Generic Biologics: The Next Frontier

USA Specialty Pharmaceuticals

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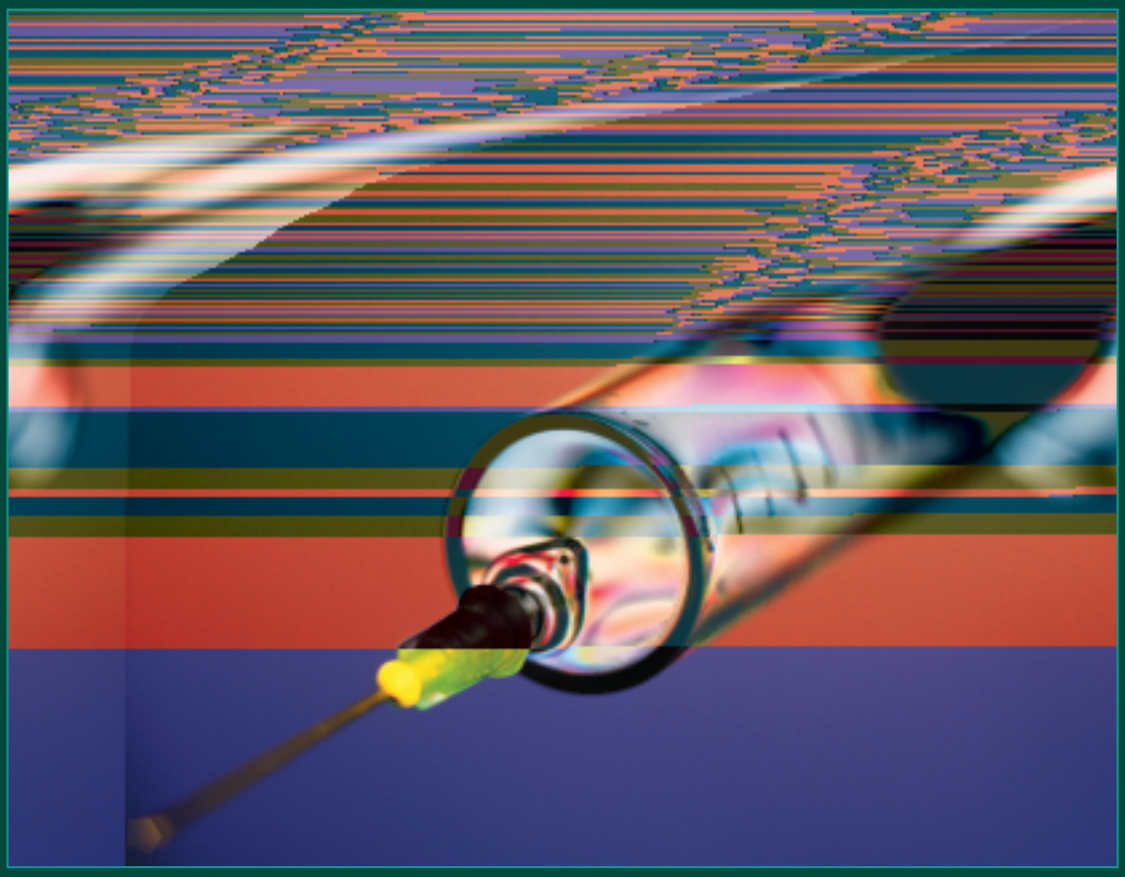

Special Report

- Biological products are approaching the end of their market exclusivity with over $10 billion in 2000 sales coming off patent over the next five years.
- There are proposed regulations to prove equivalent biotech products in the relative near term, and additional regulatory clarity is likely to come in the months ahead.
- We believe that generic biologic products represent a significant opportunity and anticipate progress on this cutting edge of technology.

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Highlights and Overview

Specialty Pharmaceuticals

Generic Biologics: The Next Frontier

- Approximately 20 years ago, the first biopharmaceutical products were patented in the United States. Over the next five years, more than $10 billion worth of products will come off patent.
- Recognizing an untapped opportunity, a handful of companies are focusing on the development and commercialization of generic biopharmaceutical products. Although no regulatory infrastructure presently exists in the United States for such an undertaking, there is potential elsewhere; and it will likely exist domestically in the coming years.
- With only a select number of companies capable of competing in this sector, the potential is significant. Generally, companies taking advantage of this have a unique combination of biopharmaceutical knowledge and manufacturing expertise.
- We believe that advances in science have brought this once nebulous picture into clearer view. Furthermore, key cases on the matter offer insight into the possibility.
- We believe that a U.S. legislative initiative to create an approval pathway is simply a matter of time, and foresee generic biopharmaceutical product launches abroad and eventually in the United States.

Executive Summary

We believe that the potential for generic biopharmaceutical products is building, and that the opportunity for first movers into the field can be enormous. Through 2006, over $10 billion worth of branded biologics are scheduled to go off patent, gaining the attention of generic pharmaceutical manufacturers, Congress and federal regulators. However, because of the intrinsic differences from conventional pharmaceuticals, as well as differences in the oversight and manner in which they are regulated, generic biopharmaceutical products face a number of unresolved issues inhibiting progress toward establishing rules for the approval and marketing of such compounds.

Nonetheless, we believe that the pieces are beginning to fall into place, with many of the biotechnology industry's arguments declining in influence. First, one of BIO's primary arguments—that different cell lines cannot produce equivalent products—is ironically refuted by Biogen, one of biotech's leaders. It's drug, Avonex®, was approved for marketing, despite the fact that clinical trials were conducted with product produced from a different cell line than the one used to produce the current marketed product. Second, the *Serono v. Shalala* ruling established that the power to determine "sameness" lay with FDA and that a therapeutically equivalent biologic can be achieved. Third, FDA has proposed a potential pathway for generic biologic approval using an established procedure. Fourth, U.S. Pharmacopeia has offered to set up standards for the characterization of generic biologics, providing a highly respected, independent voice in favor of the concept. Finally, interest in Congress appears to be growing toward examining the possibility of establishing new regulations for the approval of generic biologics as part of a comprehensive reform of the overall Waxman-Hatch framework.

Accordingly, many companies, including Sicor, Teva and Ivax, have begun making preparations for the manufacture and sales of generic biologics. By being first movers into this valuable marketplace, the most aggressive companies stand to reap the greatest benefits, and may end up years ahead of the competition.

With attention increasing on the high costs of drugs in general and the extremely high costs of biotech drugs, the political climate has begun to shift toward making these drugs more affordable to the average citizen. We believe that infinite patent lives for biotech products are unfeasible in the current political environment. Additionally, generic products have been widely successful on many fronts for conventional pharmaceuticals. As such, we believe that the United States government will take the necessary steps to establish guidelines for generic biologics as part of a comprehensive Waxman-Hatch reform, or as part of an effort to add a prescription drug benefit to the Medicare program.

Generic Biological Drugs

Biotechnology: Stedman's Definition

Stedman's Medical Dictionary defines biotechnology as the field devoted to applying the techniques of biochemistry, cellular biology, biophysics, and molecular biology to addressing issues related to human beings and the environment. It is the use of recombinant DNA for production of useful molecules, or for the alteration of biological processes to enhance some desired property.

Biologic products

Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Most biologics are complex mixtures that are not easily identified or characterized, and many biologics are manufactured using biotechnology.

Selected Biotechnology Drugs Facing Patent Expiration

Brand Name (Generic Name)	Marketing Company	Indication	2000 Sales ($, millions)	U.S. Patent Expiry
Rebetron™ Combination Therapy (Ribavirin and Interferon alfa-2b)	Schering-Plough	Chronic Hepatitis C	1,361*	2001
Ceredase® (alglucerase)	Genzyme	Gaucher disease	537**	2001
Cerezyme® (imiglucerase)	Genzyme	Gaucher disease	537**	2001
Humulin® (human insulin)	Eli Lilly & Co.	Diabetes	1,137	2002
Novolin® (human insulin)	Novo Nordisk	Diabetes	260.4	2002
Intron® A (interferon alfa-2b)	Schering-Plough	Leukemia; Hepatitis B and C; melanoma; lymphoma	1,361*	2002
Avonex® (interferon beta-1a)	Biogen	Multiple Sclerosis	761	2003
Humatrope® (somatropin)	Eli Lilly & Co.	Growth hormone deficiency	303	2003
Nutropin®/Nutropin AQ® (somatropin)	Genetech	Growth hormone deficiency	226	2003
Epogen® (epoetin alpha)	Amgen	Anemia	2,034	2004
Procrit® (epoetin alpha)	Johnson & Johnson	Anemia	1,720	2004
Geref® (sermorelin)	Serono Laboratories	Growth hormone deficiency	0.045	2004
Synagis® (palivizumab)	Abbott	Respiratory syncytial viral	420	2005
Activase® (alteplase)	Genetech	Myocardial infarction, stroke, pulmonary embolism	206	2005
Protropin® (somatrem)	Genetech	Growth hormone deficiency	1.796	2005
Neupogen® (filgrastim)	Amgen	Neutropenia	1,224	2006
Albutein® (human albumin)	Enzon	Shock and hemodialysis	4.509	2006
Total			10,197	

* and ** Figure represents the combined sales for the two compounds.

Source: IMS Health, ABN AMRO estimates and FDA Orange Book

Biotechnology: Product Lifecycle

Approximately 20 years ago, the first biotechnology products were patented in the United States. Based on intellectual property protection, these products are entering the twilight years of exclusivity. Over the next five years, approximately 18 biotechnology drugs with 2000 branded sales of over $10 billion will lose market exclusivity. Although traditional pharmaceuticals have generated more attention with over five times the brand sales of expiring patents, the biotech sector offers a significant opportunity.

Regulation of Biologics

In 1991, an agreement between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) created a regulatory framework for biotechnology products.

In 1991, an agreement between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) created a regulatory framework for biotechnology products. Prior to this resolution, all ethical products were reviewed by CDER. Afterwards, drug molecules fell under the CDER domain, while products from living organisms/tissues were governed by CBER.

At first glance, this division of labor appears to be clean. However, those biotechnology products previously approved by CDER remain under that Center's jurisdiction. For the most part, this includes recombinant human insulin and growth hormone along with certain sex hormones and antibiotics.

As part of the agreement, a dividing scheme was laid out, which has been criticized for its complexity and lack of consistency. For example, human-tissue derived products are classified as drugs, but human blood-derived products are classified as biologics. Biologics combined with radioactive components are considered biologics, while biologics combined with non-radioactive components are drugs.

Review of Statutory Guidelines

Drugs

New and generic drugs are *approved* under the Food, Drug and Cosmetic Act and the Food and Drug Modernization Act. New drug applications (NDAs) are filed under 505(b)(1), while abbreviated new drug applications (ANDAs) for generics are filed under 505(j).

Biologics

Biopharmaceuticals are *licensed* under Section 351 of the Public Health Service Act and in specific sections of the Food, Drug and Cosmetic Act. To obtain marketing approval for a new biologic, an applicant submits a biologics license application (BLA).

Precedent Sets the Tone

Review of biologic progenitors established expertise in biotechnology at CDER.

Ironically, there exists expertise in biotechnology products at CDER. This is mainly due to early biologic work and review of biologic progenitors. As we have stated, CDER previously reviewed all the biologics until CBER's inception

and the inter-center agreement. Because of this, there remains a biologic knowledge base at CDER. Alternatively, some biologic products are the result of recombinant DNA technology's improved ability to manufacture drugs.

In this scenario, a second-generation product is classified not on the size of the molecule, as biologics are generally large (macro) in size, or on the derivation (e.g., live tissue), but on Center-familiarity with a product. For example, Genzyme's Gaucher disease treatment Ceredase® (alglucerase), generated from tissue sources, was regulated as a drug, and the recombinant version of that product, Cerezyme® (imiglucerase), was also regulated as a drug, because there was expertise within CDER.

Equivalent Drug Guidelines

Therapeutically Equivalent = Pharmaceutically Equivalent + Bioequivalent + Safe & Effective.

Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (Orange Book for Approved Drug Products).

Under the statutory guidelines that govern CDER, there are established pathways to determine equivalence. For products regulated as drugs, there are three existing channels for regulatory approval.

Approval Process for Therapeutic Equivalent Drugs

ANDA - Abbreviated New Drug Application.

NDA - New Drug Application

1. 505(j) - Generics, statutory authority for ANDAs for any drug product approved as safe and effective, always interchangeable with a reference listed drug.
2. 505(b)(2) - NDA applicant does not own or have a right of reference to all of the studies essential for approval, may or may not be interchangeable with a listed drug.
3. 505(b)(1) - Full NDA, may or may not be interchangeable with a listed drug.

General criteria for products being therapeutic equivalents

- Approved as safe and effective.
- Pharmaceutical equivalents have the same active ingredient(s), the same dosage form and are identical in strength.
- Pharmaceutical equivalent.
- Bioequivalent.
- Adequately labeled.
- Manufactured in compliance with cGMP.

Regulatory Requirements for AB Rating (therapeutic equivalent)

Bioequivalents are absorbed in the bloodstream at the "same rate and extent" as a brand drug.

21 CFR 320 (c) - Pharmaceutical equivalents, drug products that contain the identical amount of identical active ingredient, i.e., the same salt or ester of the same therapeutic moiety in identical dosage form.

21 CFR 320.1 (e) - Bioequivalence, the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents…becomes available at the site of drug action when administered at the same molar dose under conditions in an appropriately designed study…

Generic Biotechnology Feasibility

In the past, there have been numerous arguments why generic biotechnology products would not be feasible. The most significant reason is the interrelated concerns over safety and immunogenicity. The crux of the other reservations generally resolves around science's ability to manufacture and measure such products. Since those early reservations, there has been a combination of technological advances, which are fulfilling the necessary requirements for such an undertaking. This is particularly true for improved production and assay techniques (e.g., *in vitro*/biochemical and analytical assays). Examples of some new analytical methods that are assisting in the standardization of biological products are:

- **MALDI-TOF Sprectroscopy.**
- **Reflectometric Interference Spectroscopy.**
- **Capillary electrochromatography.**
- **Signal Transduction Fingerprinting.**
- **Bioinformatics, including Microarray Technology and Pharmacogenoimics.**

Essentially, we now have better ways to characterize a product. With advances in technology eliminating some of the ambiguity surrounding biologics, generic versions are only constrained by an antiquated regulatory structure.

…focusing on how it should be done, not whether it can be done.

This fact is highlighted by one of the fathers of generic drug law, Senator Hatch, who believes that a pathway for generic biologic approval is inevitable given the interest in a Medicare prescription drug benefit. He is focusing on how it should be done, not whether it can be done.

To begin, Senator Hatch's health aide Bruce Artim stated at the Schwab Washington Research Group healthcare conference in Washington, D.C. on May 9, 2001, that he believes the senator "is less interested in tinkering with the provisions of old Hatch-Waxman than in engaging in debate about capitalizing on a new era in biomedical knowledge."

Hatch's consideration of generic biologics was to kick off with hearing on gene patents. The hearing was originally scheduled for May 8, 2001, but was postponed due to Bush Administration judicial nominees. We would have expected rescheduling to occur soon; but with Senator Jeffords realignment and the resultant power change in the Senate, most hearings have been shelved.

However, we consider this issue to be of bipartisan importance and believe that it will successfully be reinstated to the agenda. This is exemplified by the fact that the new Chairman of the Senate Judiciary Committe, Patrick Leahy of Vermont, is active in such healthcare issues as breast cancer and medical privacy. To aid him in this cause, Senator Leahy is supported by fellow Senators Edward Kennedy of Massachusetts, Joe Biden of Delaware, Herb Kohl of Wisconsin, Dianne Feinstein of California, Russell Feingold of Wisconsin, Charles Schumer of New York, Richard Durbin of Illinois and Maria Cantwell of Washington - all known healthcare advocates.

Sounding the Alarm

Biotechnology Industry Organization (BIO)

Safety comes to the forefront.

BIO is the voice of the biotechnology industry. The Organization's main argument against the development of generic biologics has been the inarguable issue of safety, mainly because of immunogenicity. Additionally, BIO has insisted on the inherent difficulty in achieving and demonstrating comparability between generic biologics and innovator products.

A slight change in the polio vaccine led to people contracting the disease from the immunization.

BIO has raised fears that a generic biologic would have safety issues. For example, in the 1950s, a slight change in the production process of the Salk polio vaccine led to a failure to inactivate completely the virus used in manufacturing. As a result, some people contracted the disease from the vaccine. More recently, a manufacturing change in a human growth hormone product caused an increase in immunogenicity until the process was corrected. These case reports have been used by protesters of a generic biologic pathway, namely individual companies, BIO and PhRMA.

Immunogenicity –Understanding the Safety and Efficacy Issue

Immunogenicity is the state or property of being allergenic. It is an important property distinguishing most biologic products from most small drug molecules. It originates in the manufacturing process and/or the intrinsic properties of the biologic. In the early days of medicine, it was easily exemplified by serum sickness in which an allergic reaction appears 7 to 12 days after administration of a foreign serum (e.g., horse) or certain drugs (e.g., penicillin). In a later instance, a loss of efficacy was noted over time when using porcine (pig)/bovine (cow) insulin in diabetics. This was as a result of the development of antibodies against the foreign peptide (animal insulin).

Sources of Immunogenicity

Source	Description
Impurities	Cell substrate or media components that co-purify with the protein
Product-related impurities	Fragments, aggregates and chemical modifications that are related to the product, but are not intrinsic to it
Monoclonal Antibodies	Inherently immogenic and must be evaluated for each product
Conjugates	Creation of new antigenic determinants at the conjugation or fusion site or immunogenicity of the individual components
Fragments	Exposure of new antigenic determinants

Source: Meeting of the Biological Response Modifiers Advisory Committee (July 15, 1999)

Antibody Formation

The efficacy of a biologic may be affected by the development of antibodies to it. Depending on the degree of immunogenicity, antibody formation to the foreign peptide will alter the efficacy of the drug. Typical binding antibodies are IgM and IgG, which may be detected in ELISA, RIA and other assays. It is usually the IgG, which is the neutralizing antibody (negates the effect of the biologic), directed against biologically active sites.

As a consequence of antibody formation, the safety and efficacy of the biologic is called into question. There are a number of items responsible for this, but

they are mainly due to potential changes in bioavailability, drug effectiveness,

Clinical Factors in Immunogenicity

Factor	Description
Patient population	Genetic background and autoimmune disease
Chronic illness	Disrupt the distribution of proteins, especially for kidney and liver diseases
Antibodies	Pre-existing antibodies (e.g., RF, IgM, anti-IgG, streptokinase) effect efficacy
Medication	Concomitant medications, such as chemotherapy and immunosuppressive drugs alter distribution
Dose effect	Dose-immunogenicity increases with dose, both single and cumulative, and frequency of administration
Route of administration	Subcutaneous generally more immogenic than intramuscular or intravenous

Source: Meeting of the Biological Response Modifiers Advisory Committee (July 15, 1999)

Comparability

The Biotechnology Industry Organization maintains that, because of the inherent complexity of biological products, generic versions must be judged on a case-by-case basis—the "Know thy product" mantra. Additionally, BIO has lobbied the "debatable presumption"—that no matter what information exists to characterize a biologic, the innovator will always have a critical piece of information that precludes the possibility of generic biologics.

Because of the particulars of biopharmaceutical manufacturing, the process, in large part, defines the product. Unlike with traditional chemical entities, a change made in the process cannot be assumed to be directly proportional to the resulting difference in the final product.

It is generally accepted that any generic biologic would have to be considered on a case-by-case basis. In terms of missing data, we believe that there are two options. Either science can fill in the blanks or companies can be mandated to disclose all information relevant to the product. The table below illustrates how science can accommodate for problems in the road.

What Science Says…

PK – Pharmacokinetic
PD - Pharmacodynamic

Problems	Potential Solutions
Complex chemical structure closely associated with biological activity, clinical safety and efficacy	Physio-chemical testing
Physio-chemical tests with limitation	Biological testing
Biological activity assays imprecise, unable to detect small chemical changes	Clinical relevance
Same solution formulation containing the same protein, with different PK/PD profiles when produced by different manufacturers or different processes	Standard requirements
Isoforms with different PK/PD profiles	PK/PD testing
Assays for PK are problematic	Clinical efficacy (in the absence of meaningful bioassays and/or in-vivo biomarkers)
Inherent microgenicity	Preclinical safety (e.g., impurity qualification) and Clinical safety (e.g., immunogenicity)
Determining critical differences in a product	Crossover studies

Sounding the Charge

The United States Pharmacopeia (USP)

The United States Pharmacopeia establishes and disseminates officially recognized standards of quality and authoritative information for the use of medicines and other health care technologies. In pursuit of its mission to promote public health, USP establishes standards to ensure the quality of medicines for human and veterinary use.

USP's head, Dr. Roger Williams, has suggested use of the term "pharmaceutical equivalence" when comparing moieties of biotech products to which changes have been made, and potentially for comparing products developed by different manufacturers.

As the former Director of the Office of Science at CDER, Dr. Williams publicly discussed the intent of FDA to pursue how to approve a recombinant protein product and give it an "AB" or equivalent rating to an existing product. While the recombinant protein the Agency is looking at would technically not be filed under an ANDA, it could reasonably be filed under section 505(b)(2) of the Food Drug & Cosmetic Act, making it a "me too" product with an "AB" rating.

Under Dr. Williams' guidance, USP is ready for the challenge of creating a standard, which permits a confidence interval that determines equivalence. USP believes that the way to determine what are the critical differences in a highly complex molecular structure is to perform replicative crossover studies.

Crossover studies would show proof of concept by following patients, who have been switched from the original product to the generic and vice versa. These would typically be designed as small Phase III trials. However, we believe that FDA will primarily be interested in safety studies, relying on other information, such as bioequivalence, for approval.

HCFA Policy Ignites a Controversy

Section 1861(f)(1) of the Social Security Act of 1965 states that in order to obtain Medicare reimbursements, drugs and biologics must be either included or approved for inclusion in a select number of compendia. One such reservoir is the U.S. Pharmacopeia-National Formulary (USP/NF). Although policy has been on the books for nearly 40 years, it has not been rigorously enforced until now (June 30, 2000, program memorandum).

BIO is resisting such a policy shift due to the implications of monographs for biologics, which raises the issue of intellectual property. Industry is under the impression that biologic monographs will provide a "how to" on the manufacture of biologics.

Though we view monographs as an important step in the standardization of biologics, this approach seems ill fated due to the Congressional backlash that has occurred. We feel that HCFA is under considerable pressure to reverse its policy. We will look for other avenues of success in the attempt to standardize these products.

Case Studies

As with any other area of generic drugs, understanding how generic biologics may come to the market requires a review of some key judicial and regulatory cases. We believe that there are three cases which highlight the issues that may arise. The are:

FDA approval of Avonex® for Multiple Sclerosis

The Avonex® case illustrates that after extensive characterization and analysis that two different cell lines can be proven comparable. It demonstrates that biologics can be quantified, that different cell lines and manufacturing processes can be utilized to produce the same clinically efficacious compound and that issues of safety and immunogenicity are manageable. This directly refutes BIO's claim that products produced by different cell lines cannot be equivalent.

Serono Laboratories, Inc. v. Shalala

In *Serono Laboratories, Inc. v. Shalala*, FDA's determination of what is required to establish "sameness" was upheld in an Appeals Court decision. Essentially, FDA is entitled to a "high level of deference" for "evaluations of scientific data within its area of expertise."

The significance of this ruling is that it established the authority for the determination of "sameness" solely with FDA - a point that the Agency advocated and the courts upheld. In addition, FDA exemplified that a generic or therapeutically equivalent biologic can be achieved.

Amgen, Inc., v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.

In *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, it was disclosed in district court proceedings that Transkaryotic Therapies'product is not significantly different from Amgen's product. At the same time, TKTX's product was reported to FDA as equivalent in therapeutic properties to Amgen's product. This suggests that simple amino acid changes in a biologic do not result in a different product, unless the changes result in functional differences. As such, a generic manufacturer may engineer a biologic, which would be considered the "same" as the originator's one.

Case Study of Avonex: The Advocacy of Comparable Biologics

Two Different Cell Lines Are Found To Be Unique AND Comparable

In 1995, Biogen received Food and Drug Administration (FDA) approval for its interferon beta-1a product, Avonex®, for the treatment of relapsing forms of multiple sclerosis (MS). In this case, the approval was significant, because it marked the first time that FDA has found two cell lines to be unique and comparable.

The Irony of the Situation

The biotechnology industry consistently states that no two cell lines may be proven to be comparable. However a few years ago, one company did just that.

The irony is that the company was not trying to prove a generic biologic concept; but rather, protect its own investment in resources.

Interferons

Interferons are a family of naturally occurring proteins and glycoproteins termed cytokines. They are produced by eukaryotic cells in response to viral infection and other biological inducers and mediate antiviral, antiproliferative and immunomodulatory activities. Three major interferons have been distinguished: alpha, beta and gamma. Interferons alpha and beta form the Type I class of interferons, and interferon gamma is a Type II interferon. These interferons have overlapping, but distinct biological activities.

Interferon Beta

Interferon beta is one member of the Type I family, and is produced by various cell types including fibroblasts and macrophages. Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers.

Interferon Beta-1a

Interferon beta-1a is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. The amino acid sequence of the recombinant protein produce by these cells is identical to naturally occurring interferon beta and has thus been given the designation 1a. Interferon beta-1a is a single chain, glycosylated polypeptide 166 amino acid residues in length, and with an approximate molecular weight of 22.5 kD.

Early Interferon Development

Prior to Biogen's active involvement in interferons, another company was leading the way in discovery. Rentschler Biotechnology in Laupheim, Germany, is a 70-year-old German company that develops and markets synthetic and biotechnology-based pharmaceuticals, primarily in Germany. The company's biotech activities started in the mid-1970s out of its virological research group.

Rentschler has been a pioneer in the field of interferon beta research. For example, the current World Health Organization (WHO) international standard for natural interferon beta was derived using the Rentschler product, which the Company shared with the National Cancer Institute (NCI) for its research purposes as early as 1977.

As early as 1980, Rentschler had started a project to develop a recombinant version of human interferon beta. The company first attempted an expression in E. coli, but soon faced severe difficulties in recovering biologically active material. Therefore, the company switched its research target to eucaryotic cell expression systems. The first results with a mouse cell line were reported in the scientific literature in 1981.

As a result of low recoveries in that particular cell system, Rentschler decided to concentrate its further activities on Chinese Hamster Ovary (CHO) cells. In the

mid-1980s, Rentschler succeeded in developing a process to produce recombinant interferon beta product from CHO cells.

Joint Venture

Meanwhile, Rentschler and Biogen had become partners in a company called Bioferon in Germany, which was a 50/50 joint venture. Bioferon developed and manufactured interferon products, referred to as BG9014 and BG9015. The two products were produced from the same cell line. BG9014 was the original product produced. Some changes in the manufacturing process were made by Bioferon, resulting in the new product BG9015.

Data on BG9015, manufactured by Bioferon, were submitted in a master file to FDA. The pivotal Phase III clinical trial for multiple sclerosis was conducted under an investigator initiated IND which cross-referenced the master file. During the trial, Bioferon went into receivership and there was no further production of BG9015. There was, however, enough vialed BG9015 final product to finish the pivotal trial.

Separate Paths

The joint venture was eventually dissolved, and Rentschler fully reacquired the facilities, staff and equipment, along with the intellectual property rights to BG9015, which the Company continues to produce and develop. Since the dissolution of the joint venture, there has been no scientific collaboration between the two companies.

New Cell Lines

Based on the biochemical and pharmacokinetic differences, Biogen was informed by FDA that BG9216 was not comparable to BG9015.

Thereafter, Biogen developed a new CHO cell line that carried the interferon beta gene. Using a new manufacturing process, Biogen began production of a product referred to as BG9216. These CHO cells were adapted for suspension culture. Data supporting the use of this cell line were submitted to CBER and showed that the specific activity of BG9216 was somewhat greater than BG9015, and that it contained a characteristic additional peak in the peptide map. In addition, pharmacokinetic and bioequivalence studies in humans showed that BG9216 was not equivalent to BG9015. Based on the biochemical and pharmacokinetic differences, Biogen was informed by FDA that BG9216 was not comparable to BG9015.

For these reasons FDA had determined that BG9015 and BG9418 are comparable and that clinical data derived from the use of BG9015 can support the licensure of the BG9418 molecule.

Biogen developed another interferon beta-1a cell line, and the product produced by this cell line was designated BG9418. BG9418 had been extensively characterized and compared in side-by-side analyses with BG9015. Biological, biochemical and biophysical analyses had shown that the two molecules are comparable. Biological activities of each molecule are similar using several different assays, such as anti-viral, anti-proliferation, and enhancement of MHC class I expression. Peptide maps as determined by high-pressure liquid chromatography of peptides derived by proteolysis of the two proteins are superimposable. Carbohydrate analysis revealed a similar pattern of major oligosaccharide forms on each protein. Finally, pharmacokinetic studies in humans using the two molecules revealed a pattern of clearance from the blood

that was determined to be equivalent by rigorous statistical analyses. For these reasons FDA had determined that BG9015 and BG9418 are comparable and that clinical data derived from the use of BG9015 can support the licensure of the BG9418 molecule.

Version BG9418 was shown to be equivalent to BG9015 in pharmacokinetic studies in normal human volunteers, and is the commercial version of the product.

The clinical investigation of interferon beta-1a utilized four closely related versions, which are designated BG9014, BG9015, BG9216, BG9418. BG9014 and BG9015 were produced from the same CHO cell line; whereas, BG9216 and BG9418 were from different CHO cell lines. BG9015 and BG9014 differed in their respective purification processes. The amino acid sequences of BG9014, BG9015 and BG9418 were identical to natural human interferon beta; however, BG9216 demonstrated structural differences. The carbohydrate structures of all four materials were similar to natural human interferon beta. Bioequivalence studies demonstrated that BG9015 was pharmacokinetically equivalent to BG9418 but not to BG9216. BG9015, made by Bioferon, was used in most of the clinical trials including pivotal studies of multiple sclerosis, but is no longer available to Biogen. BG9216 was used in preclinical toxicity and Phase I studies, but development of BG9216 was stopped after it was found to be pharmacokinetically different from BG9015. Version BG9418 was shown to be equivalent to BG9015 in pharmacokinetic studies in normal human volunteers, and is the commercial version of the product.

In summary, the interferon beta product used in the pivotal study and submitted to FDA for approval is not the same as the interferon beta product being produced and marketed by Biogen. FDA recognized the revolutionary nature of such a proposal—to substitute the new Biogen interferon beta, which had not been tested in multiple sclerosis for the already tried Bioferon interferon. After extensive characterization and analysis, FDA agreed with Biogen's proposal that BG9015 and BG9418 are comparable.

Avonex® Cell Lines

Product	Developer	Cell Line Origin	Cell Line Description
BG9014	Bioferon Joint Venture	CHO, same as BG9015	Original product
BG9015	Bioferon Joint Venture	CHO, same as BG9014	Secondary product; followed changes in manufacturing and purification process; filed with FDA (reference)
BG9216	Biogen	CHO, unique	Not comparable with BG9015
BG9418	Biogen	CHO, unique	Comparable with BG9015

Source: Company reports

This marks the first and only time that FDA has taken such a position. It effectively shatters the notion that therapeutically equivalent biologics are not feasible. It demonstrates that biologics can be quantified, that different cell lines and manufacturing processes can be utilized to produce the same clinically efficacious compound and that issues of safety and immunogenicity are manageable.

Case Study of *Serono Laboratories, Inc. v. Shalala:* The Authority to Determine "Sameness"

"Sameness" - Easier Said Than Done

In the summer of 1998, Food and Drug Administration's (FDA) authority to make scientific judgements as to what constitutes the "sameness" of the active ingredients in two drug products was upheld in *Serono Laboratories, Inc. v. Shalala* in a U.S. Appeals court. In the case, Serono argued that FDA violated its own regulations by approving a generic version of Pergonal®, which is a fertility drug used to induce ovulation in women or induce sperm production (spermatogenesis) in men.

Serono's main claim was that the abbreviated new drug application (ANDA) product did not have the same active ingredients, while FDA countered that although natural variations in the product existed, it was still the same active ingredient.

In the end, the U.S. Court of Appeals ruled that FDA has the scientific discretion to determine "sameness," and overturned a lower court's decision on the matter.

Fertility Product in the Spotlight

In 1969, FDA approved a new drug application (NDA) submitted by Serono Laboratories, Inc. for Pergonal®, which is used for the treatment of male and female infertility. Pergonal® is a menotropins product, meaning that it is extracted from the urine of post-menopausal women, and that it primarily contains two active ingredients - follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH actually make up less than five percent of Pergonal®, with lactose and uncharacterized urinary proteins (UUP) constituting the remainder.

Is it a Drug or a Biologic

Although Pergonal® is considered to be a biologic product, it is regulated as a drug. This is because an agreement between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) was not created until 1990 for the division of active ingredient oversight. As such, early biologics, such as menotropins, human growth hormone and recombinant insulin, are regulated by CDER.

Different Regulations

According to Section 505 of the Federal Food Drug and Cosmetic Act, abbreviated new drug applications (ANDAs) may be submitted for "new drugs" with approved NDAs. However, biologics are regulated under Section 351 of the Public Health Service Act, which does not have a generic framework for "new biologics" with approved biologics license applications (BLAs).

Are Two Fertility Products the Same

In 1990, Lederle Parenterals, Inc. submitted an ANDA to FDA for a generic version of Pergonal®, referred to as Repronex®. Ferring Pharmaceuticals, Inc. acquired the rights to Lederle's ANDA while it was pending with FDA. At which

time, Serono sought a preliminary injunction preventing FDA approval of the ANDA.

Under Section 314.93 of the Food, Drug & Cosmetic Act, FDA determines the suitability of products for ANDAs by determining that two products are the same as each other, meaning identical in active ingredient(s), dosage form, strength, route of administration and conditions of use, except where there is an existing patent of exclusivity. Furthermore, Section 320.1 defines pharmaceutical equivalents as products that contain the same salt or ester of the same therapeutic moiety, as well as other characteristics.

Backbone versus Side Chain Ribs

The chemical structure of FSH consists of two components: 1) a protein backbone with a specific amino acid sequence; and 2) carbohydrate side chains. In concluding that the FSH in Repronex® is the "same as" or "identical to" that in Pergonal®, FDA determined that the protein backbones and amino acid sequences are identical. There are, however, slight natural variations in the configuration of the carbohydrate side chains producing different isoforms of the hormone, a phenomenon known as "microheterogeneity." FDA observed that complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible. Indeed, it usually is not even possible to assure by chemical analysis that different batches of the same product "are identical at the level of the carbohydrate side chains"—including different batches of Pergonal® itself.

Serono argued that this isoform variation in FSH rendered Repronex® different from Pergonal®, and hence ineligible for an ANDA. FDA acknowledged the isoform variation, but concluded that it was not "clinically significant for the product's intended uses;" and therefore, did not preclude a "sameness" finding. In other words, FDA found that slight chemical differences between the brand and the generic products were insignificant in the determination of “sameness.”

Microheterogeneity and the Degree of Variation

Assuming that "most glycoprotein products will have microheterogeneity," FDA determined that the relevant "question is how much variation should be permitted." As per FDA:

> "To be considered to have the same active ingredients as the reference listed drug, generic FSH products based on Pergonal as the reference listed drug must have the same primary structure, i.e., the same protein backbone and amino acid sequence as Pergonal (assured by using the same natural source material), the same potency, and the same degree of batch-to-batch uniformity. The batch-to-batch uniformity of Pergonal is achieved using *in vivo* rat potency tests, specified by the U.S. Pharmacopeia (USP)…The bioactivity of each batch of generic Menotropins…is also controlled using USP rat bioassays, which provides the same

> assurance of potency and batch-to-batch uniformity as is provided by Serono for Pergonal."

After reviewing additional clinical data, FDA found "that any potential variations in FSH isoforms between the Ferring menotropins product and Pergonal® appear not to be clinically significant for the product's intended uses."

FDA reasonably interpreted statutory law to require clinical equivalence between generic and pioneer drugs, chemical identity to the extent possible, and limitations on inherent isoform variation.

Federal Register Supports FDA

The Federal Register, which defines the term "same as" to mean "identical," supports FDA's view that the regulation does not require complete identity regardless of the kind of drug at issue. FDA will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity. In most cases, these standards are described in the U.S. Pharmacopeia (USP). However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness. For example, for some drug products, standards for crystalline structure or stereoisomeric mixture may be required.

Statues lend guidance

Under section 314.93 of the Food, Drug and Cosmetic Act, FDA determines the suitability of products for ANDAs by determining that two products are the same as each other, meaning identical in active ingredient(s), dosage form, strength, route of administration and conditions of use, except where there is an existing patent or exclusivity. Section 320.1 defines pharmaceutical equivalents as products that contain the same salt or ester of the same therapeutic moiety, as well as other characteristics.

European Court of Justice - "Essential Similarity"

> A medicinal product is "essential similar" to an original medicinal product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original products as regards safety or efficacy.

Though not taken into account for this case, the European perspective offers a broader view of how "sameness" or "similarity" are being viewed judicially. In addition, it offers guidance as to how the issue will be handled in Europe.

The significance of this ruling is that it established the authority for the determination of "sameness" solely with FDA - a point, which the Agency advocated and the courts upheld.

Appeals Court Decision

In the Appeals Court decision, FDA's determination of what is required to establish "sameness" for purposes of the Act rests on the "agency's evaluations of scientific data within its area of expertise," and hence is entitled to a "high level of deference."

The significance of this ruling is that it established the authority for the determination of "sameness" solely with FDA—a point, which the Agency advocated and the courts upheld. In addition, FDA exemplified that a generic or therapeutically equivalent biologic can be achieved.

For additional information on the regulatory history of this case, please see Appendix 1.

Case Study of *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*: Therapeutically Equivalent

In the patent infringement case between Amgen and Transkaryotic Therapies, it was disclosed that Transkaryotic Therapies Inc. had told FDA that its GA-EPO product and Amgen's Epogen® were equivalent in their therapeutic properties.

Judge's Comment

According to the district court judge in the case, "A subsequent pharmaceutical manufacturer may argue to FDA that its product is as safe or as effective as another product already on the market…"

Festo Supports the Generic Industry

In addition, the recent *Festo* decision from the U.S. Court of Appeals for the Federal Circuit will facilitate the generic's objective. In the case of *Festo Corp. v. SMC Pneumatics Inc.*, the court decision narrowed the grounds on which a patent holder can show infringement based on doctrine of equivalents by stating that a patent holder gives up certain rights when claims are amended during patent prosecution.

We believe that generic biologics manufacturers will be able to engineer their products around existing patents by finding amendments made during prosecution. Since a new rule in place since November 2000 requires that many patent applications be published 18 months after they are filed, a generic company is better prepared to manufacture its own version.

Case Study Synopsis

Examined individually, these cases refute particular arguments against generic biologics. When taken together, they advocate the feasibility of generic biologics through their affirmation of the basic scientific and expert skills necessary to see this concept to fruition.

Building upon these cases, FDA has taken the necessary steps towards a proposed regulatory pathway for generic biologic approval of products regulated by CDER.

The Proposed Regulatory Pathway

Biotechnology-Derived Substances for AB-Rated Drug Products – A CDER Perspective

In a recent presentation to industry and regulatory leaders at a National Association of Pharmaceutical Manufacturers (NAPM) workshop, FDA spoke about "Biotechnology-Derived Drug Substances for AB-Rated Drug Products — A CDER Perspective." The talk highlighted that there are multiple approval processes for interchangeable drugs, but there are legal issues surrounding biologics.

The 505(b)(2) pathway to "AB" rating.

Interchangeable products will require evidence to demonstrate therapeutic equivalence, which is scientifically based, technology driven and product dependent.

The biotechnology-derived drugs can be divided into two groups—macromolecules and small molecules. Macromolecules comprise proteins, genes and mononuclear antibody-drug conjugates. Small molecules cover antibiotics, amino acids, vitamins and other cell metabolites.

Current policy on biotechnology-derived products comes from the Federal Registrar (51 FR 23309) in June 26, 1986. Points to consider in the production testing of new drugs and biologicals produced by recombinant DNA technology were issued on April 10, 1986. An IND and full NDA (505 (b)(1)) is required, and a CMC supplement is not acceptable.

Comparability protocol is appropriate when one can reliably predict and assess the impact of the change on the product and assure that the product will consistently meet approved specifications and standards.

FDA released *Comparability* for Protein Drugs guidance in 1994. Within the same manufacturer's product before and after manufacturing changes, clinical studies may be waived. This is separate from *equivalents* [21CFR 320.1 (c) and (e)], which are between products manufactured by different manufacturers.

PhRMA and BIO are sensitive to this issue because FDA has stated: "We are postulating a path for the recombinant molecule that gets an AB rating in the Orange Book, that does not come in under the [ANDA] route, it comes in under the (b)(2) route."

505(b)(2) Guidance

Section 116 of FDA Modernization Act, which delineates classification of changes and validation requirements covers both drugs and biologics.

With the quiet murmur of generic biologics getting louder, FDA has been accepting proposals for a regulatory pathway. At this point, CDER has decided that the traditional ANDA route does not allow for sufficient evidence to approve a generic biopharmaceutical. This is partly because CDER cannot ask for additional preclinical or clinical testing under an ANDA. FDA has sought a compromise application, which offers data from the innovator product and the potential for additional information.

Food, Drug and Cosmetic Act, which determines the different mechanisms under which a drug can be approved, accounts in Section 505 (b)(2) for duplicates of a naturally-derived or recombinant active moiety.

In following this approval process, a recombinant protein would technically not be filed under an abbreviated new drug application (ANDA), as generic drugs are, rather it would be filed under section 505(b)(2) of the Food Drug & Cosmetic Act, not 505(j), making it a "me too" product with "AB" substitution.

A 505(b)(2) application is a new drug application where the sponsor relies on data it does not own. It may be considered a hybrid between the regular NDA with full, independent data or data for which the applicant has the rights, called a 505(b)(1), and the 505(j), which is a generic drug application (ANDA). An approved 505(b)(2) receives NDA patent protection. The sponsor, therefore, creates a branded generic.

Currently, USP is drafting guidance for Industry on submission of scientific and technical documentation for approval of Somatotropin (hGH) and human insulin drug products under Section 505(b)(2).

A typical application process

The application process would entail:

1) Company to meet with FDA to discuss sponsor's requirements for approval.
2) Follow the 505(b)(2) path for approval.
3) Cite a listed drug.
4) Perform preclinical and/or clinical testing (e.g., safety).
5) Present investigational data to FDA.
6) If Sponsor can demonstrate *pharmaceutical* equivalence to a listed drug, then the company can obtain an AB rating.

In speaking with FDA regarding the status of the 505(b)(2) proposal, we have learned that is well into the approval process. It has passed the Medical and CNCCC review boards and now rests with Regulatory. Although there is momentum created from early acceptance, the Regulatory review board is likely to put the proposal under a microscope and scrutinise it.

Aside from the standard reasons of ensuring legal authority and regulatory feasibility, the Regulatory group must be prepared for industry's challenge. The Pharmaceutical Research and Manufacturers of America (PhRMA) has accused FDA of going beyond its regulatory authority in proposing to allow new drug applicants to use another innovators' proprietary data to support an application.

Because of the significance of this proposal, we suspect that it will not only require divisional approval (CDER), but also agency (FDA). We further believe that it may require the approval of the overseeing department—Secretary of Health and Human Services (HHS), Tommy Thompson. At that point, it may be temporarily stalled as Congressional action is given the lead in establishing a pathway. Nonetheless, with interest rising on the costs of medications and the potential for a Medicare prescription drug benefit, we believe that congressional action on the issue is simply a matter of time.

Generic Biotechnology Products - Corporate Business Strategy

Generic Biotechnology Products - an Untapped Global Opportunity

Recognizing an untapped opportunity, a handful of companies are focusing on the development and commercialization of generic biotechnology products. Although no regulatory infrastructure presently exists in the U.S. for such an undertaking, there is potential elsewhere. These companies intend to exploit the fact that several biotech drug patents in Europe and Asia are either about to expire or have already expired. In some cases, the biologic may never have been patent protected.

Generic Biotechnology Products - Global Rollout

Despite the fact that the U.S. represents the largest consumer of drugs and biologics, these companies are willing to risk development investiture with the hopes that a staggered marketing approach will eventually include the United States. Stemming from this, we foresee a phased three-part marketing rollout.

The first phase will be to an international customer base in regulatory-immature countries—Asia, Central and South America, North Africa, the Middle East and Eastern Europe. The second phase will target Western Europe and Canada, where multisource product proposals offer an entry for generic biologics. Ultimately, the goal is to launch in the United States in the third phase. This staggered approach is intended to create an immediate revenue stream while pursuing additional market opportunities around the world. With a base of sales to the less-developed countries paying off the incremental overhead expenses, the companies could leverage established operations in order to take advantage of potential changes in the United States that may open up the domestic market for sales potential.

Generic Biotechnology Products - Who to Look For…

Companies that will be able to take advantage of this opportunity have a unique combination of biopharmaceutical knowledge and manufacturing expertise. This is often because the company has provided contract manufacturing to a biotechnology company; and in doing so, honed the necessary skills for its own innovation and production capabilities. The invaluable experience and depth of expertise obtained from previous exposure to biopharmaceutical products will be a major factor in the success of the generic biologic initiative. In addition, a certain amount of international exposure is helpful.

CSF = Colony Stimulating Factor.
EGF = Epidermal Growth Factor.
EPO = Erythropoietin.
GM-CSF = Granulocyte Macrophage-Colony Stimulating Factor.
hGH = human Growth Hormone.
IFN = Interferon.
IL = Interleukin.

Generic Biotechnology Products - Selected Company Profiles

Company	Location	Pipeline Products
Barr Laboratories	Pomona, New York, U.S.A.	Not disclosed
Bio-Technology General Corp.	South Iselin, New Jersey, U.S.A.	Insulin and two other products
Cangene Corp.	Mississauga, Ontario, Canada	GM-CSF, hGH
GeneMedix	Suffolk, England, United Kingdom	GM-CSF, IFN-α-2b, EPO, Insulin, IFN-γ, IL-2, EGF
Ivax Corp.	Miami, Florida, U.S.A.	CSF, IFN and hGH
Microbix Biosystems, Inc.	Toronto, Ottawa, Canada	Urokinase
Sicor, Inc.	Irvine, California, U.S.A.	CSF, hGH, IFN, EPO

Source: Company reports

Barr Laboratories

Barr Laboratories, Inc. is a pharmaceutical company engaged in the development, manufacture and marketing of generic and proprietary prescription pharmaceuticals. It is best known for its upcoming launch of generic Prozac® for depression. The company's proprietary division, Barr Research Inc., also covers biological research and development. At this time, Barr has one biotech product, which is a vaccine for Japanese encephalitis. The vaccine is being co-developed with the U.S. Army at Walter Reed Medical Center and should complete Phase II clinical trials in 2001.

Beginning in late 1998, Barr has been mentioning the concept of generic biotechnology products. Since that time, the company has brought in Dr. Carole Ben-Maimon, who worked on Teva's Copaxone® for multiple sclerosis, to head the Barr Research Inc. division. Although Barr does not have any fermenters for biotechnology products, it has stated that it would consider an acquisition, joint venture or contract manufacturer to grow its biological franchise, when and if necessary. Despite the fact that we do not foresee Barr being one of the more active players in this area, we feel that good revenues from sales of generic Prozac® could drive R&D for generic biotech.

Bio-Technology General Corporation

Bio-Technology General Corp. (BTG) is engaged in the research, development, manufacture and marketing of biotechnology products. The company distributes its products on a worldwide basis primarily through a direct sales force in the United States and primarily through third-party license and distribution relationships elsewhere. The company seeks both broad markets for some of its products as well as specialized niche markets for others where it can seek Orphan Drug status and potential marketing exclusivity. BTG's biotechnology products are derived from E. coli and mammalian cell lines.

BTG – Bio-Generica™

In September 1999, Bio-Technology General Corp entered into a strategic alliance with Teva Pharmaceutical Industries Ltd. that focuses on the development and global commercialization of two generic recombinant

therapeutic proteins. BTG's primary role will be to develop and manufacture the products, and Teva will have exclusive marketing rights. Teva is responsible for any clinical trials, which are needed for registration and approval. The agreement calls for Teva to make payment to BTG of up to $20 million for product rights and milestone payments, along with 25-30% of net sales. Currently, BTG has two products coming out of R&D and into pre-clinical development.

BTG - Akzo Nobel and Recombinant Human Insulin

In January 1999, BTG entered into a technology transfer and license agreement with Akzo Nobel's wholly owned subsidiary, Diosynth b.v., for recombinant human insulin. The license grants Diosynth rights to the product in most countries of the world. Under the terms of the agreement, BTG transferred its recombinant human insulin technology to Diosynth, and Diosynth will manufacture the product in bulk form for the licensed territory. Another Akzo Nobel subsidiary, Organon, may in certain instances, finish the bulk and market it in finished form. BTG will receive license fees linked to the achievement of certain milestones and royalties on all commercial sales of the product.

BTG – Human Growth Hormone

BTG's human growth hormone is currently being marketed by Ferring in Europe and JCR in Japan and is also being sold by third-party distributors in several countries in South America and the Far East. In addition, regulatory approval to market BTG's human growth hormone is pending in several Latin American countries, South Africa and several Pacific Rim countries. In the U.S., approval is pending the resolution of litigation with Serono. The previous dispute with Genentech has been resolved, mostly through a new production process and cGMP facility. Teva plans to market the product in the United States, and BTG should receive 30% of net sales.

Bio-Technology General biotech products

Biotechnology Product	Active Ingredient/Type of Product	Indication
Approved/Marketed Drugs		
Bio-Tropin™	Human Growth Hormone	Indicated for the treatment growth hormone deficiency and Turner's syndrome.
BioLon™	Sodium Hyaluronate	Used as a surgical aid to protect corneal endothelium during cataract extraction, intraocular lens implantation and anterior segment surgery.
Bio-Hep-B™	Recombinant Hepatitis B vaccine	Indicated for Hepatitis B immunization.
Silkis®	Vitamin D derivative	Indicated for the topical treatment of psoriasis.
Bio-Hy™	Sodium Hyaluronate	Indicated for osteoarthritis of the knee.
Clinical Development		
Fibrimage®	Fibrin Binding Domain	Studies for the diagnosis of deep vein thrombosis (blood clot).
Puricase™	Polyethylene glycol conjugate of uricase	Investigations for the elimination of excess uric acid in individuals with gout and other conditions when alternative therapy is ineffective or contraindicated.
OxSODrol™	Superoxide Dismutase	Studies for the prevention of asthma/reactive airway disease in premature babies.
Prosaptide™	Stimulatory peptide	Studies for neuropathic pain associated with diabetic peripheral neuropathy.
Insulin	Recombinant Insulin	Studies for diabetes.
Pre-Clinical Development		
FACTOREX™	Thrombolytic adjunctive agent	Investigations for the destruction of blood clots.
BTG-262	Conjugated Monoclonal Antibody	Experiments using a monoclonal antibody to deliver a cytotoxic agent for the treatment of leukemia.
Research & Development		
Bio-Generica™	Represents a strategic relationship with Teva, where BTG will develop and manufacture recombinant therapeutic proteins that are currently marketed by various biotechnology companies and are nearing the end of their patent protection.	

Source: Company reports

The company's broad product line and international reach enhance its ability to develop and market generic biotechnology products.

Cangene Corporation

Cangene Corp. is a biotechnology company that develops, manufactures and markets specialty plasma products (hyperimmune) and recombinant therapeutic products for international markets. Using its hyperimmune business to provide a financial base and technology platform, Cangene is building new businesses in generic biotechnology ("second-entry biologics") and innovative products.

Utilizing its patented production technology, CANGENUS™, for recombinant protein manufacturing, the Company appears well positioned to take

advantage of off patented products. Currently, Cangene has two late stage generic biologics and five early stage.

Cangene Corporation biotech products

Product (Biologic Class)	Indication
Approved/Marketed Products	
WinRho SDF™	Indicated for the prevention of hemolytic disease of the newborn (HDN) and to treat an autoimmune clotting disorder called idiopathic thrombocytopenic purpura (ITP).
VariZIG™	Indicated for immunization against varicella zoster virus (chicken pox).
Phase III Clinical Trials	
Leucotropin™ (GM-CSF)[1]	Studies for bone marrow and peripheral blood stem cell transplantation
Human Growth Hormone (hGH)[1]	Studies for the treatment growth hormone deficiency and associated failure to grow.
Pre-Clinical Development	
CNJ R03	For its recombinant products, Cangene is pursuing a generic-style strategy. The recombinant (R) products in development are all in different therapeutic areas. One product has completed preclinical testing, while the remaining four are still undergoing investigational studies. We do not believe that the Company is interested in developing a recombinant insulin product. Based on the Company's experience in Infectious Disease and Hematology, we believe that EPO, IFN, IL and antibiotics would represent good fits.
CNJ R04	
CNJ R05	
CNJ R06	
CNJ R07	

[1] GM-CSF and hGH have completed Phase III clinical trials. The Company expects to file in 2002 in Canada for both products.

Source: Company reports

Cangene — Vertically Integrated

Cangene has just finished construction of a 55,000 square foot manufacturing facility in Canada. Fully 30,000 square feet are available for manufacturing, while approximately 25,000 square feet consist of laboratory space. There are bacterial fermenters, ranging from 20 liters to 200 liters to 2800 liters—representing a significant production capacity. Currently, the facility is in validation.

With its contract manufacturing subsidiary, Chesapeake Biological Laboratories (CBL), Cangene can go from fermentation to finished vial. Chesapeake Biological Laboratories is an established provider of pharmaceutical and biopharmaceutical product development and production services. With its large 71,000 square foot facility, CBL has provided services on a contract basis to more than 150 pharmaceutical and biotechnology companies and has contributed to the development and production of more than 175 products.

Cangene - Apotex Research Contract

In addition, Cangene has a research contract with Apotex, Inc., which is the largest Canadian-owned pharmaceutical company and the leading supplier of generic pharmaceuticals to the Canadian market, with a 38% market share. Cangene plans to deliver generic biotechnology products to Apotex in exchange for milestone payments. Apotex specializes in generic development and manufacturing. As part of its strategy of being an integrated pharmaceutical company, Apotex has branched into the field of biotechnology via Cangene.

GeneMedix

GeneMedix is involved in the development, manufacture and sales of generic versions of therapeutic proteins using recombinant DNA technology. GeneMedix focuses on large market biotechnology drugs that are unpatented in certain Asian, Eastern European and South American countries, and are due to come off patent in various western European territories in the next two to five years.

The company has acquired the rights to seven cell lines for the production of generic versions of therapeutic proteins. The technology is based on recombinant DNA, and the cells that are modified are either from bacterial, mammalian or yeast.

GeneMedix biotech products

Product	Development Stage	Toxicology Study	Therapeutic Equivalence Study	Estimated Launch	Launch Territory
GM-CSF	Complete	Complete	Complete	2Q01	China
Interferon-α-2b	Scale up started 1Q01	Complete	Started 3Q00	4Q02	China
Erythropoietin	Scale up started 1Q01	Complete	Started 3Q00	4Q02	China
Insulin	Process verification started 3Q00	NA	NA	NA	NA
Interferon-γ	Cell line acquired	NA	NA	NA	NA
IL-2	Cell line acquired	NA	NA	NA	NA
Epidermal Growth Factor	Cell line acquired	NA	NA	NA	NA

Source: Company reports

Ivax Corp.

Ivax is engaged in the research, development, manufacturing and marketing of branded and generic pharmaceuticals. The Company recently completed the acquisition of Indiana Protein Technologies, Inc., which gives it the capability to purify and fully characterize proteins. Indiana Proteins has a 7,000 square foot manufacturing facility with bacterial fermenters ranging from 10 to 100 liters. Indiana Proteins has experience in E. coli and mammalian cell lines.

In addition, Ivax has biotechnology capabilities at its Czech Republic and Hungarian facilities. We expect that Ivax will initially target colony stimulating factors (CSFs), interferons (IFNs) and human growth hormone (hGH), and secondarily consider recombinant human insulin and epotein for generic products. In speaking with the Company, we do not believe that any of the products have entered clinical trials, but remain at the preclinical level. Microbix Biosystems, Inc.

Microbix Biosystems, Inc. specializes in the development and manufacture of cell and tissue culture derived biologicals to address emerging world markets for generic biotherapeutic drugs and animal health products.

Microbix's first generic biologic is ThromboClear, which is a generic version of the cardiovascular drug urokinase, used to clear blood clots. ThromboClear is the only generic version of the protein drug Abbokinase. ThromboClear is completing analytical and stability testing in preparation for its ANDA submission to FDA. The company also expects to complete a 25-50 patient clinical trial in safety, dosing, pharmacokinetics (PK) and pharmacodynamics (PD).

In preparation for the ANDA, Microbix has been meeting with CDER and CBER simultaneously. Urokinase is a biologic which is regulated as a drug. The scientific expertise to evaluate the compound is found at CBER, while the ultimate regulatory authority over the drug is found at CDER. Additionally, CDER has familiarity with the ANDA process, which is somewhat foreign to the officials at CBER. We believe that the combined overview of the drug approval process is beneficial for the Company and could serve as a template for future generic biologics.

The company's work on ThromboClear has expanded its potential in new market areas such as process validation and a pipeline of other human biotherapeutics.

Microbix is currently evaluating another two opportunities in the area of generic biotherapeutics in the cardiovascular area, fitting well in the Company's skill set and capabilities. Presently, the two compounds are engaged in feasibility studies.

Sicor, Inc.

Sicor, Inc. is a mid-sized pharmaceutical company specializing in injectable generic products and active pharmaceutical ingredients. The Company's expertise in injectable products, as well as its past history in the development of biologics, will work in its favor. The Company expects the development of bioequivalent and improved forms of existing biologicals to be a new source of product revenue in future years.

Sicor has taken the initial manufacturing and licensing steps toward generic biopharmaceuticals. It is investing in FDA-compliant facilities and infrastructure for the development of biotechnology products, such as human

Growth Hormone (hGH), Interferon- 2a and 2b (IFN-), Colony Stimulating Factors (CSF) and Erythropoietin (EPO). Its Lemery division's manufacturing facility in Toluca, Mexico should be validated in 2002 and begin manufactured finished dosage forms of biotechnology products at the end of 2002.

We believe that Sicor will gradually rollout about four or five products over the next five years, starting with human Growth Hormone and Interferons in 2002, followed by additional Interferons, Granulocyte-Colony Stimulating Factor and Erythropoietin by 2006. We believe that Sicor will stay away from the crowded insulin market, which requires large production facilities, and look for more attractive opportunities.

Generic Biological Products — More to Come

As the patent and market exclusivity for biological products expires, we believe that more companies will be attracted to the space. This effect should be bolstered by improved regulatory guidelines for generic biological products. Since both drivers are expected to occur around the same time, we believe that there may be a synergistic effect in generic biological growth.

Generic Biologics — The Time Has Come

Period of Exclusivity is Drawing to a Close

In the next few years, biological products will be coming off patent. These products offer a significant opportunity in drug development and marketing.

Science Is Ready

Technology has progressed to a degree necessary to carry out the exacting demands of determining comparability and sameness of products. We now have better means of characterizing biologics. With the ability to measure biologics, we have become empowered to manage them.

Tentative Plan

The 505(b)(2) approval pathway is a preliminary attempt to achieve an approval process for generic biologics. We expect PhRMA and BIO to accuse FDA of overstepping its authority to license a biologic via this route. At the same time, we expect FDA to work with standardizing authorities, such as USP, to clear a path for progress.

We believe that the FDA's preliminary guidance for generic biologics brings a possible mechanism for approval closer. The 505(b)(2) application may usher a new era of generics one step closer to reality. At the very least, we expect the prospect of its use to force the issue to a head, requiring more concrete action.

New Regulatory Pathway Is Inevitable

We believe that the 505(b)(2) proposal has a lot of merit; however, it is a hybrid regulation not specifically intended for generic biologics and only addressing those regulated by CDER. With the cost of medications getting a lot of political attention, we foresee regulatory reform to address this issue.

We expect BIO to raise jurisdictional issues to deflect generic biologics, since new FDA approval procedures would have to be considered by the Senate Health Committee rather than the Judiciary Committee, which has historically played an active role in this issue because of Senator Hatch.

This should not derail any proposal, as the Senate Judiciary Committee has consistently worked closely with all involved parties for a balanced approach to the issue.

For instance, BIO is likely to be asked whether the association would support creating a system for generic biological approvals in exchange for generic industry support for expanded patent term restoration. BIO's main objective to Waxman-Hatch revisions is to achieve "one-for-one" restoration for drug development time.

Companies currently receive no more than half of the IND phase in patent extensions. Genzyme Senior VP-Government Relations, Lisa Raines, has argued that "in the absence of the advantages of an abbreviated approval system that are assigned to innovators, it's hard to understand the basis for which one can argue that the disadvantages alone should apply."

We expect more visibility on the matter to come from Senate Committee meetings, where hearings on Waxman-Hatch reform and gene patents are expected to occur this summer.

Possible Vehicles for Bill Approval

There exists a number of pharmaceutical-related legislative proposals, which may serve as a vehicle for a generic biologic pathway. They are the Medicare prescription drug coverage, the Prescription Drug User Fee Act, the Drug Reimportation bill and the pediatric exclusivity incentive.

This list exemplifies that there are a number of bills which may act as a vehicle. We believe that even if none of the above list are chosen, that there will be future bills, which may serve the purpose, due to the nature of the healthcare industry.

Most appropriately, we believe that new generic biologic regulations should be approached as part of a comprehensive review of the Waxman Hatch guidelines. This appears to be the position of Senator Hatch, and we believe that it is the most likely path to achieving comprehensive reform of the generic drug regulatory system. However, given the highly complex nature of the debate, we feel that opening the Waxman Hatch debate to include generic biologics would likely add at least another year to the reform process. Nonetheless, in order to achieve truly comprehensive reform, and given the impact that action can have on the affordability of drugs, we believe that the wait would be merited.

Standards Give Guidance

As technology evolves to support this initiative, it is important to maintain flexibility. At this early juncture, it would be premature to make detailed guidelines. Rather, it is beneficial to establish general guidance. We believe that the groups likely to lead the initiative are United States Pharmacopeia (USP), the International Conference on Harmonization (ICH), World Health Organization (WHO), National Institute for Biological Standards and Controls (NIBSC) and the International Association for Biologics.

The U.S. generics industry views the development of biologic monographs as a possible starting point for generic biologics. It is important to note that CBER seems to prefer developing standards in cooperation with these groups, rather than single handedly.

Opposition Is Alarmed

The Biotechnology Industry Organization (BIO) has officially assembled a task force to develop a policy on generic biologics. Previously, biotech companies representatives had expressed a generalized disbelief for the concept. As the improbable becomes more likely, BIO feels that a coherent statement is required.

We anticipate that a position statement will be announced at the BIO Annual Meeting at the end of June 2001.

The Next Frontier

As we have shown, generic biologics are in the foreseeable future. Developments in science have made it possible. Market potential has made it inevitable. Now, legislative initiative will make it feasible. With greater than $10 billion in brand sales of biologic products coming off patent over the next five years, and more to come in the years ahead, the opportunity for growth in this area is significant.

We believe that a select number of companies have taken the initial steps towards capitalizing on this potential. Although product launches in the U.S. may be less timely, launches abroad should occur relatively soon. As the safety and efficacy are proven, the concept will be proven. Also, the American public is keenly interested in equally efficacious products at reduced cost.

Appendix 1. Serono v. Shalala

On June 21, 1990, Lederle Laboratories filed an Abbreviated New Drug Application via the 505 (j) regulatory pathway for Repronex®, a generic alternative to Serono's infertility drug Pergonal®.

The application was transferred to Ferring Laboratories on July 3, 1996.

The ANDA was approved on January 30, 1997. On the basis of this approval, FDA assigned an "**AB**" rating to Repronex® in the "Orange Book."

Ferring performed two randomized, active controlled, multi-center studies in in vitro fertilization (IVF) and ovulation induction (OI), which showed that the drug could effectively be given either subcutaneously (sq) or intramuscularly (IM). This is in contrast to Serono's Pergonal®, which may only be administered intramuscularly.

On October 26, 1998, Ferring filed a New Drug Application (NDA) via the 505(b)(2) regulatory pathway for Repronex® for either a subcutaneous or intramuscular route of administration.

On August 27, 1999, the Repronex® NDA was given final FDA approval. On the basis on this approval, FDA assigned a "**BX**" rating to Repronex in the "Orange Book."

Ferring's Repronex® could no longer be considered "AB" rated in comparison to Serono's Pergonal®, because of the additional route of administration.

Companies Mentioned in this Report

Company	Exchange	Ticker	Price[a]	Rating
Abbott Labs	NYSE	ABT	51.65	Buy
Akzo Nobel	NASDAQ	AKZOY	42.90	N/R
Amgen	NASDAQ	AMGN	68.82	Add
Barr Laboratories	NYSE	BRL	77.01	N/R
Biogen	NASDAQ	BGEN	64.14	Add
Bio-Technology General Corp.	NASDAQ	BTGC	13.39	N/R
Cangene Corp.	TSE	CNJ	7.95[b]	N/R
Eli Lilly & Co.	NYSE	LLY	87.04	N/R
Enzon	NASDAQ	ENZN	76.41	N/R
GeneMedix	LSE	GMX	94.50[c]	N/R
Genentech	NYSE	DNA	55.00	Buy
Genzyme	NASDAQ	GENZ	56.87	N/R
Ivax Corp.	AMEX	IVX	37.10	Add
Johnson & Johnson	NYSE	JNJ	103.06	Buy
Microbix Biosystems, Inc.	TSE	MBX	90.56	N/R
Novo Nordisk	NYSE	NVO	43.17	N/R
Schering-Plough	NYSE	SGP	42.30	N/R
Serono Laboratories, Inc.	NYSE	SRA	24.66	N/R
Sicor, Inc.	NASDAQ	SCRI	19.00	Add
Teva Pharmaceutical Industries. Ltd.	NASDAQ	TEVA	63.50	Buy
Transkaryotic Therapies, Inc.	NASDAQ	TKTX	28.70	N/R

a Prices quoted as of the close June 7, 2001.

b Priced in Canadian dollars.c Priced in British pounds.

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