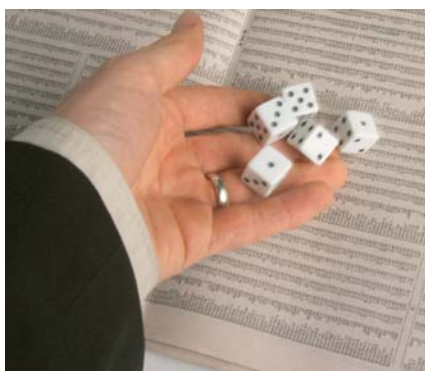


Does a *Biogenerics* Industry Really Exist?

Seth Yakatan and Clifford Mintz



Biogenerics cause a lot of angst—or a lot of excitement—in biotechnology these days, depending on your perspective. But do they really have a future? For another perspective on this issue, see “The Battle over Generic Biologics.”

A careful examination of today's global biotechnology industry reveals that several major issues are threatening its continued financial success and profitability. These include drug reimportation, mounting consumer pressure for lower cost therapies, increased political and governmental pressure in response to consumer backlash, and the need for better and more efficacious medicines. None of those threats looms larger than the specter of follow-on biologics, also known as *biogenerics*. The term *biogeneric* has been applied to so-called copycat versions of approved and marketed biopharmaceuticals whose patent expiry is near. Despite the current, spirited debate surrounding the use of *biogenerics* to describe this new class of biopharmaceuticals, this article uses it for simplicity.

Historically, the manufacture and sale of generic drugs has proved to be a financially lucrative business model. Globally, the generic pharmaceutical business generated approximately \$33 billion in revenue in 2002 ^{~1}. The financial success of the generic pharmaceutical industry has led many industry thought leaders and company executives to consider developing and manufacturing generic versions of blockbuster biopharmaceuticals near patent expiry such as Epogen (erythropoietin-alpha, EPO), Neupogen, (granulocyte colony

stimulating factor, G-CSF), and Avonex (interferon-beta). Like their classical pharmaceutical cousins, biogenerics are expected to be interchangeable or substitutable for innovator products and sold at discounted prices that result from lesser development costs.

NO GUARANTEES


Although the potential for biogenerics appears great, they face an uncertain future. Much of the uncertainty is driven by the lack of clear regulatory pathways for approval of such drugs in the European Union (EU), United States, and Japan. That, in turn, stems largely from the scientific debate over the concept of chemical and biological similarity between biogeneric and innovator products ^{~2}.

Despite the lack of a clear regulatory framework, no fewer than 25 biopharmaceutical companies have stated their intentions to enter the biogenerics market. However, regulatory uncertainty has substantially inflated the financial risk associated with the fledgling biogenerics industry. Consequently, the industry is seriously undercapitalized, and the early entrants and start-ups are largely unable to attract sufficient funds to drive the industry forward with financial certainty. Furthermore, in the absence of defined regulatory approval pathways, it is not clear whether development costs will actually be lower for biogenerics than for innovator products. If biogeneric development costs are not substan-

BIOLOGICS FACING PATENT EXPIRY


BRAND	ACTIVE SUBSTANCES	MARKETER	YEAR OF APPROVAL	2003 SALES IN \$MILLIONS	BIOGENERIC UNDER DEVELOPMENT?
Epogen	Epoetin alfa	Amgen	1989	2400.0	Yes
Procrit	Epoetin alfa	Ortho Biotech	1990	3984.0	Yes
Neupogen	Filgrastim	Amgen	1991	1300.0	Yes
Humulin	50% human insulin isophane suspension, 50% human insulin (recombinant DNA origin)	Eli Lilly	1992	1060.0	Yes
Intron A	Interferon alfa-2b, recombinant	Schering Plough	1986	1851.0	Yes
Avonex	Interferon beta-1a	Biogen	1996	1168.0	Yes
Engerix-B	Hepatitis B vaccine, recombinant	GlaxoSmithKline	1989	*540.0	Yes
Rebif	Interferon beta-1a	Ares-Serono	2002	630.8	No
NeoRecormon	Epoetin beta	Roche	1991	998.0	No
Cerezyme/ Ceredase	Glucocerebrosidase	Genzyme	2003/1991	734.0	No
Humatrope	Somatropin	Eli Lilly	1987	371.0	Yes
ReoPro	Abcicimab	Eli Lilly/Centocor	1994	364.0	No
Betaseron	Interferon beta-1b	Schering AG	1993	929.0	Yes
Kogenate	Antihemophilic factor, recombinant	Bayer	2000	497.0	No
Enbrel	Etanercept	Amgen	1998	1300.0	No

* Sales figures for 1999


Source: 



tially lower than corresponding innovator costs, it will not be possible to sell biologics at steeply discounted prices. Nevertheless, the promise of a substantial financial upside coupled with increasing consumer demand for biopharmaceutical products has prompted many analysts and company executives to bet on the future success of the biologics industry.

A POTENTIAL GOLD MINE?

A key factor driving the growth of the biologics industry is the upcoming patent expiry of several blockbuster biopharmaceuticals. Over the next three years, many top-selling biopharmaceutical products will come off patent, creating real opportunities for biologics manufacturers. Industry analysts predict that more than 50% of the 2001 therapeutic protein market could be susceptible to loss of market share (via patent expiry) by the end of 2005. That equals \$13.5 billion in annual product sales 1. No wonder

so many companies want to enter the biologics market.


Most of the major biopharmaceuticals that face patent expiry are currently being developed by biologics manufacturers (Table 1). Several other products, including insulin and human growth hormones, have already lost patent protection—at least for the drug substance—and are already susceptible to generic competition .

The potential economic incentives and financial opportunities offered by the biologics market are substantial. Currently, the world market for biopharmaceuticals is about \$20 billion per year 3. If we assume that biologics can achieve a penetration rate comparable to classical generic pharmaceuticals, the global biologics market size could be at least \$3 billion .

Another biologics industry driver is increased demand from consumer groups, government agencies, and healthcare insurers for access to lower

cost biopharmaceuticals. Several state and national governments have enacted legislation to encourage greater use of generic drugs that offer equivalent pharmaceutical care at substantially lower costs. As healthcare and prescription drug costs continue to rise and state and national healthcare budgets come under increasing scrutiny, lower priced, therapeutically equivalent biologics will become an extremely attractive prospect for consumers, government agencies, and large payers alike.

NOT SO FAST . . .

The development, manufacture, and sale of biologics have long been anticipated by industry thought leaders, financial analysts, and innovator biopharmaceutical companies. Some products—EPO, G-CSF, and others—are already being sold in the so called gray or unregulated markets in Asia, Africa, and South America .

may represent a good start for the biologics industry, several major challenges must be overcome before the industry can realize its full potential.

As already mentioned, no legal regulatory framework is in place in Japan, Europe, or the United States to permit biologics to gain regulatory and market approval, although both the EMEA and the FDA have repeatedly promised that guidance on biologics will be forthcoming in the “very near future” ~4-6. In December 2003, the EMEA’s Committee for Medicinal Products for Human Use issued a guidance document that sought to establish quality, safety, and efficacy between an original biopharmaceutical and its “biosimilar counterpart” ~7.

It has been clearly established that product comparability between innovator and biologic products cannot be determined solely by chemical and biophysical characterization.

Following the issue of the guidance, the European parliament approved new pharmaceutical legislation setting out a legal framework for the registration of “biosimilar” drugs. But the EMEA must still develop guidelines for the practical implementation of the initiative. The EMEA has indicated that those guidelines will be issued no later than November 2005. In contrast with the progress in Europe, the FDA has been reluctant to issue any guidance on biologics. Moreover, at a public hearing on the subject in September 2004, the agency did not indicate when guidance would be forthcoming.

Thus biologic products cannot be marketed or sold in the United States, Europe, or Japan. Furthermore, when regulatory pathways are finally developed, they will probably be different from one nation to another. That will undoubtedly contribute to significant differences in development time, manufacturing costs, and the pricing of biologics in those markets.

Science Limits Business: Given the scientific complexities of protein biology and biopharmaceutical manufacturing, a contentious debate surrounds biopharmaceutical product comparability, making it unclear whether biologics can actually be developed, manufactured, and sold at prices lower than those of innovator products. Opponents of biologics claim that because of protein complexity, interchangeable chemical identity and biological activity between two products would be difficult to achieve and even more difficult to prove without clinical trials. Proponents argue that chemical identity is not necessary as long as there is therapeutic equivalency and a similar safety profile between innovator products and their biologic counterparts.

Initially, proponents of biologics thought they might be able to gain regulatory approval for their products using an abbreviated approval process similar to the one used for generic classical pharmaceuticals (which typically does not require manufacturers to conduct expensive and time-consuming human clinical trials). But that is now highly unlikely because it has been clearly established that product comparability—product efficacy and safety—between innovator and biologic products cannot be determined solely by chemical and biophysical characterization ~2-3. Consequently, most industry analysts and regulators believe that some form of human clinical trials will be required for the approval of biologics in Europe, Japan, and the United States. That will undoubtedly increase the costs, development times, and pricing for most biologic products.

Making a Challenge: Another factor that may influence the pricing of

biologics is the high cost of manufacturing biopharmaceuticals. Facilities operating under cGMP regulations are expensive to build, staff, operate, and maintain. For example, Amgen recently spent approximately \$800 million to build a dedicated manufacturing facility for Enbrel, a top-selling treatment for rheumatoid arthritis ~8.

One way biologics companies might cut manufacturing costs is to outsource production to contract manufacturing organizations (CMOs) that specialize in biomanufacturing. Although that may appear to be a viable cost-saving strategy, industry experts have determined that there is a global shortage of available commercial biomanufacturing capacity ~9. Consequently, biomanufacturing availability at CMOs is currently first come, first served, which generally favors innovator companies. Unfortunately, that leaves biologics companies with only two biomanufacturing options: build a cGMP manufacturing facility or manufacture product when CMO production facilities are available. Neither option is likely to make the market price of biologics as low as previously thought.

Patent Blockade: Established biopharmaceutical companies, with substantial financial resources at their disposal, have begun to block development of biologics using a variety of strategies. These include vigorous patent infringement litigation, increasing product patent protection through bioprocess improvements or reformulation, and extending the product lifecycle of existing biopharmaceuticals through development of therapeutically superior second-generation innovator products.

Several landmark patent infringement cases are already in progress, e.g., Amgen vs. Transkaryotic Therapies for the production of a generic version of EPO. Moreover, although the composition-of-matter patents on several products soon will expire or already have expired, innovator companies have extended patent protection by patenting improvements or changes to bioprocess and

For the biogenerics market to develop fully, biogenerics manufacturers must aggressively increase their lobbying efforts and wage an aggressive public awareness campaign regarding the safety, efficacy, and quality of their products, which will require a substantial financial investment.

manufacturing processes. For example, the composition-of-matter patent for EPO expires at the end of 2004. However, Amgen was able to extend its patent life by patenting the technique required to produce EPO in mammalian cells. Amgen's process patents are enforceable in the United States through 2013.

Innovators Outdo Themselves: Clinically superior second-generation versions of several top selling biopharmaceuticals have already appeared on the market. In 2003, Amgen began to market Aranesp, a second-generation Epopoetin product, and Neulasta, a longer acting version of its popular drug Neupogen ^{~8}. Likewise, Schering Plough introduced PEG-Intron in 2001, a second generation version of Intron, its top selling treatment for chronic hepatitis C infections ^{~10}. Not surprisingly, these clinically superior second-generation products have begun to replace their first-generation counterparts as the therapeutic treatments of choice.

The ultimate success of the biogenerics industry is contingent

upon the reception of its products by its customer base—patients, physicians, and managed care professionals. Patients and physicians may be reluctant to switch to biogenerics out of unwarranted fears—promulgated by innovator companies—concerning biogeneric product quality or safety. To overcome that, biogenerics manufacturers will have to spend money on intensive marketing and advertising campaigns if they hope to garner market share from innovator companies. These additional costs are also likely to prevent biogenerics from being sold at the steeply discounted prices originally envisioned.

JUMPING OFF

For the biogenerics industry to move forward in earnest, European, Japanese, and US regulatory agencies must develop clearly defined regulatory processes for the approval and sale of biogeneric products. That will finally permit biogenerics manufacturers to accurately determine the costs associated with the development, manufacture, and sale of their products. Once investors can examine both development costs and likely biogeneric pricing, they are likely to inject some much-needed capital into the biogenerics industry to facilitate its growth.

Biogenerics companies must also address the current shortage of biomanufacturing capacity. This is critically important because biopharmaceutical manufacturers must be able to produce sufficient quantities of material to provide consumers with ready access to their products and keep prices low. To that end, several companies, such as GeneMedix and Sicor, have built their own biomanufacturing facilities. Others, such as Dragon Pharmaceuticals and BiogeneriX, have formed partnerships with biomanufacturing companies and CMOs in countries where labor costs are low. Although a number of CMOs have recently announced expansion of their biomanufacturing capacity, their role in the biogenerics industry has yet to be defined, largely because of preexisting relationships between


CMO and innovator biopharmaceutical companies. It is not yet clear whether CMOs will risk alienating innovator companies and possibly lose revenue streams to manufacture products for fledgling biogenerics companies. The apparent reluctance of large, established CMOs to work with biogenerics companies has prompted the formation of smaller, financially hungry CMOs very willing to provide reasonably priced biomanufacturing services to the biogenerics industry. This development, along with the advent of low cost, sterile, disposable biomanufacturing equipment, may enable biogenerics companies to overcome the present biomanufacturing bottleneck.

REFERENCES

- ^{~1} BioPortfolio Limited. The Future Battle Between Biopharmaceuticals & Biogenerics: Executive Summary. *BioSeeker* 2003. October 2003, www.bioportfolio.com/cgi-bin/acatalog/BioSeeker_2003.html.
- ^{~2} Cumming DA. Glycosylation of Recombinant Protein Therapeutics: Control and Functional Implications. *Glycobiology* 1991; 115–130.
- ^{~3} Polastro ET. The Future of Biogenerics. *Contract Pharma* October 2001, www.contractpharma.com/Oct013.htm.
- ^{~4} FDA Generic Biologics “Structure” To Come Soon: Policy Debate in 2005. *The Pink Sheet* 5 April 2004: 7–8.
- ^{~5} FDA “Follow-on” Biologics Guidance: A Preview. *The Pink Sheet* 10 May 2004: 4–5.
- ^{~6} European Commission. *Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code Relating to Medicinal Products for Human Use*. 2003; OJ L 159/46.
- ^{~7} *Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins As Active Substance: Quality Issues*. Committee for Proprietary Medicinal Products. December 2003, EMEA/CPMP/BWP/3207/00 Rev 1, www.emea.eu.int/pdfs/human/bwp/320700en.pdf.
- ^{~8} Amgen. www.amgen.com (Accessed 2 September 2004).
- ^{~9} Fermentation and Cell Culture Technology: Problems and Predictions. *BioPharm Int'l*. December 2003, www.biopharminternational.com/biopharm/issue/issueDetail.jsp?id=2984.
- ^{~10} Schering-Plough. www.spcorp.com (Accessed 2 September 2004).

Opposition to development of biogenerics from industry leaders has been expectedly fierce. After all, innovator companies don't want to lose market share for their top-selling branded biopharmaceuticals to competition from lower cost biogenerics. Not surprisingly, over the past five years, several groups have waged an extremely aggressive lobbying campaign to shape and influence biogeneric regulatory approval pathways. Furthermore, they have attempted to discredit biogeneric products on the basis of inferior quality, safety, and efficacy.

Surprisingly, the biogenerics industry has done little to respond to or refute those accusations. Apparently, many biogenerics companies have taken a wait-and-see attitude, largely because they lack the financial resources to mount counterlobbying measures. For the biogenerics market to develop fully, biogenerics manufacturers must aggressively increase their lobbying efforts and wage an aggressive public awareness campaign regarding the safety, efficacy, and quality of their products, which will again require a substantial financial investment.

The development of and reliable access to safe and reasonably priced biogeneric drugs will undoubtedly improve worldwide healthcare outcomes. The biogenerics industry is clearly in the early and most critical stages of its development. A large infusion of investment capital and a clear regulatory framework for approval of its products are desperately needed to ensure the future success of this industry. If both things occur in the next few years, biogenerics companies are likely to be able to fully realize their economic potential and legitimize their standing in the healthcare industry. 

Corresponding author **Seth Yakatan** is a cofounder of Katan Associates, 1-310-406-8236 seth@katanassociates.com. **Clifford Mintz** is CEO of BioInsights.