This piece of writing review is an accelerated pathway to bring biogenerics to market that protects patents and balances financial needs of brand name and generic drug companies, similar to Hatch-waxman, is the way to accomplish this goal. Biologic products represent an ever-increasing component of prescription pharmaceutical spending in United States, with sales growing at approximately 17 percent annually to about $38 billion in 2006. Term ‘biogeneric’ is usually taken to mean therapeutically equivalent version of currently marketed recombinant DNA-derived protein product that is manufactured by company that is on biotech therapies have expired or are due to expire. As biologics patents expire; generic versions are not yet being developed. But majority of biologics drugs manufactured using biological are licensed under PHS Act, which does not specify a process for generic, or otherwise equivalent. Yet there is currently no regulatory process for approving generic versions of these products. The absence of such a regulatory approval process for biogenerics artificially extends patent protection to brand name biologics. This leads to reduced incentives to discover and develop new brand biologic products.

**Keywords:** Biogenerics, Regulatory status of biotechnological products, biotechnology

**INTRODUCTION**

Generic drugs represent one of the greatest values in the world’s healthcare business and are of profound significance in the area of biopharmaceuticals. Because biopharmaceuticals are currently among the most expensive therapeutics on the market, and a growing number of world blockbuster biopharmaceuticals have already lost or are scheduled to lose patent protection in 2006 or soon after, the biogenerics industry anticipates an explosive worldwide expansion. Although biogenerics are not always easy to define, they are generally considered to be the generic forms of non-patented biological products—molecules developed using biological processes usually through modern biotechnology activity. Given the complicated process of creating biologics and the complex nature of biological products, biogenerics are not technically generic biologics in the traditional sense. In other words, biogenerics are not technically generic biologics unless they have been proven to show the same bioequivalence as the biologics.

The first patents of biopharmaceuticals derived from recombinant DNA will expire shortly, which raises the possibility of marketing generic products (‘biogenerics’) with limited documentation, similar to that which occurs with conventional pharmaceuticals. We propose the term off-patent biotechnological products (OPBPs) as an alternative to biogenerics when describing such products. It is questionable whether the majority of OPBPs can be classified as similar to the innovator products, considering the size and complexity of the molecules and the many factors that influence biological activity. There are three classes of OPBPs, each of which needs to meet different regulatory demands when seeking marketing authorization. [1]

One of the fastest growth areas in the pharmaceutical industry are biotechnology drugs, which grew at an average rate of 17 percent over the past two years, greater than any other sector of the pharmaceutical market. Right now, there are many biologics in the approval pipeline and it has been projected that 50 percent of drugs approved for the marketplace in 2010 will be the result of biotechnology. The Biotechnology Industry Organization (BIO), the trade association that represents biotechnology companies, notes that the word biotechnology comes from bio—the use of biological processes, and technology—to solve problems or make useful products. BIO points out those biological processes have been used for thousands of years to produce many products and commodities such as hardier crops, farm animals, and clothing. Using single celled organisms to make something isn’t really new either. For example, man has used microorganisms to make many food products such as cheese and bread, and to preserve dairy products, for 6,000 years. [17] (Debbie Strickland; 2007)

But during the 1960s and 1970s, the understanding of biology research reached a point where the smallest parts of organisms could be used—molecules such as DNA—to produce a product or develop a process. Therefore, today the term biotechnology means using cellular and biomolecular processes to develop better foods or discover miraculous cures [17] (Debbie Strickland; 2007). It is difficult to simply describe a biologic product, as it has many facets. This report focuses only on therapy-related biotech products. The FDA’s Center for Biologics regulates most therapy-related biologics. Their
definition includes vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or they may be living entities such as cells and tissues [14] (Food and Drug Administration, 2007). More simply, a biologic therapy is made from a living organism and can come from a human, an animal, or a microorganism.

Some examples of biologic drugs are:

• Epogen, a product made by Amgen, which stimulates bone marrow to produce red blood cells. It is used to treat anemia in patients that has been caused by chronic renal failure or other reasons such as chemotherapy and HIV.

• Genotropin, a product made by Pfizer, which is used to treat growth hormone deficiency.

• Humalog, an insulin product made by Eli Lilly, which is used in diabetes treatment.

• Pulmozyme, a product made by Genentech, which is used with other treatments in cystic fibrosis patients to improve lung function.

Many patents on biotech therapies have expired or are due to expire. For example, the patent on Genotropin expired in 2004 and Humalog’s patent is due to expire in 2013 [19] (Steve Miller, et al; 2007). Epogen patents expired in 2004 in the European Union and are believed to expire in the U.S. by 2015. [16] (Elise Wang, et. al, 2006)

As biologics patents expire, the generic versions are not yet being developed, unlike what occurs for chemically-based drugs. A few drugs have been approved through the abbreviated pathway found in the Hatch-Waxman Act including Hylenex, GlucaGen, and Omnitrope. While the manufacturers were required to provide new scientific data for their products, the FDA also relied on the information found in the past approvals of the brand name drugs. None of these drugs however, has been rated by the FDA to be therapeutically equivalent. In other words, they are not substitutable for the brand name drug.

Biologic therapies, for the most part, are licensed under the Public Health Service (PHS) Act, not the FD&C Act, and therefore do not fall under the Hatch-Waxman Act that provides the mechanism for an ANDA process to bring a generic version of a biologic safely and quickly to the market. There is also the understanding that a chemically-based drug is quite different from a biologic. In a March, 2007 hearing before the House Committee on Oversight and Government Reform on safe and affordable generic biotech drugs. [15] (Janet Woodcock, M.D.; 2007)

Generic products have now been available for over two decades, the market remains at an embryonic stage. However, with the impending loss of protection for several blockbuster drugs, demand for generic alternatives is set to take off. At the time of press, generic and biogeneric drugs are mounting a robust challenge to branded medications across most regional pharmaceutical markets. Global revenue is poised to expand from an estimated US $ 35.3 billion in 2003 to nearly US $ 71.8 billion in 2010. Such strong revenue growth is projected to derive from the escalating demand for pharmaceutical products across the world [7] (Murby, M. et al.; 1996). Efforts to control expenditure on expensive prescription drugs are also likely to accelerate the introduction biogeneric products. Although the approval process for biogenerics is still unclear, evolving regulation is set to impact uptake levels positively. Anticipated regulatory reforms are expected to support the launch of promising biogeneric products from 2005 to 2008. The generics and biogenerics market is forecast to expand strongly in Europe. Annual growth rates are, however, expected to rise at a slightly slower pace than those in the US [3] (Jenkins, N. et al.; 1996)
The first patents covering recombinant-DNA-derived biopharmaceuticals will expire in the near future, which leads to the possibility of marketing generic biotech compounds [11] (Kumarasamy, R. et al.; 1994). The current EU definition of a generic product is based on a ruling of the European Court of Justice in which: A medicinal product is essentially similar to an original product where it satisfies the criteria of having the same qualitative and quantitative composition in the form of active substances, of having the same pharmaceutical form and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original products as regards safety and efficacy. In the case of conventional xenobiotics there is long experience in the marketing of generics. These can be submitted for marketing authorization with relatively limited documentation that demonstrates that they are essentially similar to the original innovative product [5] (Lai, M.C. and Topp, 1999). Their regulatory dossier, that is the data required for submission to the regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicine Evaluation Agency (EMEA) to obtain marketing authorization, are relatively limited. In general, regulatory dossiers have two parts: a chemical/pharmaceutical part that shows similarity between the two products using techniques such as nuclear magnetic resonance and mass spectrometry; and a bioequivalence study, which is a comparative bioavailability study that establishes equivalence between the generic and the reference product. Usually, the comparative bioavailability study is restricted to a crossover study in volunteers that compares pharmacokinetics and/or pharmacodynamics. The question is whether such limited information is sufficient to ensure the efficacy and safety of the majority of biopharmaceuticals that are derived from recombinant DNA. [10] (Wang, W.; 1999)

Biogenerics – An Economic View

This study determined that the market for existing biologics would grow from $38 billion in 2006 to approximately $55 billion in 2020; new discoveries would make the biologics market far larger, but any new discoveries would face generic competition in a time frame well beyond the scope of this analysis. In determining the potential savings from biogeneric competition, the analysis utilized price discount assumptions suggesting that biogeneric competition could generate savings of 10-25 percent in the initial year when compared to the brand biologic price, rising to a range of 25-47 percent in the fifth year of competition. (The biogeneric human growth hormone, Omnitrope, was introduced at a 20 percent discount to the brand biologic product when approved in Europe.) The analysis also assumed that biogenerics could capture market share of 3-10 percent in the first year of introduction, growing to 15-50 percent in the sixth year of competition. [19] (Miller MD et. al.; 2007).

As discussed, the regulatory approval process for the generic versions of most existing drugs is governed by the FD&C Act, which specifies how applications for such approvals shall be made. Specifically, it directs that applicants can seek approval for a generic drug by relying on FDA’s approval of the original (“brand”) drug being copied. [18] (Arlington, Va, 2006). The drugs eligible for this treatment primarily are chemical-based products [12] (Eli Lilly, 2007). But the vast majority of so-called biologics – drugs manufactured using biological, as opposed to chemical, processes – are licensed under the PHS Act, which does not specify a process for generic, or otherwise equivalent, biological products, and FDA has appeared to have concluded that the PHS Act does not authorize it to establish a generic drug approval pathway for these products. Thus, for most biologic drugs coming off patent, there is no process for certifying biogenerics. The FDA, in May 2006, made its first approval of a biogeneric product – Sandoz’s Omnitrope, a generic version of Pfizer’s Genotropin, a human growth hormone, but only after Novartis, Sandoz’s parent company, filed a lawsuit against the FDA demanding resolution. (Growth hormone was one of the few biologies approved under the FD&C Act.) In addition, the FDA did not qualify Omnitrope as interchangeable with Genotropin. The FDA’s official policy is now to hold off on issuing new guidelines for further approvals. [14] (Food and Drug Administration, 2007).

The regulation of biogenerics should be seen in this context. The goal of regulation is to preserve the public health by providing strong assurance of the safety of medicines. It does so by weighing costs and benefits using all the available tools of science. The issue of the appropriate regulatory treatment for biogenerics from a scientific perspective is beyond the scope of this paper. From an economic perspective, however, the issue is this: the delay in specifying a regulatory approval process artificially extends the patent protection granted brand name biologics. This prevents competition from pushing down prices to consumers and pressuring firms to increase their research and development to produce new products that will replace lost sales or generate greater sales. This analysis estimates the size of those benefits by comparing a world in which there are no bioequivalent drugs to one in which there is a statutorily based process for their entry into the market.

Biopharmaceuticals

Most biopharmaceuticals are large, complex molecules that, for several reasons, are heterogeneous. Some heterogeneity is caused by the combination of vector and host cell used to produce the biopharmaceutical, and includes clipping (premature termination of translation) and differences in the sites and amount of glycosylation. Protein modification might occur during production, depending on the fermentation and cell culture conditions. The extraction and purification procedures can also add to the heterogeneity, as can process-related impurities and the introduction of contaminants that might appear in the final product. Lastly, formulation and storage conditions might alter the biological properties and, thus, the response, as a result of physicochemical or physical changes in the excipients and or bioactive species. Although some heterogeneity is natural and has no consequences for the efficacy or safety of the products, some variants do have adverse biological and clinical effects. For example, variations in glycosylation influence the biological efficacy of erythropoietin and the lack of glycosylation has been used to explain the immunogenicity and loss of efficacy of granulocyte–macrophage colony stimulating factor and interferon 8B (IFN-8B). Furthermore, impurities and formulation factors cause immunogenicity of factor VIII and...
human IFN-a2a, respectively. Although some of these effects can be attributed to detectable product heterogeneity, present techniques are not capable of predicting all of the biological and clinical properties of proteins. An example of the unpredictable nature of biological properties is given by human IFN-ß1a in the treatment of multiple sclerosis. [15] Liu, D.T.; (1992) Although the material used for a Phase III trial and the material already approved for marketing by the EMEA were produced at different sites, the same gene was used to make the two materials and they were formulated and stored identically, and administered using the same dose, route and frequency. When tested for biological activity, the two products were indistinguishable by every measure both in vitro and in vivo. However, because different processes were used for manufacturing and purification, the immunogenicity of the products was markedly different. Thus, the incidence of neutralizing antibodies was five times higher in patients injected with the Phase III material than observed with the already marketed product. Subtypes of human IFN-a provide an opposite example: although the primary structures of IFN-a2a and IFN-a2b differ considerably from that of the consensus IFN-a, they share virtually all biological and clinical properties. Because all the steps in production, purification and formulation can influence the biological and clinical properties of the final product, and current methods are not sufficiently sensitive to predict these properties, it is important that each step is monitored carefully using in-house standards. The analytical methods have, in part, been developed (or at least refined) for each specific product. For many products, particularly the initial products for which the patents expire shortly, the production process has undergone continuous improvement, based on manufacturing and clinical experience. The features of any biopharmaceutical are the result of the basic characteristics of the molecule, such as the amino acid sequence and three-dimensional structure, in addition to the specific production, purification, formulation and storage conditions. [9] (Storring, P.L. et al.; 1998). To produce a biopharmaceutical of the constant, required quality, a company also needs the experience and in-house standards to apply the methods used to analyze the structure of the product. Guidelines from the EMEA, the FDA, the Japanese Ministry of Health and Welfare, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) require manufacturers to show that they control their production processes and are capable of manufacturing reproducible batches that not only meet product specifications, but also conform to the definition of the product as established through full characterization. Modifications of the established process are only accepted if the manufacturer shows that the product of the new process is comparable to the initial product. Comparability studies include re-validation of the process, re-evaluation of process and product-related impurities, and re-characterization of the product in side-by-side analyses by all available state-of-the-art methods, and stability studies with the product derived from the new process. These comparability studies must include clinical studies that examine the pharmacokinetic, pharmacodynamic and immunogenic properties of the new product in addition to some efficacy and safety studies. Biogenerics when making specified changes in the production process of a particular product the manufacturer must show that the biological and clinical aspects of the product are the same as that produced previously. If the compounds to be compared are manufactured by the same company, because the change is defined, the possible effect might also be relatively predictable. However, when the same product is made by a different manufacturer that will occur after the patents expire, the large number of variables that influence the properties of the product make comparison more complicated. Little, if any, of the expertise, analytical methods and in-house standards, specifics of the production process, historical process and validation data, and characterization data that are required for comparison are available publicly: these are proprietary knowledge. In the majority of cases, based on either the patent or published data, it is inconceivable that another manufacturer would be able to manufacture a product that could be assumed to be similar enough to the original that only a limited documentation of physico–chemical characteristics would be sufficient to show equivalence. Moreover, as discussed above, even the most sophisticated analytical tools are not sensitive enough to predict the biological and clinical characteristics of the product. Thus, with the possible exception of small peptides for which the function–structure relationships are well known and which have a well understood biological function, the concept of generics cannot be extrapolated to biopharmaceutical products. [2] (Dorr, R.T.; 1993)

Off-patent biotech products

The very term ‘biogenerics’ is misleading; thus, we propose the term off-patent biotech products (OPBPs). Apart from the EMEA, no regulatory body has issued guidelines concerning OPBPs. A recent EMEA Committee for Proprietary of Medicinal Product (CPMP) draft is devoted mainly to comparability issues when a manufacturer makes changes in the production process, although a small part covers the ‘multisource’ situation where a new manufacturer wishes to market an already marketed product. The EMEA recognizes that the new manufacturer will not have access to all the information that is necessary to make a full comparison, but that some comparisons can be made against published data, such as in monographs. Therefore, comprehensive preclinical and clinical comparability studies might be required, depending on the nature and complexity of the product, the biological and clinical experience, and the side-effects (mainly immunogenicity).

The general, brief discussion of the ‘multisource’ situation by the EMEA cannot be considered a note for guidance for potential manufacturers of OPBP and it is likely that the first products will be evaluated on a case-by-case basis until sufficient experience is accumulated to allow comprehensive guidelines to be issued. However, we think that it is possible to distinguish three categories of OPBPs for which different approaches for the marketing authorization dossiers apply (Table 1). Category 1 OPBPs are the small peptides, such as calcitonin, that have a well established function and structure and/or long clinical and regulatory experience of different variants. In this case, the requested documentation can be similar to the conventional generic drugs. Category 3 OPBPs are products that cannot be made identically to the original, such as monoclonal antibodies. For these products every indication needs to be documented with the appropriate clinical trials. The majority of the OPBPs will be Category 2.
These should be treated as essentially similar products and the marketing authorization documentation must include all elements required of a full dossier that is full details of:

(1) The gene and its expression vector
(2) The expression system, including a full description of master- and working-cell bank
(3) The fermentation/culture Process
(4) The purification process
(5) Formulation, filling, finishing, storage and shipping processes
(6) Cleaning and shipping validation studies
(7) Physico–chemical and biological characterization of the purified product
(8) Analytical methods and their validations
(9) Stability data on drug substance and drug product
(10) Standard pharmacological and toxicology data

Only if the OPBP is demonstrated to be clinically equivalent to the innovative product in a Phase III trial for a registered indication in a patient population that is representative of both efficacy and toxicity can the results be extrapolated to other indications. We suggest that Category 2 should be subdivided to form a category (Category 2b) for products such as erythropoietin and thrombopoietin. Because the antibodies induced by erythropoietin and thrombopoietin can neutralize important host factors, immunogenicity might lead to serious problems. For these products, the clinical data submitted should include enough patients to evaluate the possible immunogenicity. In addition, a commitment to post marketing surveillance to monitor immunogenicity should be part of the marketing authorization. Because of the limited costs needed to achieve marketing authorizations, generics and therefore also OPBPs help to reduce health costs. Although the documentation needed for an OPBP is extensive, development costs are still far less than the original product because the manufacturer does not need to invest in, for example, the original research to identify the molecule or isolate its gene, and does not have the costs for the development of production methods or to identify indications. Moreover, as outlined above, in some circumstances indications could be registered based on documented equivalence rather than a full complement of clinical trials. Although cost reduction in medical care is a desirable and worthwhile goal, it must never be to the detriment of the documentation needed for an OPBP is extensive, development costs are still far less than the original product because the manufacturer does not need to invest in, for example, the original research to identify the molecule or isolate its gene, and does not have the costs for the development of production methods or to identify indications. Moreover, as outlined above, in some circumstances indications could be registered based on documented equivalence rather than a full complement of clinical trials. Although cost reduction in medical care is a desirable and worthwhile goal, it must never be to the detriment of the marketing authorization.

Table 1. Categories of off-patent biotech products

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Submission for</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Calcitonin, insulin</td>
<td>marketing authorization</td>
</tr>
<tr>
<td>2a</td>
<td>GM-CSF, INF-a</td>
<td>As for conventional generics</td>
</tr>
<tr>
<td>2b</td>
<td>EPO, TPO</td>
<td>As for category 2a with extrapolation of possible indication</td>
</tr>
<tr>
<td>3</td>
<td>mAB</td>
<td>As for new chemical entity</td>
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