Biogenerics 2007: How far have we come?

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Abstract

The recent approval of a follow-on version of Pfizer's Genotropin (recombinant human growth hormone) signalled the beginning of the end of an era in which biopharmaceuticals enjoyed immunity from competition even after expiration of their patent protection. This paper describes many of the key scientific challenges facing the nascent 'biogenerics' industry and the evolving regulatory framework that will shape its competition with innovator companies. We describe key differences between the biogeneric and traditional generic drug business models and the M&A activity that been undertaken in pursuit of the expertise and resources needed to be competitive in this commercial space. We conclude with a discussion of the commercial opportunity presented by recent and upcoming European patent expirations and the challenges presented by competition from second-generation innovator products.

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INTRODUCTION

In April 2006 the European Commission granted market authorisation to a product widely regarded as the first 'biogeneric' drug to be approved in a major pharmaceutical market. Sandoz' Omnitrope, a follow-on to Pfizer's recombinant growth hormone product

Genotropin (somatropin), now competes with seven other recombinant growth hormone products, most of which are branded, proprietary products, in a market having an estimated worldwide value of about $2.5bn.[1] The FDA, which had deferred a decision on the Sandoz application citing its 'nature and complexity' until directed to act on it by a court order, granted US market authorisation in May of 2006.

A less widely heralded event, but one with potentially greater implications, is the approval in August 2007 of Sandoz' follow-on version of erythropoietin-α, marketed by Amgen as Epogen and by Ortho Biotech as Eprex. Erythropoietin products are widely used in the treatment of anaemia, secondary to chronic renal failure or chemotherapy. The market for these products is estimated to be $1.4bn in Europe[2] and $7bn worldwide,[1] suggesting that Sandoz' erythropoietin product could become the world's largest selling non-proprietary drug. Furthermore, because erythropoietin is glycosylated (vide infra), the technological challenges presented in developing a follow-on version of this protein are higher and in many ways more representative of those faced by the biogenerics industry than those presented by the simpler human growth hormone protein.

Other entries into this field include a second follow-on version of human growth hormone developed by Biopartners and approved by the European Medicines Agency (EMEA) in 2006,[3] follow-on versions of erythropoietin and granulocyte colony-stimulating factor (G-CSF) being developed by Bioceuticals and Biogenerix, follow-on versions of interferons-α and -β being developed by Biopartners, and a follow-on version of G-CSF being developed by Pliva. Datamonitor[4] recently counted over 80 follow-on versions of biopharmaceuticals in development, and estimated that six key product classes with over $20bn in 2004 sales are potentially at risk. These observations evoke images of a tsunami of generic biotechnology drugs that will undercut the earnings of major biotechs and lead to dramatically reduced costs for consumers. But real story is likely to be far less dramatic.

NOT AS EASY AS IT LOOKS

In January of 2005, one of the contributors to this paper co-authored a piece in *BioExecutive International* entitled 'Does a Biogenerics Industry Really Exist?'[5] This paper identified several key challenges faced by developers of generic versions of biotechnology drugs that represent barriers to reproducing the successful business model used by traditional generic drug manufacturers. These include the absence of a well-defined statutory framework for obtaining regulatory approval, the complexity of determining product comparability and interchangeability, the high cost of manufacturing, the utilisation of aggressive IP strategies by innovators, and the market uncertainties introduced by the potential for the introduction of incrementally improved products by innovators. Most of these challenges arise because the drugs themselves and the processes used to manufacture them are far more complex for biotechnology drugs than for traditional drugs.

Traditional drugs such as aspirin, Lipitor, and Viagra are relatively simple molecules prepared by traditional chemical synthesis methods. Such compounds typically have molecular weights of less than 500, corresponding to less than 100 atoms total. Changing the identity of even a single atom in such a small molecule will lead to a significant change in its physical and spectroscopic properties. Thus, it is relatively simple both to purify these drugs and to measure their purity with a high degree of certainty and precision. Chemists can easily reverse engineer such drugs and make near-perfect copies.

The smallest biotechnology drug, recombinant human glucagon, has a molecular weight of greater than 3,000, and relatively large biotechnology drugs such as monoclonal antibodies may have molecular weights in the range of 150,000. Small variations in the cell

line or cell culture conditions used to produce these proteins can lead to the production of different variants of the protein, to the production of multiple variants, or to a product containing a different impurity profile.[6,7] In the case of glycosylated proteins, small changes in the manufacturing conditions can lead to changes in both the extent of glycosylation and in the identity of the sugar groups attached to the protein (glycoforms). These changes can lead to dramatic differences in the potency, immunogenicity, and serum half-life of the protein but may be quite difficult to detect using state-of-the-art methods for physical characterisation.[8,9] Many protein drugs contain a mixture of active ingredients having the same backbone sequence, but small differences in post-translational modification (microheterogeneity).[10] In such cases, would-be generics manufacturers face the challenge of reproducing a mixture rather than a purified substance. Broadly speaking, the manufacturing and analytical difficulties increase with the molecular weight of the protein and with the extent of glycosylation and other post-translational modifications.

Because of the limited ability of state-of-the-art physical methods to establish the precise structure and homogeneity of biotechnology drugs, manufacturers and regulatory authorities have historically depended on tight control of the manufacturing process as a major component of ensuring that different batches of a biotechnology drug will have the same *in vivo* properties. The ability of innovators to prevent others from using their manufacturing processes through patents, trade secrets, and preventing access to proprietary cell lines presents a manufacturing and regulatory barrier to would-be biogenerics manufacturers that has no counterpart in the world of small molecule generics. The uncertainties resulting from the manufacture of follow-on biotechnology drugs under conditions different than those used by the innovator suggest that it may be impossible to develop a true 'generic' version of a biotechnology drug. Indeed, regulatory authorities in Europe and in the US have shunned the use of the term 'biogeneric', preferring the nomenclature 'biosimilars' and 'follow-on biologicals' to describe products that potentially qualify for an abbreviated regulatory pathway based on similarity to an approved biopharmaceutical product.

RECENT PROGRESS TOWARDS A REGULATORY FRAMEWORK

In the US, prior to 1984 would-be generics manufacturers were required to submit a full NDA when seeking approval to market their own version of an innovator's drug product. The passage of the Hatch–Waxman Amendment to the Food, Drug and Cosmetic Act dramatically simplified the approval process for products identical or similar to previously approved drug products by opening two new regulatory approval paths.[11] Section 505(j)(2) permits generic manufacturers to file an Abbreviated New Drug Application for products that are identical to an approved reference product with respect to the active ingredient, dosage form, strength, route of administration, labelling, performance, and conditions of use. The submitter is permitted to rely on the Food and Drug Administration's prior determination that the innovator's product is safe and efficacious, and the clinical data in the application is generally limited to that necessary to demonstrate that the pharmacokinetic profile of the applicant's product is similar to that of the innovator's. Section 505(b)(2) permits applications for products not identical to an approved reference product to reference safety and efficacy data from studies 'not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted'. These data may include published studies or the FDA's own finding that a referenced product is safe and effective. Because most biotechnology drugs were approved under the provisions of

the Public Health Services Act rather than the Food, Drug and Cosmetics Act, these abbreviated approval pathways are not generally available for follow-on biological products. Thus at the time of writing, the FDA lacks statutory authority to approve follow-on versions of most biotechnology drugs. Important exceptions include many early (and relatively simple) agents such as recombinant human insulin, recombinant human growth hormone (somatropin), and glucagon that were approved under the Food, Drug, and Cosmetic Act. In the case of Sandoz' somatropin product Omnitrope, the US approval came through a 505(b)(2) application naming Genotropin as the reference product. The Orange Book lists Omnitrope with a therapeutic equivalence code BX, indicating that insufficient data exist to determine whether it is therapeutically equivalent to any other human growth hormone product.[12]

In 2007 the expense of biotechnology drugs, their increasing proportion of total US and US Government prescription drug expenditures, and the well-publicised approval of two biosimilar drugs in Europe served to draw attention of US legislators to the issue of follow-on biologicals. Issues of critical importance to innovators and generics manufacturers that are likely to be addressed in any new legislation include (1) the degree of similarity between an applicant's and an innovator's drug required in order for the product to qualify for an abbreviated approval pathway, (2) the number and type of independent safety and efficacy studies that must be included in an application for a follow-on product, (3) the degree of similarity and level of testing required for a follow-on biological to be approved as interchangeable with its reference product, or whether any provision is made for interchangeability at all, (4) the number of years of marketing exclusivity guaranteed to innovators, and (5) the nature and extent of regulations limiting the ability of the innovator to delay marketing of a follow-on product by patent infringement lawsuits.

Key legislation introduced into the US Congress this year includes (1) H.R. 1038/S.623,[13] the 'Access to Life-Saving Medicine Act', (2) H.R. 1956,[14] the 'Patient Protection and Innovative Biological Medicines Act', and (3) S.1695,[15] the 'Biologics Price Competition and Innovation Act' (BPCIA). As might readily be surmised from their descriptive names, H.R. 1038/S.623 strongly reflects the interests of the generics industry, while H.R. 1956 primarily reflects the interests of innovators. The BPCIA, passed by the Senate Health, Education, Labour, and Pensions Committee on June 27, provides what may be the best available preview of what a final compromise bill will look like. It provides an abbreviated application pathway for products that are shown to be similar to an approved reference product based on (1) analytical studies showing that the products are 'highly similar', (2) animal studies, and (3) 'a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed'. Remarkably, the current version of the bill allows the Secretary of Health and Human Services to waive some or all of these requirements. The bill permits a follow-on product to be designated as interchangeable with the reference product if it 'can be expected to produce the same clinical result as the reference product in any given patient', and if patients can be repeatedly switched back and forth between the follow-on and the reference product without increased risk in terms of safety or reduced efficacy. The effective date of the approval of an application made via the abbreviated approval route may not be less than 12 years after the original approval date of the innovator's product. The current version of the bill sharply limits the ability of innovators to delay the marketing of a follow-on product by patent infringement litigation, in some cases limiting pre-approval

litigation to the defence of a single patent. Owing to the failure of efforts to attach this or related bills to 2007 legislation reauthorising the Prescription Drug User's Fee Act, it currently appears unlikely that a US regulatory framework for follow-on biopharmaceuticals will be in place prior to 2010.

While legislation will determine the broad statutory framework under which biological follow-on products are approved and marketed in the US, the day-to-day regulatory decision-making will lie in the hands of the FDA. In a recent *Nature Reviews Drug Discovery* article,[16] FDA deputy commissioner Janet Woodcock and coauthors provide a historical perspective on how the agency has made decisions analogous to those that will be involved in the approval of biological follow-on drugs. The article implicitly downplays the significance of the Omnitrope approval, pointing to several prior examples of biological agents that were approved based, in part, on the safety and effectiveness of similar products arising from different manufacturing processes. These include (among others) two forms of recombinant glucagon that were approved via the Section 505(b)(2) process based on their similarity to a previously approved product of animal origin, a recombinant version of salmon calcitonin (Fortical) approved via the Section 505(b)(2) process based on its similarity to a previously approved synthetic product, and the approval of a recombinant interferon-β1a (Avonex) based, in part, on clinical data acquired with material manufactured using a different cell line.[17] In the article's conclusions, the authors state that 'For follow-on protein products produced through rDNA technology, establishing a high degree of structural similarity between the follow-on and the original product has been a crucial first step in enabling the FDA to consider what available existing scientific information might pertain to a follow-on product and to determine the extent of the clinical studies of safety and efficacy necessary to support approval'. Other critical considerations cited in the article include the extent to which the mechanism of action of the reference product is understood, the extent of clinical experience with the reference product, the availability of mechanistically related pharmacodynamics assays, comparative pharmacokinetics and immunogenicity, and the robustness of the manufacturing process. With respect to the issue of interchangeability, the article includes a quote from the deputy commissioner's congressional testimony stating that any determination of interchangeability would require clinical trial data indicating that repeatedly switching between the follow-on product and the reference product produced no adverse effects on safety or efficacy due to immunogenicity. The deputy commissioner further notes that due to the risk posed to patients by conducting such trials, 'the ability to make determinations of substitutability for follow-on protein drugs may be limited'.

Legislation regulating the pharmaceutical industry in the European Union makes much less distinction between biotechnology-derived and traditional small molecule drugs, and thus the statutory framework needed for the approval of biological follow-on products is largely in place.[18] Provisions specific to follow-on biological products are found in Directives 2003/63/EC and 2004/27/EC of the European Parliament. Directive 2003/63/EC anticipates that in the case of biological follow-on products, it may not be possible to demonstrate 'similarity' to an approved reference compound using only the data required for generic drug applications. In such a case, 'the type and amount of additional data (ie toxicological and other non-clinical and appropriate clinical data) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines'. Furthermore, in the case of a reference product having multiple approved indications, 'the efficacy and safety of the medicinal product claimed to be similar must be justified, or if necessary, demonstrated

separately for each of the claimed indications'. Directive 2004/27/EC further elaborates that 'Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product'.

The EMEA has begun to fill out this broad statutory framework with a number of specific guidance documents.[19] The *Guideline on Similar Biological Medicinal Products* introduces the basic principles of the 'similar biological medicinal product' approach. The document explicitly states that similar biological medicinal products are not generics, and comparability studies are required to demonstrate the similar nature of the quality, safety, and efficacy of a new similar biological product to the chosen reference product. The applicability of the similar biological approach is stated to depend on the 'state-of-the-art of analytical procedures, the manufacturing process employed, as well as clinical and regulatory experiences'. Other documents describe the EMEA's position on biosimilar quality issues, clinical and non-clinical comparative safety and efficacy studies, and provide product class-specific guidelines. Available annexes to the *Guideline on Similar Biological Medicinal Products* provide product class-specific guidance for follow-on erythropoietin, somatropin, G-CSF, and insulin products. These documents include specific recommendations regarding the number and duration of clinical trials required to demonstrate clinical similarity, preferred clinical trial inclusion criteria, and the identity of preferred pharmacodynamic markers.

As a practical matter, the implementation of the statutes and regulatory guidance described above will be modulated by regulatory experience. A recent example that may encourage greater regulatory requirements for clinical safety and efficacy data is provided by the EMEA's rejection of Biopartner's marketing application for a biosimilar version of interferon α-2a. The agency's press release cited several reasons for the rejection, one of which was the observation that hepatitis patients treated with the biosimilar drugs had experienced higher rates of relapse and more side-effects compared to patients treated with the innovator's drug.[20]

NOT AN INDUSTRY FOR THE FAINT OF HEART

The traditional generics industry is in many ways a prototypical commodity business. Upon the expiration of innovator patents, non-differentiated products compete in a highly price-sensitive market, unencumbered by large marketing and R&D costs. Entry costs for new product lines are moderate, upfront expenses are low risk, and success is critically dependent on operational efficiency. As outlined in the previous paper in this series, success in the biogenerics business will require a different set of skills and resources. Successful players will need to develop and validate complex biopharmaceutical manufacturing processes, perform state-of-the-art bioanalytical comparisons, collect clinical safety and efficacy data, and navigate an ill-defined regulatory pathway prior to obtaining marketing approval. These upfront expenditures, estimated at up to $40m,[21] will all occur with no guarantee of eventual success. Nor will expenditures in support of the product cease upon regulatory approval. Regulatory guidance from the European Union and from the US FDA suggests that the simple model of generic substitution by pharmacists will be rare or non-existent in the two largest pharmaceutical markets. Manufacturers of follow-on biopharmaceuticals will need to conduct their own marketing campaigns, and will need to overcome physician concerns about the safety and efficacy of follow-on products that will generally have a less comprehensive dossier of clinical data than the innovator's product that they seek to displace.

Major players in this sector will include companies that have both the financial resources to undertake significant at-risk investments and the necessary expertise in biopharmaceutical manufacturing, quality

Table 1: Follow-on biopharmaceutical market opportunities*

Therapeutic class	2006 Worldwide sales	Therapeutic area	Key market challenges
Erythropoietins	$12bn	Cancer and haemodialysis-associated anaemia	Competition from Aranesp (darbopoetin alfa), a second-generation erythropoietin that has more convenient dosing, 33% (and growing) market share, and significant remaining patent life
Insulin and insulin analogs	$9bn	Diabetes	Highly fragmented market. Multiple brands with high recognition, multiple insulin analogs with improved properties, and significant remaining patent life
Interferon-β	$4.4bn	Multiple sclerosis	Potential for increasing competition from other treatment modalities
G-CSF	$4.4bn	Cancer chemotherapy-associated neutropenia	Competition from Neulasta (pegfilgrastim), a second-generation G-CSF that has more convenient dosing, 51% (and growing) market share, and significant remaining patent life
Human growth hormone	$2.5bn	Growth hormone deficiency	Significant innovator investment in the development of convenient dosing devices
Interferon-α	$2.3bn	Viral hepatitis, certain cancers	Competition from second generation products that have more convenient dosing, 70% market share, and significant remaining patent life

*Data from References 1,20

control, formulation, regulatory issues, and marketing. Novartis, through its Sandoz subsidiary, has demonstrated its capabilities by obtaining marketing approval for two products in the European Union and one in the US. Other major generics companies have leveraged their financial resources by building or acquiring companies with biopharmaceutical expertise. Teva acquired the Lithuanian biopharmaceuticals company Sicor in 2004, and now markets biosimilar versions of interferon α-2b and G-CSF in eastern Europe and several other minor markets. Other Teva initiatives include strategic partnerships with Transpharma, Procognia, and Protalix as well as the recent purchase of a majority stake in Tianjin Hualida Biotechnology. Barr Pharmaceuticals recently completed its acquisition of Croatian generics manufacturer Pliva, and thereby acquired the latter company's erythropoietin and G-CSF biosimilar programmes. Biopartners, which has received marketing approval for a biosimilar human growth hormone, had its marketing application for a biosimilar interferon-α rejected by the EMEA, and currently has an interferon-β product in advanced development. Biopartners is owned by Credit Suisse and was formed by the purchase of Merck KGaA's interest in a joint venture with LG Chemicals (Merck Biopharmaceuticals). Less well-funded efforts have encountered significant difficulties. Examples include GeneMedix, which was recently acquired by Reliant Life Sciences after restructuring and several years of financial difficulties, and Germany's Stada, which recently out-licensed one and terminated a second of three biosimilar products being developed by its Bioceuticals affiliate.

MARKET OPPORTUNITIES

In the short term, the main commercial opportunity for biosimilar products will remain in Europe, where the regulatory pathway is more developed and less favourable patent protection for innovators renders a broader range of products susceptible to competition. Innovator products with expired patent protection in the European Union, of low structural complexity, and significant market potential represent the best opportunities for biogenerics companies. Important candidates meeting these criteria are described in Table 1 along with some

significant market challenges that will be encountered in each class. Notably, many of the therapeutic classes being targeted by biogenerics companies are dominated by second-generation products that require less frequent dosing and for which several years of patent protection remain. This raises the interesting question as to how competitors can best take advantage of first-generation product patent expiries. Although this paper has primarily focused on the approach of closely mimicking the first-generation product in order to obtain an abbreviated approval pathway, in some cases the expiration of patents on first-generation products will also reduce barriers to the development of novel second-generation products. Examples include the collaboration between Biogenerix and Neose to develop a long-acting version of G-CSF and Biopartners' campaign to develop a long-acting version of human growth hormone. Blockbuster monoclonal antibodies such as those targeting tumour necrosis factor or anticancer antibodies targeting growth factors or their receptors are absent from the table. These are comparatively recent products with considerable remaining patent life, and it is likely that developing biosimilar versions of these complex proteins will be technically challenging. Recent estimates by PricewaterhouseCoopers suggest sales of biosimilar versions of the therapeutic product classes in the table will total over $2.2bn by 2010.[22]

BIOGENERICS: A TSUNAMI OR A SLOWLY RISING TIDE?

A previous paper in this series, published in early 2005, enumerated a broad range of issues that differentiate the biogenerics business from the traditional generics business. These included the absence of a well-defined statutory framework for obtaining regulatory approval, the complexity of determining product comparability and interchangeability, the high cost of manufacturing, the utilisation of aggressive IP strategies by innovators, and the market uncertainties introduced by the potential for the introduction of incrementally improved products by innovators. Recent developments in this rapidly evolving story include the approval of a biosimilar human growth hormone product in the US, and the approval of two biosimilars human growth hormone products and a biosimilar erythropoietin in the European Union. The European approval pathway for biosimilars has been clarified by the adoption of seven guidance documents, four of which are specific to particular product types. A recent publication by the FDA in a prominent journal has provided significant insights into agency's views on the scientific issues involved in the approval of biosimilar products. Although the statutory framework for biosimilar approval in the US is clear only for the small number of products for which a 505(b)(2) application is possible, some insights regarding the form of the final statutes can be gleaned by examination of recently introduced legislation and the congressional debate. One critical issue for which a degree of clarification has developed is that of interchangeability, that is, biosimilars approved by regulators as directly substitutable for the reference innovator product. European legislation and regulatory guidance appear to exclude the possibility of such products, and statements made by the US FDA commissioner suggest that such products will be rare or non-existent in the US in the absence of statutes limiting the FDA's discretion. It also appears increasingly clear that few if any biosimilar products will be approved in the US or the European Union without significant clinical safety and efficacy data.

Companies wishing to compete in this sector will need significant financial resources to overcome the substantial upfront and at risk expenses associated with bringing a new biosimilar product to market. They will need to acquire bioprocess, bioanalytical, regulatory, and clinical trial experience beyond that employed in bringing a traditional generic to market. In terms of the cost and effort needed

to bring a product to market, and the level of profits that might be available to successful companies, the biopharmaceutical follow-on will in many ways lie between the two extremes represented by the traditional generics business and that of discovering and developing new chemical entities. The full development of opportunities in this business space will likely build slowly as the regulatory situation becomes clearer in the US and in Europe, and as the rate of key patent expirations accelerates.

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