Thomas J. Kowalski
is a partner in the New York office of Frommer Lawrence & Haug LLP.

Pamela Fekete
is an associate in the New York office of Frommer Lawrence & Haug LLP. Her practice focuses on infringement studies and patent litigation, primarily relating to pharmaceutical litigation under the Hatch–Waxman Act.

Anne-Marie C. Yvon
is a scientific advisor in the New York office of Frommer Lawrence and Haug LLP. She is a registered patent agent whose work focuses on the prosecution of biotechnology patents.

Keywords: *generic biologics, biogenerics, biotechnological pharmaceuticals, follow-on biologics*

Thomas J. Kowalski
Frommer Lawrence & Haug, LLP,
745 Fifth Avenue,
New York, NY 10151, USA

Tel: +1 212 588 0800
E-mail: Tkowalski@FLHLaw.com

The quest for generic biotechnology pharmaceuticals in the USA

Thomas J. Kowalski, Pamela Fekete and Anne-Marie C. Yvon

Date received (in revised form): 10th December, 2004

Abstract

As patent protection expires on the first generation of biotechnology products, such as human growth hormone and erythropoietin, there is an impetus for the development and marketing of generic equivalents. Currently there is no statutory or regulatory framework governing generic biotechnology products. This paper explores the potential solutions that have been suggested by members of the pharmaceutical industry and government, both in the USA and internationally.

In the USA, a company can bring a generic version of a certain pharmaceutical product to market either when the product loses patent protection, such as by expiration or invalidation by a court ruling, or under the Hatch–Waxman Act. The Act provides a mechanism for companies to file a New Drug Application under Section 505(b)(2), relying on safety and efficacy studies not performed by or for the applicant (referred to in this context as a 'paper NDA'), or an Abbreviated New Drug Application (ANDA) under Section 505(j). As first generation biotechnology products are approaching the loss of patent protection, many companies are interested in marketing competitive versions of these products. There is currently no established statutory or regulatory scheme for effecting this result. While the Food and Drug Administration (FDA) has indicated that the 505(b)(2) route might be available for this purpose,[1] it recently indicated in a response to several citizen petitions regarding 505(b)(2) that it will specifically address the use of 505(b)(2) for biologic-type products at some future time.[2] Therefore, unlike traditional pharmaceutical products, for which a steady stream of generics have been reaching the market in a pattern that directly correlates with patent expiry, the path to 'biogenerics' is less straightforward.

Even the terminology used to describe biotechnological and biological products is unsettled. 'Biological products' are regulated under the Public Health Service Act (42 USC §262) and defined as a 'virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.'[3] This definition does not appear to include biotechnological products, such as recombinant insulin and human growth hormone. (Even if it did, however, there is no provision in the Federal Biologics Act for an abbreviated application process.) The terms 'biogenerics' and 'follow-on biologics' have been suggested for generic biotechnology products; however, recent indications from the FDA are that any official term for generic versions of biotech drugs will include the word 'protein'.[4] In this paper, we will use 'biogenerics', for lack of a better term.

Biotechnology products currently provide treatment for some of the most debilitating diseases, including hepatitis,

multiple sclerosis, anaemia in patients with chronic renal failure, and immunological deficiency resulting from cancer treatment. These critical patient populations are still waiting for legislation analogous to the Hatch–Waxman Act that will provide both an incentive to the innovators of biotechnology to keep pursuing this cutting edge technology, and a pathway for generic companies to provide low-cost equivalents.

Legislation is needed to provide a regulatory scheme for bringing generic biotechnology products to market

With several biotechnological products facing expiration of patent coverage before 2007, the time is ripe for legislation outlining an approval process for biogenerics. Table 1 shows the first-generation products are facing patent expiration according to IMS Health.

At the IIR Global Generic Strategies conference in Barcelona in March-April 2004, Federico Pollano, Head of Business Development at BioGeneriX, forecast '[i]n 2010, nearly 50% of all new approved pharmaceuticals will be of biotechnological origin.'[5] This anticipated growth, however, will not necessarily translate into the same potential for biogenerics. As Pollano noted, 'biopharmaceuticals are defined by their production process, any change can impact safety and efficacy and therefore demands new approval.'[5] The fact that it is impossible to exactly replicate a biological process poses a potential difficulty in demonstrating equivalence to the brand product.

Sandoz, the generic division of Novartis AG, provides a practical example of the difficulties of gaining approval of a biogeneric drug in the USA. Sandoz filed for FDA approval of its generic recombinant human growth hormone, Omnitrope, under Section 505(b)(2).[5] While the FDA notified Sandoz in September of this year that it found no deficiencies in the application, the agency stated that it was unable to approve the application due to 'uncertainty regarding scientific and legal issues.'[6] Opponents of the Section 505(b)(2) route of biogeneric approval argue that a full complement of data should be required for generic biotech products, owing to the inherent complexity of protein products. They argue that differences in manufacturing processes could result in differences in the protein product and its clinical effects, and that studies of each new product are the only way to ensure safety and effectiveness.[7] On 14th and 15th September, 2004, the FDA held a workshop on the scientific considerations related to developing biogenerics. Draft guidance from the FDA on this topic is expected during the coming year.[8]

At the same time, the Generic Pharmaceutical Association (GPhA) is lobbying for legislation to create a process for generic biologics. GPhA representative William Schultz, of Zuckerman Spaeder, stated before the 23rd June, 2004, Senate Judiciary Committee session '[w]e urge Congress to direct FDA to play an active role in advising the generic biopharmaceutical companies about study design, data requirements and other issues, as it currently advises brand companies seeking authorization to market their products.'[9]

The GPhA set forth three principles to

Table 1: Blockbuster biotechnology products with patent expiry before 2007

Product	Innovator company	Active substance	Patent expiration	Global sales, 2002 (in US$bn)
Humulin	Lilly	Human insulin	2001	1.0
Intron A	Schering-Plough	Alpha-interferon	2002	2.5
Procrit	Amgen/J&J	Erythropoietin	2004	4.3
Epogen	Amgen	Erythropoietin	2004	2.3
Neupogen	Amgen	Filgrastim (granulocyte colony-stimulating factor, GCSF)	2006	1.4

Source: 'Biogenerics: A Difficult Birth?' IMS Health, 18th May, 2004.

guide Congress in drafting generic biologics legislation.[9] First, the FDA should have flexibility to tailor the preclinical and clinical data requirements based on a scientific risk–benefit approach. Second, the FDA should be able to impose only those regulatory requirements necessary to ensure similarity or sameness to the reference product. Finally, Congress should monitor the agency's progress in implementing the programme – perhaps including a requirement of periodic reports from the agency to Congress.

Pharmaceutical sales in the biotechnology market are expected to double over the next five years

In the same Senate Judiciary Committee hearing, Senator Orrin Hatch (Republican, Utah) acknowledged that 'cost factors alone compel examination and public discussion of the merits of developing a fast track review and approval system that can reduce the price of biopharmaceuticals once patents expire.'[10] Senator Hatch noted that some therapies cost over US$10,000 per year or per course of treatment. For example, human growth hormone can cost US$25,000 per year. Senator Hatch further stressed the growing medical and economic importance of biologics, with the biotechnology market posting a total of about US$30bn in sales last year, which is expected to double to over US$60bn by 2010.[10]

Senator Hatch urged the industry not to pursue 'scorched-earth' litigation but, rather, to identify 'the legitimate scientific and legal obstacles that must be overcome to create a fast track approval system for off-patent biologics.'[10] He further proposed studies by United States Pharmacopeia or the Institute of Medicine in collaboration with the FDA, in order to help identify and address the issues presenting an obstacle for the implementation of such a fast track process. Senator Hatch commented that he expects many, if not all, generic biologics will require at least some form of human clinical testing as a prerequisite to approval. In general, Senator Hatch's comments demonstrated support for an abbreviated approval system for off-patent biologics that balances the incentives for both brand and generic firms. He is currently preparing legislation based on existing European Union policy.[11] Senator John Rockefeller (Democrat, West Virginia) has also introduced legislation containing provisions for FDA regulation of generic human biologics.[11]

Following legislation by the European Parliament, in December 2003, the European Agency for the Evaluation of Medicinal Products (EMEA) published guidelines on the appropriate pathways for approval of generic biologics. Six months earlier, the EMEA had recommended that the European Commission grant-marketing authorisation for Sandoz's Omnitrope product. In spite of the EMEA's recommendation, approval was denied by the European Commission owing to purported filing irregularities. Sandoz has reported its belief that the appropriate filing pathway was used, and has filed suit against the European Commission.[5] In October of this year, Sandoz received approval from the Australian Therapeutic Goods Administration to market Omnitrope in Australia.

Furthermore, there is an emerging need for a regulatory and legislative framework that would encompass animal biologics. Generic products now account for 40 per cent of world animal health sales, totalling US$5.36bn in 2002.[12] More than 70 per cent of anti-infectives and endoparasiticides sold in 2002 were generics, and there are many more approaching patent expiry during the next five years.[12]

In order to advance the interests of patent holders, companies seeking to market generic products, and the public at large, the framework for regulating biotechnology products must include intellectual property considerations as well. Currently, patents covering approved drug products are listed by the FDA in a publication commonly known as the 'Orange Book'. The analogous FDA publication for approved animal drug products is known as the 'Green

Book'. A similar publication for biotechnology products will need to be implemented.

In addition, to facilitate policing and enforcement of unexpired patents, any regulatory scheme for biogenerics would ideally include analogous provisions to those in the Hatch–Waxman Act that require generic companies to notify the brand company when they seek approval of a generic product. For example, a company filing an ANDA must certify in its application that patents covering the product (i) have not been filed with the FDA; (ii) have expired; (iii) will expire by the time the generic product hits the market; or (iv) are invalid or will not be infringed by the manufacture, use or sale of the new drug. This system has worked successfully in the traditional pharmaceutical arena for 20 years, and can serve as a model for biotechnological pharmaceuticals as well.

The Hatch–Waxman provisions for approval of generic drugs can serve as a model for regulation of biogenerics

In summary, a great incentive for enactment of legislation and regulations governing generic biotechnology products exists in the USA. Such action may serve to limit unnecessary expenditures by pharmaceutical companies in developing new products and avoiding lengthy, complex litigation. In turn, these savings can be passed on to the public in the form of affordable, life-saving products.

References and notes

1. See Draft Guidance for Industry: Applications Covered by Section 505(b)(2); US Food and Drug Administration, October 1999 (URL: http:// www.fda.gov.cder/guidance/2853dft.pdf).
2. See Letter from Janet Woodcock, Director of the Center for Drug Evaluation and Research, 14th October, 2003 (URL: http://www.fda.gov/cder/ogd/505b2-CPresponse.pdf).
3. A similar definition of 'biological products' is included in the Virus, Serum, Toxins Act, which governs the administration of biological products to animals. These products are regulated by the US Department of Agriculture's Animal and Plant Health Inspection Service; however, the FDA regulates new 'drugs' for use in animals, which can include some biotechnological products. Therefore, any regulations adopted for the approval of human biogenerics would likely apply to some veterinary products as well.
4. *See* 'FDA calls for uniform name for biogenerics', *IP Law Bulletin*, 27th October, 2004.
5. *See* Turner, N. (2004), 'Biogenerics: A difficult birth?', *IMS Health*, 18th May.
6. 'FDA holds off on biogenerics decision', *IP Law Bulletin*, 7th September, 2004.
7. *See* 'Public Workshop on the Scientific Considerations Related to Developing Follow-On Protein Products Before the Food and Drug Administration, HHS' (2004) (Statement of Sara Radcliffe on behalf of the Biotechnology Industry Organization) (URL: http://www.fda.gov/ohrms/dockets/dockets/04n0355/04N-0355_emc_000001-01.pdf).
8. 69 Fed. Reg. 50,386 (16th August, 2004).
9. *The Pink Sheet*, 28th June, 2004, p. 8.
10. 'The Law of Biologic Medicine', United States Senate Committee on the Judiciary, 23rd June, 2004.
11. *See* 'Hatch eyes Generic Biologics Bill modeled on E.U. approach', *IP Law Bulletin*, 11th October, 2004.
12. *See* 'Generics in the animal health industry: Threats and opportunities', *Animal Pharm*, No. 538, p. 12.