides because of the more complex nature of these molecules, including attributes such as tertiary structure and glycosylation patterns. While it is of interest to contemplate the concept of generic biologics, I believe there are a number of issues that need to be addressed before one can really say that a biologic manufactured by one process in one facility is equivalent to the same biologic manufactured by a different process in a different facility. Until a track record has been established, I believe demonstration of efficacy and safety will still be the norm rather than the exception for biologics.

PESTKA. The rate of utilization of biogenerics likely will be slow because the regulatory agencies and the generic companies are traveling on new ground. Even the definition of a generic will need to be redefined. We already know that some biotherapeutics have different properties when produced in *E. coli* or when produced in animal cells, for example, because the products themselves are significantly different. In addition, the use of generic products will


Dr. David Webster


Nanske Wood

> Ultimately, if biogenerics get closer to becoming a reality, it will be interesting to see if biopharmaceutical companies, particularly those with biological production capacity, **WILL PLAY IN THE BIOGENERIC SANDBOX** as well.

be slow because of the complicated intellectual property landscape that has evolved around many biotherapeutics. Expression vectors, host cells, purification methods, and formulations may have intellectual property barriers. Another factor is the cost of entry into this market since the production costs of protein biotherapeutics and clinical trials are high. But generic companies that move in this direction may have an opportunity to develop multiple biotherapeutics and develop a strong position, particularly if they start early. Efforts and resources of small companies might be better placed if they focus on making new and better products. For example, small companies have taken the approach to develop and to produce improved forms of interferon and other biotherapeutics and to use them for new indications. This approach should make a significant impact on the treatment of diseases for which there are no current therapies. This strategy also will add to the total market of biotherapeutics and make the greatest impact on patients.

GERNGROSS. A generic manufacturer may know what the molecule is, but in the case of therapeutic proteins the manufacturing process profoundly impacts what that molecule ends up looking like. Current FDA rules do not mandate that companies that make biologic drugs disclose exactly how the drugs are made. For a biogenerics entry, all this work has to be figured out and then implemented to come up with a molecule that is identical to what has been made before. The manufacturing of biogenerics is going to be very difficult.


Dr. Christopher Searcy

PESTKA. Generic products that are essentially identical to the innovator or original product eventually will be allowed once regulatory agencies can be assured that they meet proper safety and efficacy requirements. Thus, detailed, clear specifications must be carefully developed by regulatory agencies so that generic companies have a clear standard to achieve and a well-defined pathway to follow for approval.

> One way that biotech companies can extend the life cycle of their protein drug products or create differentiated versions is to **APPLY ADVANCED FORMS OF DRUG DELIVERY**.

A Complex PROCESS

SEARCY. It is very important to understand the difference between biotechnology medicines, which are highly complex and are derived from living organisms, in contrast with chemical drugs, which typically consist of smaller, synthesized and chemically defined molecules. Making a generic biologic will be much more complicated than making a generic small-molecule chemical drug.

PHILLIPS. The question at the heart of the current dialogue and investigation is how much more testing will be required across a variety of biologics? This is an important issue for all biotechnology companies to be aware of. Safety and preservation of efficacy of all biologics should be the future focus as sensible steps are identified.

GERNGROSS. Aspirin is aspirin, and if a company makes a generic form of aspirin then it can be determined without any doubt that the molecule is identical to what was made before. With biological drugs, this is much more difficult because biological drugs are very large molecules that cannot in essence be characterized down to the individual molecule. It is almost a given that the industry is going to have to redo some of the safety studies.

WEBSTER. Much of the value of a biologic is in the company's ability to manufacture it and replicate that manufacturing over millions of doses. That is not a trivial task. There is a big question as to whether generic companies can replicate that process as easily as they do with small molecules.

YAROSH. The uptake of biogenerics will be much slower than for chemical generics because the technology for chemical synthesis and analysis is more widely shared than the specialized technology for many biologicals. This is true not only for the product, but for the validated bioassays and the preparation of biological substrates needed to match the innovator product.

GERNGROSS. Biogenerics are unlikely to displace biomolecules that come off patent. There will be improved versions of those molecules, such as versions that have to be administered less frequently, that have a higher tolerance, or are less immunogenic. It is unlikely that there will be exact versions of the same biologic molecule that will compete on price.

RADER. The first branded biologic products that will be considered for biogenerics will be products coming off patent. These products essentially use 1980s technology, and generic versions of many of these products already are on the market internationally. These include recombinant insulin and human growth hormone products regulated by the FDA as drugs for which generic regulations are largely in place. Although multiple, substantially identical active ingredient, generic versions of these products already are marketed in the United States, they were not approved as generic drugs. For example, the sponsors conducted the usual safety and efficacy trials and gained approval based on showing pharmacological equivalence to a prior product.

SCHMIDT. As research and manufacturing processes have gotten better, companies are more easily able to replicate drugs. The first and early adopters, the first companies in with the technology, incur the greatest expense.

RADER. The real fight concerning generic biologics will be about the more complex products regulated as biologics such as factor VIII, which is an extreme example. Factor VIII is the largest and most complex recombinant DNA product on the market, and even the companies that have been making it for years have repeatedly had problems in manufacturing it, even with their expertise and experience. Producing some biologics is very difficult. Examples of the difficulty faced even by originators and their partners/licensees in manufacturing substantially identical products are Ortho/J&J's problems with serious adverse effects with Eprex (recombinant erythropoietin; EPO), which is supposed to be identical to EPO (Epogen) from Amgen, which is not showing the same adverse effects. And the recent delay in approval of Raptiva because of the product manufactured by Genentech has different pharmacokinetics than the product manufactured by its partner, Xoma.

SCHMIDT. Another consequence is the erosion of biological products to biotechnology products. Typically a biotechnology product is much more expensive to the end user or to the payer than a biological product. For example, one of the top biotechnology products is recombinant factor VIII for use in people with hemophilia A — a very successful product. Hemophilia used to be treated by a plasma-derived biological factor that several manufacturers made. And that biological product was a part of the profitability profile for the manufacturers. If a plasma manufacturer was making three different products from one liter of plasma and because of a biotechnology advancement it only makes one product, it becomes much more expensive to manufacture that one product. Or, when a biotechnology product replaces a biological product, patient care could be impacted dramatically. Recombinant factor VIII, which is a great advancement for the hemophilia community, could have a deleterious effect on the market for primary immune deficiency products because the product is much more expensive and potentially less available.

Going GLOBAL

LAMBLE. Manufacturing is one of the key issues with biogenerics because biological proteins are very costly to manufacture. Biogeneric companies are preparing for this market by setting up businesses outside the major markets, in places such as China. To prepare for an abbreviated regulatory approval pathway in the United States, these companies have to get these foreign manufacturing plants up to good manufacturing practice standards (GMP), so that when the approval pathway is put in place, they are ready to run in the new market. In the meantime, to sustain business these companies are entering markets that don't have the patent protection laws of Europe and the United States, such as China and Eastern Europe.


Dr. Daniel Yarosh

Branded biotech companies must **EXPLORE DEVELOPING MARKET MANUFACTURING OPTIONS** whether they are challenged by biogenerics or not.

Major Players — Biogeneric Companies in 2002

Apotex
Location: **Canada**
Key areas of development: **NA**

Barr Laboratories
Location: **U.S.**
Key areas of development: **NA**

Bio-Technology General
Location: **U.S.**
Key areas of development: **Insulins**

Cangene
Location: **Canada**
Key areas of development: **Colony-stimulating factors and growth hormones**

E. Merck (Merck KGaA)
Location: **India**
Key areas of development: **Growth hormones and interferons**

GeneMedix
Location: **U.K.**
Key areas of development: **Colony-stimulating factors, interferons, erythropoietins, insulins, interleukins, and growth factors**

Ivax
Location: **U.S.**
Key areas of development: **Colony-stimulating factors, interferons, and growth hormones**

LG Chemicals
Location: **Korea**
Key areas of development: **Erythropoietins, insulins, and interferons**

Microbix Biosystems
Location: **Canada**
Key areas of development: **Plasminogen activators**

Rhein Biotech
Location: **India, Argentina**
Key areas of development: **NA**

Sicor
Location: **U.S.**
Key areas of development: **Colony-stimulating factors, growth hormones, interferons, erythropoietins**

Stada
Location: **Germany**
Key areas of development: **Erythropoietins, interferons, and colony-stimulating factors**

Teva
Location: **Israel**
Key areas of development: **Growth hormones**

Source: Datamonitor, New York. For more information, visit datamonitor.com.


Michael Steiner

> The uptake of biogenerics will not be as aggressive as with some small-molecule generics because of the **DIFFICULTIES IN GAINING THE EXPERTISE TO PRODUCE THE BIOLOGICAL MOLECULES**.

YAROSH. Branded biotech companies must explore developing different market manufacturing options, and they probably should whether they are challenged by biogenerics or not. It is unclear whether contract manufacturers can accommodate, under one roof, the variety of technical expertise needed to assist an array of biotech companies. This will be a specialized business.

WEBSTER. One big issue is the potential for entry from generic producers outside the United States. The biggest pool of competency for generic biologic manufacturing is overseas. Some countries — such as Russia, which has a very big generic vaccine industry — have incredible resources for producing generic biologics. If U.S. generic firms want to get in the business they will have a lot of foreign competition. If a regulatory pathway does open, U.S. consumers will benefit by having a lot of foreign firms capable of ramping up quickly. Then it becomes a question of safety and whether these foreign companies can meet strict FDA regulations.

PESTKA. Investment by generic companies in manufacturing facilities in developing markets such as China probably will not make a major impact in the next three to five years as oversight and quality control issues will not make it easy for small companies to develop plants in China or other countries where costs are much lower. However, in the long term it will be natural for companies to develop production in countries where costs are lower. This has been the pattern in almost all industries in the past such as the steel, electronics, textile, and automobile industries so it will be followed in the pharmaceutical industry as well. In fact, when major innovator companies begin using labor in countries where costs are substantially lower, it will be much more difficult for the generic companies to compete on the basis of cost alone.

STEINER. The biological industry is expected to face a manufacturing capacity bottleneck. There has been a manufacturing facility build-up in developing markets such as China and Singapore. Several biopharmaceuticals, most of which are still patent protected in Western countries, already are being marketed in those countries because of the lack of patent protection. But it might be difficult for generic companies to manufacture and export these products to the United States or Europe after their patent protection has expired because of the very stringent review procedures of their regulatory authorities. An obvious manufacturing strategy is to acquire biotech companies that have a manufacturing capability. That is the most straightforward way to overcome the manufacturing capacity bottleneck.

WOOD. Some biogeneric manufacturers hope to side step U.S. legislative issues by marketing biogenerics in markets outside the United States where proteins do not have patent protection and thereby establishing some initial market credibility. Several biogeneric companies also are taking a wait-and-see attitude.

SEARCY. If generic companies do successfully invest in manufacturing facilities in countries such as China or form alliances with contract manufacturing organizations, biotech companies with branded products will need to be prepared to improve and differentiate their brands so that they stay ahead of the generic companies.

SCHMIDT. As products go from branded to generic, there is a potential consequence for wholesalers and drug distributors. Distributors work on certain margin percentages, so it's always better if there's a higher-cost product because the percentage from a higher-cost product is more lucrative than a less expensive product.

Defending the BRAND

LAMBLE. Obviously, one of the first strategies to defend a biotechnology brand is for innovator companies to adopt a very aggressive legal stance. The second is to reposition the branded biological therapy through enhanced formulations and extended-release versions that offer a clear advantage over a generic coming into the market. An ideal strategy is to accelerate the release of a follow-up product, for example using pegylated technologies such as Amgen's Neulasta.

MAEBIUS. Pioneering companies need to look at their patent portfolios. They need to determine if they have developed a strong position beyond the initial expiration of the patent that covered the basic biologic product that was on the market.


Nicole Lamble

> **A KEY ISSUE IS THE ACCEPTANCE** by physicians in terms of how confident they are in the safety of biogenerics.

BIO: Biogenerics Require Original Nonclinical and Clinical Data

THE BIOTECHNOLOGY INDUSTRY ORGANIZATION (BIO) HAS MADE PUBLIC ITS POSITION that the approval of follow-on biotechnology products, biogenerics, must be based on the same rigorous standards applied by the Food and Drug Administration (FDA) for the approval of pioneer biotechnology products. According to the organization, the science does not exist to provide an alternative to a full complement of data, including clinical evidence, to demonstrate safety and effectiveness for follow-on biotechnology products.

In a citizen petition submitted to the FDA in April 2003, BIO urged the agency to conduct open and meaningful debate on the scientific, legal, and policy issues concerning follow-on biotechnology products if the FDA is considering creating an approval mechanism for them.

"Even if a generic company does submit a complete filing, it hasn't shown that the product is the same," says Gillian R. Woollett, MA, D.Phil., VP of science and regulatory affairs at BIO. "All that it has shown is that what was submitted has purity, potency, identity, and/or is safe and effective for the use for which it is proposed, but it doesn't show that the two products are substitutable."

In a letter sent to FDA Commissioner Mark B. McClellan, M.D., Ph.D., before the submission of the citizen petition, BIO President Carl B. Feldbaum urged the agency leader to "actively solicit public participation" if the FDA is considering a regulatory change related to biotechnology products.

POLICY CHANGES REQUIRE TRANSPARENCY

"We strongly believe that any changes in a policy so significant to the biotechnology industry should involve a process that is transparent, public, and open to all those interested in helping develop science-based regulations for biotechnology medicines," Mr. Feldbaum says. "Such openness has been a long-standing FDA tradition and serves the best interests of patients, the public, and manufacturers. We ask that the FDA actively solicit public participation so that all parties — government, the scientific community, the biotechnology industry, our patients, and others — may express their views."

Currently, most biotechnology products are covered under the Public Health Service Act as biological products. Certain biotech products, such as insulin and human growth hormone, were, for historical reasons, approved by the FDA as new drugs under the Federal Food, Drug and Cosmetic Act. The act allows for abbreviated approvals for generic drugs that are proven by their manufacturers to be equivalent to the innovator drug, but it does not specifically address biotechnology medicines. In recent statements made by FDA officials, the agency has indicated its willingness to establish a follow-on pathway for some biotechnology products.

FOLLOW-ON PRODUCTS REQUIRE RESEARCH

BIO representatives believe that FDA approval of any follow-on biotechnology medicine must be based on a full complement of original nonclinical and clinical data because of the unique scientific nature of biotechnology products. Without this information, the follow-on products could pose an unnecessary and potentially serious risk to patients. A follow-on biologic could induce immunogenicity that would preclude the efficacy of the innovator.

"The crux of the argument is safety and, therefore, at some level ethics," Dr. Woollett says. "Much, but not all, of the work surrounding follow-on biologics is doable, in so far as the science has progressed. But science-based regulatory mechanisms have yet to be created that would also allow innovators to significantly refine their processes, let alone allow a follow-on manufacturer to start from scratch."

The issues surrounding follow-on, or generic, biotech drugs have become more urgent following the introduction of a "functionally equivalent standard" by The Centers for Medicare and Medicaid Services (CMS) as part of an agency rule on its outpatient prospective payment system, which became effective Jan. 1, 2003.

Under the functionally equivalent standard, CMS treated one new biological as if it were the same as an older product for payment purposes because the agency found the therapies to be "functionally equivalent," simply because the older, existing medicine costs less even though the two drugs differed significantly in important therapeutic respects in terms of side effects, dosing, and modes of administration.

Members of Congress and BIO have spoken out about this decision, declaring that CMS overstepped its statutory bounds when it implemented without notice or an opportunity for public input on a "functionally equivalent" rule in determining payment amounts for erythropoietic products. In addition, several members of Congress say the functionally equivalent standard runs counter to existing law and should not have been implemented in the first place, let alone without any opportunity for public discussion before its implementation.

"The FDA is the only organization that can determine equivalence, CMS is not in a position to make that judgment," Dr. Woollett says.

I DON'T THINK BIOGENERICS WILL EXIST. The fundamental point of BIO's petition is: on what basis can it be shown that a follow-on product is the same?

Dr. Gillian Woollett

In biotechnology there is a greater ability to patent downstream than there may be in the pharmaceutical area. There is much more processing and innovation that occurs in the production of the biotech molecule or drug than occurs in the pharmaceutical industry. There also may be patents at many different levels that all form potential barriers to entry even after the initial patents expire. For example, when a company first discovers a basic protein it gets a patent on the protein. Then the company can patent the DNA sequence as well as the processes used to make that protein. Then further down the road, the various methods of treatment and combination therapies using the protein are discovered and those are patented. Pioneer companies should aggressively patent all aspects of their production system as they continue to innovate throughout the life cycle of biologic products.

WOOD. Manufacturers of biopharmaceuticals can prepare for new legislation by getting involved in the legislative process. BIO has taken a stand and is communicating its position to Washington. Biopharmaceutical manufacturers also can employ strategies that have been used in the past to combat generics, including creating alternative delivery systems or new formulations of the existing product; using litigation to delay the introduction of a potential biogeneric (in this case it could possibly be years); lobbying congress to create bills to extend the patent life of their product; and working with biogeneric manufacturers to identify the best way to move forward together as the biogeneric product gets closer to launch — this method should be investigated cautiously to avoid illegal activities from a Federal Trade Commission perspective.

SCHMIDT. Many of the standard practices of life-cycle management apply to biotech drugs. Most companies that have biotech drugs have been very successful at branding the product, creating brand awareness, and creating the proper reimbursement profile. Those are the best ways to manage the life cycle and extend the life cycle of a product. A biotech company can have a huge advantage down the road if it has created dramatic brand awareness within the patient population, and patients are asking for the brand and they believe there's a difference between the original and a generic biotechnology product. Most biotech drugs are for chronic diseases and the patient populations are well-educated. Therefore, the conversion from a branded biotechnology product to a generic will be more difficult, which would extend the life cycle of a biotechnology product.

PESTKA. The standard procedures that innovator companies have used for other molecules to retain and improve market share will be used for biologic products. Decreasing the number of injections or treatments required, such as with sustained-delivery formulations, is one approach that already has been used. These improvements have provided benefits for patients for some indications. Thus, a generic version of the original product may have a more limited use for a small subset of overall indications.

GERNGROSS. Biotech companies can manage the life cycles of their branded drugs through new technologies that can improve the product's pharmacokinetic behavior. An injected therapeutic protein degrades over time, but by improving the protein's glycosylation, for example, a company can make the molecule longer lasting, which reduces the number of administrations and improves the quality of care for the patient. The drug has the same underlying molecule and binds to the same receptor, but it lasts longer and therefore it is an improved version that can displace an old version.

SEARCY. The use of drug delivery to provide noninvasive, or minimally invasive, delivery of these agents is gaining momentum. Nektar's PEG and inhalation technologies are particularly applicable to enabling the improvement and/or differentiation of proteins.

Amgen applied PEG technology to create Neulasta (pegfilgrastim), an improved version of Neupogen to treat neutropenia. Pfizer similarly added PEG technology to Somavert (pegvisomant) to improve the therapy for acromegaly. Roche and Schering-Plough both used a form of PEG to improve interferon-alpha therapy for hepatitis C. The PEG version now is considered standard treatment. All four of these transformed therapeutics are now on the market.

Building Cross-Border Alliances

ACCORDING TO CAROL CHERKIS, PH.D., LIFE SCIENCES CONSULTANT FOR NEWCAP PARTNERS INC. AND PAUL J. MEYER JR., ASSOCIATE WITH THE INTELLECTUAL PROPERTY PRACTICE AT SQUIRE, SANDERS & DEMPSEY LLP, THE BIOTECHNOLOGY-PHARMACEUTICAL INDUSTRY HAS PROVEN THAT CROSS-BORDER ALLIANCES BETWEEN COMPANIES RESULT IN SOME OF THE WORLD'S BEST COLLABORATIONS.

But those alliances are built on more than just good science. The most successful collaborations have been formed with careful legal planning that minimizes a company's exposure to getting burned on the alliance's greatest asset — the intellectual property that goes into and comes out of it.

The truth is that cross-border alliances are not as seamless as they may appear and, in some cases, can turn into complex nightmares for companies that do not perform adequate due diligence and, ultimately, fail to protect their businesses and intellectual property.

However, sensible companies that employ thorough business and legal planning in everything from partner selection to exit strategies can successfully avoid these situations and stay focused on what really matters — the collaboration.

CHOOSE FRIENDS WISELY

Partner selection is no easy task. Just as complicated is figuring out how a company will develop intellectual property with another company. Companies that carefully select their partner can be confident that they will maximize the value of the alliance.

Particular countries/regions in the world may be best suited to establishing the cross-border alliance. The two most important considerations in selecting a region are to first have the ability to justify a presence and develop a business rationale for doing business in that region and second, to determine whether the country of interest offers any favorable financial incentive for forming alliances. Answering these two questions will help in narrowing the location of the alliance, if the company does not already have an alliance partner in mind.


Dr. Carol Cherkis


Paul Meyer Jr.

Once a country or region has been targeted for further inquiry, more specific questions must be answered. For example:

- What are the regulatory policies and what is the scope of IP protection in the region/country? Are compositions and methods of treatment adequately covered by the country's patent laws? If not, are there significant risks for entering the market of the alliance partner?
- Are there sufficient enforcement/remedies for violations of intellectual property rights, especially for trade-secret theft?
- Is there a quantifiable return on investment for the alliance?
- Are there requirements in the host country that will significantly reduce the value of the alliance, for example a requirement to compensate an employee for developing IP?

The company should understand the existing alliance base inside the country. A country/region that is home to conflicting alliances may be less appealing, while the reverse is true for an area with more complementary existing alliances.

It is also important that the company determines which strengths are most desirable in an alliance partner. When a company knows that the partner will bring significant experience in manufacturing and distribution (in addition to intellectual property) to the table, there are expanded opportunities for collaboration.

RUN A BACKGROUND CHECK

Proper due diligence is the hallmark to avoiding most pitfalls in any alliance. Successful alliances ensure that the legal and intellectual property issues are addressed and that both parties share the same under-

STEINER. A big protection for biotechnology and biologic companies with branded products is the relevant expertise that they have in house to extract biological molecules, because that is a main lever of competitive advantage. Having this expertise is almost as important as holding a patent. The generic competitor doesn't have access to this methodology, to the strain, the growth material, or the cells.

YAROSH. Greater use and protection of trade secrets as well as confidentiality in manufacturing and assay of biologics are strategies that can be employed to protect branded biologic products from generic competition. In addition, companies also can defend against generic biologics through greater exploration and patent protection of biological variants with improved characteristics, for example, generation stacking.

standing of any negotiations before the formal relationship is established.

This type of investigation enables companies to know for certain, and perhaps most importantly, whether the partner is the rightful owner of any intellectual property he claims. If the partner is the rightful owner, due diligence also will reveal the value of the partner's intellectual property, as well as the strength of the proposed partner's intellectual property portfolio, which may include blocking patents and other important knowledge assets. Any investigation also should include a risk assessment to see whether the proposed partner is involved in, or is likely to be involved in, any high-stakes intellectual property litigation.

Once completed, the due-diligence phase provides valuable information in terms of how best to structure the alliance — including its tax treatment — and how to address any anticipated intellectual property or regulatory challenges. Moreover, the due diligence will likely provide some issues for further discussion and negotiation.

STRUCTURE THE ALLIANCE TO PROTECT INTERESTS

Negotiations should be conducted with the goal of building trust between partners. As with any alliance, the partners should draft a mutually acceptable nondisclosure agreement, understand the partner's commitment to the alliance, and identify the alliance's goals.

Other common issues faced during negotiations include managing any downsides to the alliance and any cultural issues. For example, in some foreign jurisdictions, negotiations involving certain technologies can trigger compulsory licensing provisions.

In other cases, there may be antitrust issues or basic cultural issues that may impact how businesses in those countries view intellectual property.

The partners must be mindful of how they are going to protect their intellectual property. For a company contributing intellectual property to an alliance, no aspect is more important to it than retaining maximum control over its intellectual property to the greatest extent consistent with achieving its individual goal. Likewise, each company engaging in an alliance must consider ownership of intellectual property generated by the alliance.

CREATE THE KNOWLEDGE ASSET

When the alliance actually begins producing the intellectual property, the partners must determine how the intellectual property will be managed and how it will be audited.

The alliance should ensure that the appropriate party has the responsibility for maintaining the IP. For example, the parties must determine who will file patent applications before established bar dates/disclosures. Also, the alliance must be aware of any issues particular to the host country, such as requirements to "work" a patent.

Protection of the intellectual property is important, as well. The alliance partners should vigorously protect the alliance's intellectual property and diligently respond to any confidentiality issues in exchanging information between partners. Further, the partners should determine whether additional parties, such as consultants and employees of the alliance, also might access and use the intellectual property.

To gauge whether the alliance is meeting expectations in terms of quality and return on investment, the partners should also provide for an audit of the work.

WHEN THE ALLIANCE ENDS

Partners in any alliance should start their collaboration with the end in mind. In other words, a well-planned termination agreement will make for a smoother transition when it comes time for the collaborators to part ways.

A top priority for every alliance should be to decide which party owns any jointly developed intellectual property. This includes any obligations that survive the termination, such as maintenance of licenses to use the intellectual property that is produced by the alliance and maintenance of the value of the intellectual property.

The Supply Chain Can Provide a Competitive Advantage

AS THE COMPLEXITIES SURROUNDING THE HEALTHCARE INDUSTRY INCREASE, MORE COMPANIES ARE OUTSOURCING THEIR SUPPLY-CHAIN OPERATIONS. THIS IS ESPECIALLY IMPORTANT IN THE BIOTECH INDUSTRY, WHERE SPEED TO MARKET, SCALABILITY, AND REGULATORY KNOWLEDGE IS CRITICAL TO MAINTAIN A COMPETITIVE EDGE.

The following key trends in the biotech industry have specific supply-chain ramifications.

INCREASING PACE OF INNOVATION

Biotech Trend: With the mapping of the human genome and advances in genomics and proteomics, product life cycles are shortening, and the pace of new biotech product introduction is accelerating.

Supply-Chain Ramification: Need for scalable, quickly implementable distribution conduits to speed product to market with maximum operational efficiency and economy.

MIGRATION OF PRODUCTION AND CONSUMPTION

Biotech Trend: Increasingly, biotech innovations are occurring outside traditional pharmaceutical production geographies. At the same time, consumption of biotech materials is no longer confined to large institutions operating within major metropolitan areas.

Supply-Chain Ramification: Need for global supply-chain capabilities, capable of handling bulk shipments and parcel quantities with equal agility and precision.

INCREASING PRODUCT SOPHISTICATION

Biotech Trend: The heightened effectiveness of new biotech materials coincides with more complex handling and storage requirements.

Supply-Chain Ramification: Need for disciplined environmental control, time definite and expedited delivery, visibility, and reporting.

HEIGHTENED OVERSIGHT

Biotech Trend: Increasing regulatory oversight and customer-compliance requirements are impacting all facets of biotech distribution.

Supply-Chain Ramification: Need for end-to-end visibility and accountability, with complete audit-trail reporting, and the ability to act upon supply-chain information to enhance service.

INCREASED COMPETITION

Biotech Trend: The biotech arena is aggressively contested, with a myriad of alternative products, providers, and channels.

Supply-Chain Ramification: Sustainable success requires the extended supply chain to become a competitive advantage, driving top-line sales by enabling penetration of increasingly lucrative markets, while driving down bottom-line costs.

Source: UPS Supply Chain Solutions, Alpharetta, Ga. For more information, visit ups-scs.com.

PESTKA. Biotechnology companies are modifying their products for new needs and uses. Examples of this are pegylated interferons and glycosylated erythropoietins with a longer half life in serum that need to be administered less frequently to patients. This pattern of improving the product is similar to what has been done for other pharmaceuticals to maintain patent protection and market share.

WEBSTER. One big strategy that differentiates biologics from branded pharmaceuticals is the way the company contracts and sells the biologic to managed-care and group-purchasing organizations. With pharmaceuticals, manufacturers typically lock into long-term contracts because traditionally the price path starts out very high and then declines over time. With biologics, even if there is generic entry, if manufacturers lock into long-term agreements, they will be leaving money on the table. There is the potential that a generic competitor might have manufacturing problems at any given time and supply is always an issue. Just because there are generic manufacturers doesn't mean that the supply of biologics might not increase in value over time.

LAMBLE. One of the key things that biotech and pharma companies can do to protect their branded biologics is to promote the safety of the original product to physicians and emphasize the importance of having a proven track record compared with potential biogeneric competition.

Legal TANGLES

RADER. Small, start-up, biotechnology companies are going to have trouble protecting their products against generic competitors in the courts, if only because most generic companies are better financed and are used to protracted court battles. But biotech companies that have decent financing, well-developed business plans, and their own production facilities — in other words, small- to mid-tier biotech companies — can readily take on the challenge from biogenerics. These companies have the resources and confidence to take on generic manufacturers and sponsor lengthy legal battles.

WOOD. At this point, many of the products at risk from biogenerics come from large pharmaceutical players, for example, Procrit (Ortho Biotech), Humulin (Eli Lilly), and Engerix-B (GSK/Biogen). These companies might be willing to dedicate significant resources to protective legal strategies. It is difficult to predict the impact new legislation will have on the viability of legal strategies in the future.

LAMBLE. Branded biotech companies will put up a lot of resistance to biogenerics in the form of lawsuits. For biogeneric manufacturers the actual initial costs to develop their drugs are going to be quite high. When biogenerics do reach the market, these products won't have the same price discounts that small-molecule generic products do. Small-molecule generics enter the market at about 50% of the branded price, whereas biogenerics will come in at about 80% of the branded price.

YAROSH. Litigation over any issue for a biotechnology company is expensive and potentially crippling. Larger companies often exploit this advantage during negotiations and business dealings, so this is nothing new to smaller biotech companies. Because of the long drought in IPOs and capital investment, biotechnology companies already are seeking, and will continue to seek, mergers and alliances with big pharmaceutical companies for funding. Alliances, however, do not remove the threat of litigation if the partners do not agree on what to do.

MAEBIUS. Patent litigation may not necessarily drive biotechnology companies to partner with big pharma companies. The bigger drivers are the distribution capabilities of a large pharmaceutical company. Most biotechnology companies just don't have this distribution and marketing capability. Big pharmaceutical companies, on the other hand, have a lot of resources, including a lot of marketing people and huge sales staffs. In addition, they can distribute products quickly.

WEBSTER. Big biotech companies certainly have the resources to defend high-value products. For smaller companies, in some senses, the cost of losing a patent dispute is much lower, because there is not as much at stake. For big products, biotech won't have any problem funding patent disputes.

Physician/Payer ACCEPTANCE

SEARCY. Biogenerics have the potential to be disruptive to innovator companies especially if efficacy can be demonstrated through clinical trials or general usage. Generic companies, however, still have to deal with physician, patient, regulatory agency, and payer skepticism.

LAMBLE. It will take a while for physicians to accept biogeneric products, in particular products for patients who are being treated for chronic conditions, which biologic proteins often treat. Physicians will be reluctant to switch their patients from the branded biotechnology drug unless they are absolutely confident in the generic version.

SCHMIDT. The uptake of biogenerics will depend on how the federal payers look at these products. Depending on how good a job latter entrants do in convincing government payers that their products are the same and the reimbursement level for their generic is much lower, there may be rapid conversion.

STEINER. In the beginning, there will be a lot of skepticism by doctors and a reluctance to prescribe biogenerics. Generic biopharmaceutical companies will have to overcome this obstacle by proving that the quality and safety profile of their product is the same as the innovator brand. There will have to be a lot of convincing to get doctors to prescribe biogeneric drugs.

MAEBIUS. It is impossible to produce a truly identical generic version of a biotechnology drug because of the unpredictability of producing proteins in living cells and the inevitable minor variations, for example, differences in glycosylation. The medical profession might be a little slow to prescribe those first few biogeneric versions that come through the pipeline for patients in view of these potential differences. On the other hand, the intense pressure to reduce healthcare costs will create a powerful incentive for physicians.

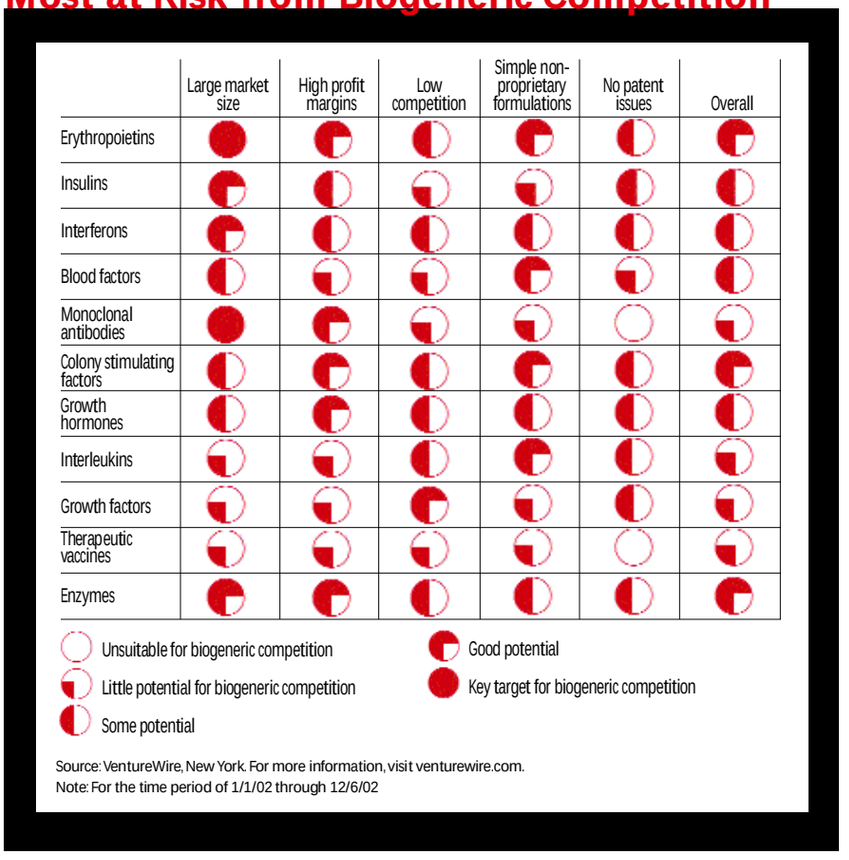
PESTKA. Because of the pressures to reduce healthcare costs, doctors will try biogenerics if the costs are sufficiently different to make them worthwhile for their patients. The issue about a biogeneric product's quality will be secondary because the FDA and other regulatory agencies will have set the standards. Once those standards are set, biogeneric products should be quite comparable to the original products.

WOOD. If biogenerics are able to demonstrate equivalency in both efficacy and safety at a significantly lower price point, physicians will be pressured to prescribe biogenerics. The question remains whether a biogeneric manufacturer will be able to bring the cost down to a level where there's a big enough incentive for a physician to change his or her prescribing habits.

YAROSH. Physicians are very much aware of the cost of drugs. In many cases they will be compelled to use biogenerics. They discover very quickly in their practices which generics products perform like the branded products. Market forces will determine the success of each biogeneric. ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Therapeutic Protein Classes Most at Risk from Biogeneric Competition



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Note: For the time period of 1/1/02 through 12/6/02