Original Article

A follow-on biological drug is not a biogeneric: Lessons from Omnitrope and Valtropin

Received (in revised form): 28th January 2009

Robert I. Roth

has obtained MD, and PhD, and is Medical Director at The Weinberg Group Inc. Before joining The Weinberg Group Inc., Dr Roth was Director of Medical Research at LifeScience Economics, and was a faculty member in the Department of Laboratory Medicine at the University of California, San Francisco. Dr Roth provides consultation in all phases of the research, development and marketing of FDA-regulated drugs, biologics and medical devices.

Nicholas M. Fleischer

has obtained RPh and PhD, and is the Vice President of Clinical Pharmacology & Biopharmaceutics at The Weinberg Group. Before joining The Weinberg Group, Dr Fleischer held several scientific review and managerial positions at the United States Food and Drug Administration. Since joining The Weinberg Group, Dr Fleischer has been actively involved in managing programmes specifically geared toward the problem solving of pharmaceutical issues for large and small drug firms, always with an eye toward enhancing the client's position.

ABSTRACT Recent years have seen the approvals, more so in the EU than the United States, of follow-on biological drugs. These products have been new formulations of recombinant therapeutic proteins, developed to compete with the marketed originator products. Intended to closely mimic the originator products in terms of chemistry and therapeutic properties, these so-called 'biosimilar' products were initially conceived to be developed according to abbreviated development programmes, presumably at a substantial cost savings to both the drug developer and the consumer. With several such products now recently approved, however, it has become clear that their development programmes have been quite extensive and not particularly abbreviated. Accordingly, cost savings to consumers appear to be relatively modest.

Journal of Generic Medicines (2009) **0,** 000–000. doi:10.1057/jgm.2009.8

Keywords: biogenerics; biosimilar medicinal products; follow-on biologics; abbreviated development

INTRODUCTION

Blockbuster recombinant protein therapeutics coming off patent have long been in the sights of manufacturers wishing for abbreviated (that is, generic) and thus cheaper development requirements. Similar interests derive from patients wishing for price breaks on these typically highly expensive protein drugs. The top initial candidates for abbreviated development have been recombinant somatropin (growth hormone) and recombinant insulin because of their relative simplicity and long history of clinical use. Also of initial consideration for development has been recombinant erythropoietin. In April and May of 2006

Correspondence: Robert I. Roth
The Weinberg Group Inc., One Market, Steuart Tower,
Suite 1450, San Francisco, California 94105, USA
Q1 E-mail: bob.roth@weinberggroup.com

Sandoz GmbH received marketing approval in the EU and United States, respectively, for Omnitrope® [somatropin (rDNA origin human growth hormone) injection]. At approximately the same time, BioPartners GmbH received EU marketing approval for Valtropin® [somatropin (rDNA origin human growth hormone) for injection]. The following year, multiple versions of recombinant erythropoietin Epoetin alpha (Hexal Biotech Forschungs GmbH's Epoetin alfa Hexal®, Medice Arzneimittel Putter GmbH's Abseamed® and Sandoz GmbH's Binocrit®) and Epoetin zeta (Hospira's Retacrit®, STADA Arzneimittel AG's Silapo®) formulations were approved in the EU.

Initially these products were considered in the popular press as the first test cases for the concept of the 'generic biological' or 'biogeneric' drug product. More recently, however, consideration of such products has transformed conceptually into the less clearly defined realm of a 'follow-on protein product' or 'biosimilar', meaning a medicinal protein product demonstrated to be pharmaceutically comparable but not necessarily identical to an authorised reference protein product. In support of the clear difference between 'biogeneric' and 'biosimilar', the development databases for Omnitrope®, Valtropin® and the recombinant erythropoietin products appear to be much closer to that of an innovator drug than a generic drug. Only the drug manufacturers know the extent to which development costs for their products may have been less than for an entirely novel recombinant version of these therapeutic proteins; however, considerable clinical development was conducted for these biosimilar products. Furthermore, only time will tell the extent to which patients and insurers reap the benefits of a reduced price for these follow-on products, with preliminary evidence suggesting that pricing discounts may only be in the range of 20–25 per cent.

The recent approvals of Omnitrope®, Valtropin® and Epoetin products have finally set the precedent for follow-on biologicals, removing the logjam for the field of biosimilar recombinant protein therapeutics. At the same time, these approvals have distanced the approval of such follow-on products from the conceptual equivalent of a standard generic drug, and have clearly identified the practical distinction between 'biogeneric' and 'biosimilar'.

MANY RECOMBINANT PROTEIN DRUGS COMING OFF PATENT

Recombinant protein drugs are relatively new, based on cloning technology developed in the 1970s and coming to fruition with the approvals of recombinant human insulin and human growth hormone in the early 1980s. In the past 20–25 years, recombinant proteins have become an important component of the therapeutic approach to manage or cure a variety of diseases spanning cancer, cardiovascular disease, autoimmune diseases, metabolic conditions and many others. Many of these products, which are blockbusters with respect to revenue, are recently or soon to be coming off patent. As a group, these drugs are exceedingly expensive to patients and insurers. Accordingly, drug manufacturers, the Food and Drug Administration (FDA) and the European Medicines Agency, and health-care advocates have extensively discussed the idea of interchangeable (for example, substitutable) versions of recombinant protein drugs, and there is considerable impetus to establish an approval pathway that at least in part resembles the generic drug process. Recognising the potential development cost savings for similar versions of these highly expensive products,[1–3] 'biosimilar' protein drugs theoretically could be produced and marketed at a substantial pricing discount to the innovator drug.

Although the ultimate goal of many stakeholders is to produce true generic versions of recombinant protein therapeutics,

so-called 'biogenerics', others have a more modest goal of producing less expensive but not necessarily identical versions of such drugs, so-called 'biosimilar', 'multi-source' or 'follow-on protein' medical products. Top candidates for development in such abbreviated development form have been recombinant somatropin (growth hormone) and recombinant insulin, although various other recombinant drugs such as erythropoietin, filgrastim (granulocyte colony-stimulating factor) and various of the interferons have also been identified as key targets.

'BIOSIMILAR' DRUG DEVELOPMENT ISSUES IN THE UNITED STATES: INFLUENCE OF CITIZEN PETITIONS

Several versions of recombinant insulin and recombinant growth hormone have received marketing approval as new therapeutic products by the full new drug development process. By many criteria, such proteins can be considered well-characterised. Yet despite the many similarities between specific versions of insulin and similarities between specific versions of growth hormone, complex product characteristics and important technical aspects of cell-based manufacturing processes have long been considered impediments to production of follow-on recombinant products by any kind of abbreviated development. Furthermore, many recombinant drug products have been approved in the United States via the Public Health Service Act regulatory pathway whereas others, highlighted by insulin and growth hormone, have been approved via the Food, Drug and Cosmetic Act pathway. Accordingly, many recombinant protein products have not qualified for a post-patent generic drug option.[2]

FDA's 'reinvention initiative' for so-called well-characterised biotechnology products[4,5] was an initial acknowledgement of the vast capabilities of modern protein characterisation technologies. For well-characterised biotechnology products, some of the technical differences in complexity between traditional small molecule drugs and some recombinant protein drugs have become regarded as less critical than previously considered. However, opposing viewpoints from the innovator and generic industries have illustrated how the concept of biosimilar biotechnology products is very complicated, and many valid scientific issues related to requirements for product characterisation and clinical evaluation has been raised. These issues, which have been presented in the form of citizen petitions by the Biotechnology Industry Organization (BIO) and individual innovator companies (Pfizer, Genentech),[6–9] have linked the potential approval of follow-on growth hormones, or follow-on biological drugs in general, to resolution of a variety of scientific, policy and legal issues. The debate broadly has focused on the twin issues of (1) absence of a regulatory pathway to approval and (2) the technical question of whether two independently manufactured proteins can ever be identical.[2,10] Given that citizen petition issues need to be resolved in part through public consideration, it is not surprising that the debates continued without final regulatory decision for many years.

THE RECENTLY CHANGING REGULATORY PICTURE

There still is no clear definition of a 'biogeneric' (that is, defined as substitutable) drug product, or a regulatory pathway in the United States or EU for such a product's approval. However, the regulatory picture for a product better termed as 'biosimilar' has recently been clarified by definition of a new drug category in the European Union (EU) termed Similar Biological Medicinal Products,[11] and by the US FDA's acknowledgement of the validity of 'follow-on protein products' constituting similar versions but not necessarily exact copies of approved and licensed protein pharmaceuticals.[12] To some extent these

regulatory concepts allow developers and regulatory agencies to side-step the question whether strict chemical identity between two chemically and structurally complex protein products is achievable, and to what extent abbreviated clinical development programmes might suffice to adequately predict equivalent clinical efficacy and safety profiles for the follow-on biological products.

The recent regulatory changes in the United States and the EU have created the potential for development of follow-on biologics with fewer requirements than for standard new drugs, and have clearly indicated an acceptance of the concept of an abbreviated development and regulatory pathway for biosimilar biological drugs. However, the operational question remains unsettled for exactly what data set would be sufficiently robust for product approval. The precedent approvals in 2006 of two new versions of somatropin (Sandoz's recombinant human growth hormone Omnitrope® in the EU and the United States, and BioPartners GmbH Valtropin® in the EU) provide the first view of approvable follow-on biosimilar biological drugs. These approvals provide initial insight into the issues of regulatory pathways for such products and the aggregate of data submitted in support of their applications.

PATHWAYS FOR APPROVAL OF BIOSIMILAR HUMAN RECOMBINANT GROWTH HORMONE

The EU approvals of Omnitrope® and Valtropin® were according to the newly codified Similar Biological Medicinal Product category. This directive provides little technical detail, but acknowledges that biologic submissions need to be evaluated on a case-by-case basis for the need of toxicological, other nonclinical, and clinical efficacy and safety data. Similarly, the FDA approval of Omnitrope® was according to the well-established 505(b)(2) new drug application (NDA) process which allows the use of supportive information, derived from studies of related products, not obtained by the applicant. The 505(b)(2) NDA development process historically involves requirements for applicant data that are decided on a case-by-case basis, in direct contrast to the clearly defined data requirements for approvals of generic drugs via the 505(j) 'abbreviated new drug application' (ANDA) regulatory pathway. Thus, neither the EU nor FDA recent actions on the follow-on recombinant growth hormone products should be considered examples of 'generic' biological drug approvals. Rather, these approvals follow what is best considered a subgroup of the new drug regulatory pathway. The use of the term 'biogeneric' in many press reports of the Omnitrope® and Valtropin® approvals is misleading and unjustified, and there currently is still no regulatory pathway for the approval of generic biological drug products.

OMNITROPE® AND VALTROPIN® DATA PACKAGES: INITIAL PRECEDENTS FOR FOLLOW-ON BIOLOGICS

In general terms, a generic drug has physicochemical identity to the innovator drug and bioequivalence to the innovator, typically on the basis of comparative pharmacokinetic profiles. Development programmes for generic drugs are established to meet these relatively limited data requirements. In contrast, new drugs are characterised by physicochemical analyses, animal toxicology and toxicokinetics, human pharmacokinetics, and human evidence of safety and efficacy. As illustrated below for the EU and US approvals of Omnitrope® and the EU approval of Valtropin®, direct physicochemical and pharmacokinetic comparisons to the innovator drugs Genotropin® and Humatrope® were conducted as would be required for an abbreviated (generic) new drug application. However, the aggregate of all new data

Table 1: Approved biosimilar products: Similarities to developmental data for generic drugs

Data	*Omnitrope® (vs Genotropin®)*	*Valtropin® (vs Humatrope®)*
Physicochemical characterisation	Same primary amino acid sequence, similar secondary and tertiary structure (NMR and other undisclosed spectrometric analyses)	Same primary amino acid sequence, similar secondary and tertiary structure (mass spectrometry, electrophoretic, chromatographic and other spectroscopic analyses)
Purity	Comparable overall purity and impurity profiles	Comparable overall purity and impurity profiles
Bioequivalence from comparative pharmacokinetics	90% confidence intervals of AUC_{inf} and C_{max} within the typical acceptance range of 80–125%	90% confidence intervals of AUC_{inf} within the typical acceptance range of 80–125%, and C_{max} within a widened acceptance range of 70–143% (not strictly qualifying for bioequivalence according to US ANDA requirements)

obtained to support these biosimilar drug applications much more closely resemble the development package for a standard new drug rather than for a generic drug. In fact, based on the European Medicines Agency' published review of the Omnitrope®[13] and Valtropin®[14] marketing applications, and FDA's published review of the Omnitrope marketing application,[15] surprisingly extensive clinical and preclinical comparative databases with the reference growth hormone medicinal products were generated.

On the one hand, comparability to the reference medicinal products included analyses expected for a 'generic' formulation of a drug (Table 1).

On the other hand, additional evidence of comparability to the reference medicinal products was obtained from analyses which would *not* be expected for a typical generic drug, demonstrating that preclinical and clinical development efforts were clearly more like that of a new drug than an abbreviated new drug (Table 2).

OMNITROPE® AND VALTROPIN® APPROVALS, AND THE FUTURE FOR BIOSIMILAR PROTEIN DRUGS

As noted above, the citizen petition process has included considerable discussion of scientific and regulatory issues for follow-on biological products, including specific petition requests that FDA withhold approval of Omnitrope® until which time that petition issues had been resolved. Interestingly, FDA approval of Omnitrope® preceded resolution of the petition issues.

At the time of approving Omnitrope®, FDA officially denied the citizen petition requests for withholding approval.[16] It was specifically noted that Omnitrope® and Genotropin® were sufficiently similar to justify reliance in part on FDA's previous findings of safety and efficacy of Genotropin®. However, other petition arguments remained unresolved, and FDA agreed with the request for continued public process to discuss issues regarding approval of follow-on protein therapeutics in general. In-depth discussions of various scientific issues in the petition response made clear several important points from the FDA perspective:

- A biosimilar drug product need not meet strict criteria of sameness to the innovator. FDA acknowledged that 'highly similar' active ingredients were a sufficient standard for determination of sameness.
- A biosimilar drug product can be established as highly similar to the innovator drug without reference to proprietary chemistry-manufacturing data of the innovator.

Table 2: Approved biosimilar products: Developmental data not required for generic drugs

Data	*Omnitrope® (vs Genotropin®)*	*Valtropin® (vs Humatrope®)*
Nonclinical pharmacodynamic	Similar responses in rat weight gain (the primary pharmacodynamic assay) and rat tibial width (the principal potency assay)	Somewhat lower relative response to Valtropin in rat weight gain and rat tibial width pharmacodynamic assays
Nonclinical toxicology	14-day repeat dose toxicity profile in rats, toxicokinetics, and local tolerance (not comparator controlled)	28-day and 90-day repeat dose toxicity profile in rats and mice, toxicokinetics in rats, reproductive toxicity in rats and rabbits, single dose IV pharmacokinetics in rabbits
Additional human pharmacokinetics	Additional pharmacokinetic data from studies in healthy volunteers: two formulations of somatropin active ingredient, and Omnitrope® vs placebo	
Additional human pharmacodynamics	Similar results for measurements of insulin-like and other growth factors	No marked differences in effects on insulin-like growth factor and IGF binding protein 3
Clinical responses in growth hormone-deficient children	Comparable height, height-velocity and height-velocity standard deviation score responses over treatment periods up to 15 months, demonstration of rare anti-growth hormone antibodies that were non-neutralising and did not interfere with growth responses, and similar adverse reaction profiles Data from a pivotal comparative Phase 3 study with three substudies, and an open-label pivotal safety study	Comparable height, weight, height velocity and height velocity standard deviation score responses over treatment periods up to 12 months, demonstration of non-neutralising anti-growth hormone antibodies (~3%) that did not interfere with growth responses, and similar adverse reaction profiles Data from a pivotal comparative Phase 3 study in one indication and a single-arm study in a second indication
Additional clinical efficacy data		Expected growth-promoting effects on height and weight in girls with Turner's syndrome
Additional immunologic data	Frequent demonstration of induced anti-host cell protein (*E. coli*) antibodies, considered to be of no clinical significance	Infrequent demonstration of induced anti-host cell protein (*S. cerevisiae* yeast) antibodies, considered to be of no clinical significance

- A biosimilar drug product need not be produced by the identical manufacturing process as that of the innovator.
- Differences in formulation between innovator and biosimilar drug products may be allowable, and do not necessarily impact critical features such as product stability and risk of immunogenicity.
- Current medical knowledge may be applicable to potential drug risks such that certain preclinical animal toxicology studies required of new drugs are deemed unnecessary.

With Omnitrope® FDA clearly has set precedent for approval of follow-on recombinant protein drugs via the 505(b)(2) NDA process. Yet the Agency's ruling on the relevant citizen petition requests just as clearly warned that not all petition issues were resolved, and that the Omnitrope® approval was not a blanket acceptance of the concept of biosimilars. Concluding remarks in the ruling specifically noted that the Omnitrope® approval was not a signal that every protein product approved under Section 505 of the Food, Drug and Cosmetic Act was necessarily

a candidate for follow-on approvals through an abbreviated pathway. Furthermore, even though similarity of Omnitrope® to Genotropin® was sufficient to allow 'referenced' Genotropin® data, the products were not deemed therapeutically equivalent, and Omnitrope® was not AB rated to Genotropin®.

Review of the recent approvals of recombinant growth hormone drug products also provide an instructive way to compare the clinical developmental data sets between analogous products approved via the 505(b)(1) full NDA and 505(b)(2) NDA processes. As noted above, considerable preclinical and clinical data were obtained in support of the Omnitrope® (approved in 2006) and Genotropin® (approved in 2007) 505(b)(2) new drug applications. Subsequently, the FDA granted approval of Cangene Corporation's Accretropin™ (somatropin) Injection (approved in 2008 via the 'full' 505(b) pathway), a new formulation of recombinant human growth hormone.[17] Accretropin™ was approved on the basis two small, single-arm open-label trials: one in 44 paediatric patients with growth hormone deficiency and a second in 37 paediatric patients with short stature due to Turner Syndrome. Thus, clinical investigations in support of the follow-on growth hormone products were relatively equivalent in scope to the standard new drug product; furthermore, the clinical programmes for the follow-on products, but not for Accretropin™, provided data to allow providers and users to understand how the new drug performs vs existing alternative products for the approved indications. In some respects one could conclude that the development programmes performed for the follow-on growth hormones were more extensive and informative than that conducted in support of the new 505(b) growth hormone product.

The 2006 approvals of biosimilar recombinant growth hormones in the EU and the United States will soon clarify whether the biosimilar drug development pathway meets the touted goal of the biogeneric industry: cost savings to consumers. Preliminary evidence suggests that discounts for biosimilar protein products is likely to only be approximately 20 per cent, a dramatically smaller cost advantage to consumers than is typical for standard generic drugs.[18,19] In terms of dollars saved, however, it should be noted that 20 per cent discount represents significant saving for drugs that typically cost many tens of thousands of dollars per year. Whereas lower drug pricing, with presumably reduced development costs, will certainly stimulate biosimilar drug development it is unclear the extent to which patients will achieve the level of savings anticipated from the initial concept of a biogeneric drug.

ADDITIONAL INSIGHTS FROM THE EU APPROVAL OF FOLLOW-ON ERYTHROPOIETINS AND FOLLOW-ON FILGRASTIM

With the very high market value of erythropoietin therapy in the treatment of anaemia of chronic renal failure, zidovudine-treated HIV, cancer chemotherapy, and as adjunctive therapy to reduce transfusions in surgery patients, biogeneric erythropoietin has long been at the top of the list of desired new therapies. Hexal Biotech Forschungs GmbH and Sandoz's Epoetin alfa Hexal® (marketed as well as Binocrit®) and Medice Arzneimittel Putter GmbH's Abseamed® is a recombinant formulation of erythropoietin, marketed by the noted manufacturers under separate trade names, that was approved in 2007 as a biosimilar drug product by the EU.[20] Very similar formulations of Epoetin zeta (Hospira's Retacrit® and STADA Arzneimittel AG's Silapo®), differing from erythropoietin alfa in carbohydrate content, were approved later in 2007 as biosimilar products. All five biosimilar versions of recombinant erythropoietin are referenced to,

and have been tested against, the reference medicine Eprex/Erypo.

Epoetin alfa Hexal®/Binocrit®/Abseamed® provide a view of the extent of product development undertaken for this biosimilar drug product. In addition to a limited extent of nonclinical pharmacologic and toxicologic investigation, and five comparative pharmacodynamic/ pharmacokinetic studies in human volunteers, this biosimilar drug was studied in pivotal intravenous (chronic renal failure) and supportive subcutaneous (cancer chemotherapy) phase 3 comparative clinical trials with ERYPO® (Janssen Cilag). These were long-term (1-year) parallel group studies totalling nearly 600 patients, demonstrating comparable efficacy and safety between the investigational and reference drugs. It is interesting that the follow-on and reference products were concluded to be biosimilar despite the demonstration of glycosylation differences between the active ingredients. Similarly, the nonclinical and clinical development programmes for the follow-on Epoetin zeta formulations of recombinant erythropoietin (Retacrit®/Silapo®) included several PK and long-term safety and efficacy trials, totalling hundreds of subjects, thus demonstrating an extensive investigational approach.

A similarly large extent of product development was apparently undertaken for filgrastim biosimilar proteins recently approved by the EMEA. Biograstim® (CT Arzneimittel GmbH), Ratiograstim® (Ratiopharm GmbH) and Tevagrastim® (Teva Generics GmbH), a biosimilar version of granulocyte colony-stimulating factor marketed by the noted manufacturers under separate trade names,was approved in the EU in 2008. Comparator (Neupogen) and placebo-controlled pharmacokinetic, pharmacodynamic, and safety and efficacy trials provided a broad clinical database (over 500 subjects received the biosimilar product) to complement a similarly extensive nonclinical database.

CONCLUSION

Omnitrope® and Valtropin®, biosimilar growth hormones, and a variety of follow-on recombinant erythropoietin approvals, constitute the initial acceptance of 'biosimilar' recombinant protein therapeutics. Several long-held arguments have been side-stepped regarding the distinction between identical vs similar for the characterisation of follow-on protein products. However, based on review of the EU and FDA regulatory summaries for these products, it is not clear the extent to which drug development data could be considered 'abbreviated' in comparison to data typically obtained for a new recombinant growth hormone product. Given the substantive extent of preclinical and clinical data submitted in support of these applications, it is entirely inappropriate to refer to biosimilar products with the term 'biogeneric'. Such products are clearly not generic by usual drug terminology, have very substantial product development data sets to support their approvals and are not currently designated as interchangeable with their originator products. It is also difficult to predict that savings to patients will approach the discount levels characteristic for typical generic drugs, although due to the very high cost of many recombinant protein therapeutics the absolute cost savings may prove substantial.

Disclaimer: The authors have not previously presented any of the material discussed in this paper. The authors received no outside support for preparation of this paper.

REFERENCES AND NOTE

1. *Health News Daily*. (2000) Generic biologic expedited approval should be established, Waxman says. When will we see legal generics of top biopharmaceuticals? Contract Pharma. Vol. 2, issue 100, 25 May.
2. Zeid, R. L. (2000) Regulatory and development issues in the demonstration of therapeutic equivalence for multisource biotech-derived pharmaceuticals. *Drug Information Journal* **34**: 919–959.

Q3

3. Polastro, E. T. (2001) The future of biogenerics. When will we see legal generics of top biopharmaceuticals? Contract Pharma, http://www.contractpharma.com/Oct013.htm.
4. Zoon, K. C. (1998) Well-characterized biotechnology products: Evolving to meet the needs of the 21st century. In: F. Brown, A. Lubiniecki and G. Murano (eds.) *Characterization of Biotechnology Pharmaceutical Products*. Basel, Switzerland: Karger, pp. 3–8.
5. Zoon, K. and Garnick, R. (1998) Definition of a well-characterized biotechnology product. In: F. Brown, A. Lubiniecki and G. Murano (eds.) *Characterization of Biotechnology Pharmaceutical Products*. Basel, Switzerland: Karger, pp. 191–197.
6. Food and Drug Administration. (2003) Docket 2003P-0176. Follow-on therapeutic proteins, http://www.fda.gov/ohrms/dockets/dockets/03p0176/03p-0176-cp00001-01-vol11.pdf.
7. Food and Drug Administration. (2004a) Docket 2004P-0171. Standards for 'similarity' or 'sameness' of biotechnology-derived products, http://www.fda.gov/ohrms/dockets/dockets/04p0171/04p-0171-cp00001-01.pdf.
8. Food and Drug Administration. (2004b) Docket 2004P-0231. Deny approval of NDA 21-402 for Omnitrope 5.8 mg somatropin [rDNA orgin] for injection, http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-cp00001-vol1.pdf.
9. Food and Drug Administration. (2004c) Docket 2004N-0355. Scientific considerations related to developing follow-on protein products, http://www.fda.gov/ohrms/dockets/dockets/04n0355/04n-0355-c000009-vol4.pdf.
10. Roth, R. I. and Fleischer, N. M. (2005) Scientific issues for biogenerics/biosimilars. *Journal of Generic Medicines* **2**: 125–132.
11. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (2003) OJ L 159/46.
12. DHHS: Scientific considerations related to developing follow-on protein products. 69 FR 50386.
13. European Medicines Agency. (2006a) Scientific discussion, Omnitrope powder for solution for injection, http://www.emea.europa.eu/humandocs/Humans/EPAR/omnitrope/omnitrope.htm.
14. European Medicines Agency. (2006b) Scientific discussion, Valtropin powder for solution for injection, http://www.emea.europa.eu/humandocs/Humans/EPAR/valtropin/valtropin.htm.
15. Food and Drug Administration. (2006) Summary basis of approval, Omnitrope [Somatropin (rDNA origin)] injection, http://www.fda.gov/cder/foi/nda/2006/021426s000TOC.htm.
16. Food and Drug Administration. (2006) FDA responses to Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355, http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-pdn0001.pdf.
17. Food and Drug Administration. (2008) Summary basis of approval, Accretropin [Somatropin (rDNA origin)] injection, http://www.fda.gov/cder/foi/appletter/2008/021538s000ltr.pdf.
18. Fractured European market undermines biosimilar launches. (2008) Summary basis of approval, Accretropin [Somatropin (rDNA origin)] injection. *Nature Biotechnology* **26**: 5–6.
19. Biosimilar news APM Health Europe. (2007) http:www.amphealtheurope.com/print_story.php?numero=L9443.
20. European Medicines Agency. (2007) Scientific discussion, Epoetin alfa HEXAL solution for injection.

Q4