REGULATORY FOCUS

How Safe Are Biosimilars?

Implications of FDA and EMA Guidances and European Experience since 2006

By Hoss A. Dowlat

This is the first of a two-part series on the pre- and postapproval clinical safety of known EU-approved biosimilar therapeutic protein medicinal products. It compares and contrasts EU experience with the long-awaited, overarching FDA biosimilars guidances.

It also anticipates the safety of as-yet-unapproved potential biosimilars, including the recombinant mAbs, insulins, heparins and interferons. Biosimilar medicinal development strategy, perception of general risk, interchangeability, substitution and other aspects of acute or chronic use and first/second line or adjunct therapy are addressed.

Introduction

The regulatory burden of biosimilar approvals is substantial, both logistically and economically, but the reward is a portion of more than $100 billion (US) in sales, more than $25 billion each in oncology or immunology or inflammation, and more than $15 billion in diabetes.[1]

Biosimilars are, of course, a new paradigm in drug development, and are currently in a position of acceptance similar to that of generic medicines in the 1980s. Stakeholders in biosimilars are not only patients but also the pharmaceutical industry, regulators and physicians. Besides the heavy regulatory burden, peer acceptance by key medical opinion leaders is an issue that continues to be discussed in individual cases.[2]

This resistance to accepting biosimilars is made evident by slow penetration of EU national markets, unfavorable survey results in the EU and US, critical articles and lectures by opinion leaders and a lack of interest in a deeper understanding of biosimilars by some medical journals and associations. In particular, small molecule generics, such as narrow therapeutic range medicines, can still experience a barrier to acceptance due to their risks of subpotency or adverse drug reactions (ADRs) on overdosing.

Pharmacy-level substitution of generic medicines is widely practiced, following a decision made nationally or regionally by the payer, and not by the EU Commission. For biosimilars, interchangeability is also decided at the national or regional level.

The fact that biosimilars are biological substances mostly endogenous to the human body, or analogs of the same, is perceived positively by the patient (i.e., they are considered "natural"). [3] And yet, the regulator and the prescriber are particularly cautious.

The regulator is driven by concerns about unexpected risk (e.g., ADRs that may be immunogenicity connected), while the prescriber aims for the best therapeutic outcome from an expensive treatment (as physicians tend to place more importance on effecting a cure than on ADRs, if the ADR can be managed). Patients rate side effects (the lay term for ADRs) as their main concern before electing to take any medicine.

The EU

The European Commission, the European Medicines Agency (EMA) and the Committee for Medicinal Products for Human Use (CHMP) have established a legal and regulatory framework of directives, regulations and guidelines for the pharmaceutical industry that have permitted 13 European biosimilar approvals (although these involved only seven sponsors, as some products are identical biosimilars with different trade names and duplicate or triplicate applications.)[4]

Unlike unbranded generics, biosimilars face the challenge of market penetration in different EU countries, in particular fierce detailing of physicians by originator companies that monopolize the market and further protect their interests with new generations of analogous molecules. The perceptions of EU physicians vary depending upon region (eastern or western Europe) and type of disease.

The fourth EU stakeholder is the payer or health technology assessment (HTA) body, an added complexity that involves many national, regional or hospital controls and approvals to permit the listing of biosimilars and decide on their pricing at the retail and hospital level across Europe. The approval process at the HTA level can take many months to more than a year.[5] These same principles apply to biosimilars in the US or other international regions.

The US

It remains to be seen how readily major regions other than the EU, such as the US, accept biosimilars. The first indications from FDA are that, for some drugs, alternatives to long European biosimilar development pathways are possible, such as that exemplified by enoxaparin sodium,[6] a low molecular weight heparin (LMWH) classified as a biosimilar in the EU.[7] FDA approved enoxaparin through an Abbreviated New Drug Application (ANDA) pathway, deemed it an acceptable substitute and required a minimum of pharmacokinetic (PK) data. In contrast, the EU has an LMWH guideline with requirements for an extensive package of PK, pharmacodynamics (PD), clinical efficacy and immunogenicity studies, which might be relaxed according to a new EMA 2011 concept paper.[8]

FDA fingerprinted enoxaparin sodium by its five criteria, each of which captures different aspects of the substance's "sameness." This principle was applied to approve what the agency considered a highly complex but well-characterized polysaccharide.

The extensive EU guideline on LMWHs was considered by FDA but not applied. Immunogenicity was also resolved based on the decision on sameness, largely using the quality data. And this precedent, even though enoxaparin was not a protein, was described by senior FDA staffers in the August 2011 *New England Journal of Medicine* article, "Developing the Nation's Biosimilars Program," which may be viewed as a policy paper.[9]

This overall concept of fingerprinting, using FDA's five criteria and its prior experiences, is expected to be further uniquely adopted by FDA in its pragmatic approach to approval of biosimilars, based on a rich history in biologics: "The FDA has traditionally relied on integrating various kinds of evidence in making regulatory decisions", considering "a totality of the evidence" approach.[10]

The same paper provides examples where the EU experience was evaluated by FDA; for instance, the authors stated this about the mAb CHMP/EMA guidance: "The guideline thus suggests an increasing alignment with the totality-of-the-evidence approach favored by the FDA."

In confirmation, FDA itself restated in the current 2012 *Scientific Considerations* biosimilars guidance that it will consider "the totality of the evidence" in its evaluation.[11] This has been, in fact, the practice for the past five years during biosimilars assessments by CHMP/EMA.

FDA is expected to follow a "stepwise approach" to demonstrating biosimilarity, which can include "a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness."[12] Neither efficacy nor benefit is emphasized, as both are already implicit in the continued license of the originator medicine.[13,14,15]

These aspects are similarly brought to our attention by the CHMP/EMA guideline on biosimilar mAb development,[16] which is in effect a retrospective and reflective position document illustrating the EU concept of biosimilars development in general, not only for mAbs. The EU mAb guideline describes an mAb development scenario in an oncology setting, but its principles can be applied more widely to immunomodulatory mAbs and other molecules. FDA has drawn parallels to it in the 2011 *NEJM* paper (but not by direct reference in the 2012 guidelines themselves).

After much speculation and anticipation, we now we finally have the benefit of reading the FDA February 2012 draft guidances, *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, *Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* and *Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (regulatory aspects).[17,18,19]

These guidances, although offering certain new features compared with the EU-required program of biosimilar drug development (described below), present a wide scope of drug development requirements similar to those of CHMP/EMA. Apart from many references to the possibility of a "targeted"[20] and "abbreviated" drug development program, FDA guidances do not make it clear that biosimilar drug development could be curtailed. Therefore, it was surprising how extensive the study demands appear to be.

Additionally, there are very detailed data requirements to be ascertained through frequent FDA meetings. However, with a view to personal experience with FDA, I expect the actual US development may well be curtailed, based on FDA consultation at the individual therapeutic review division level. FDA decisions would be made on a case-by-case basis by product and division, but these guidances[21,22,23] would provide an overarching perspective similar to the European biosimilars framework defined by overarching CHMP/EMA guidelines.[24-29]

Upon consultation with a therapeutic division, various FDA offices would be involved at the advice, review and approval stages, and the new acting associate director for biosimilars in the Office of New Drugs, Dr. Leah Christl, and future FDA oversight mechanisms would assist with the coordination and consistency of FDA guidance across the therapeutic divisions.

There is a biosimilars user fee program to cover product development meetings and investigational new drug (IND) applications; scientific, regulatory, policy infrastructure; and standards.[30] FDA will offer at least five separate meetings within a one-year period to a biosimilar applicant, relating to review of an application and guidance on additional clinical and analytical tests.

The timeliness of this initiative fits with current demands, as FDA has apparently received (as of December 2011) 31 pre-IND meeting requests for biosimilars that reference 11 products, and has held around 21 pre-IND meetings with sponsors.[31] Also, around seven IND applications for biosimilar development programs have been opened.[32]

Current Positive Trends in Biosimilars Development and Medical Experience

EU biosimilars experience will be compared and contrasted below with the new FDA biosimilars guidances, beginning with the ultimate goal of achieving interchangeability.

Interchangeability Provides Assurance of Efficacy Without Compromising Safety

The issue of interchangeability concerns both the risk to the patient of new ADRs upon switching a treatment to the biosimilar equivalent and the possible risk of compromising treatment potency.

In a worst-case scenario, the switch can elicit an immunogenicity response such as a hypersensitivity reaction. All the evidence from pre- and postapproval findings with approved biosimilars and those under development suggests there are no new untoward effects and efficacy is not compromised in any way.

There are different understandings of what interchangeability means.

From an EU perspective, EMA has made a statement opposing the idea of automatic substitution of biosimilars (for example, at the pharmacy level): "Since biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional."[33]

From a US perspective, interchangeability means, in practical terms, automatic substitution similar to the AB rating of a generic version of the drug listed in the *Orange Book* and approved under the *FD&C Act*, allowing a substitution at the pharmacy level.

The *Biologics Price Competition and Innovation Act* of 2009 (*BPCI Act*), defines *interchangeable* or *interchangeability*, as "a term that means that the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product."[34,35]

Some future FDA-approved "biosimilars" are foreseen by the FDA guidance as not being interchangeable with the FDA-licensed biological reference product, but perhaps surprisingly, the conditions are not laid down for industry in the current guidances. Approval of interchangeability is, after all, the desirable goal of biosimilars. FDA's position is expressed in the Q&A guidance in the context of a combination product with a device, but the principle would apply more generally:

> "Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, FDA may consider whether the differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients, for patients to be safely alternated or switched between the reference product and one or more interchangeable products without the intervention of the prescribing healthcare provider." (FDA Q&A: A. I.4)[36]
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> "... and meet the other standards (concern multiple switching between biosimilar and reference product-author) described in section 351(k)(4) of the PHS Act." And, "FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product." (FDA Q&A: A. I.14).[37]

That is, the current FDA guidances cover general requirements for both non-interchangeable and interchangeable tiers of biosimilars, but unfortunately lack any specifics of what would be needed to obtain industry's real objective of approval for the authorized interchangeable biosimilar.

Interchangeability by Other Stakeholders

The European Generics Association (EGA), which has more than four members with biosimilars medicines, takes the following position: "[Interchangeability] refers to the medicinal/pharmaceutical practice of switching one medicine for another that is equivalent, in a given clinical setting. A product is considered to be interchangeable if it can be administered or dispensed instead of another clinically approved product." Whereas, "substitution refers to the practice of dispensing …at pharmacy level and without consultation of the prescriber."[38]

The World Health Organization (WHO) defines interchangeability as "the medical practice of switching one medicine for another that is equivalent, in a given clinical setting."[39]

Furthermore, WHO says: "The decision to allow automatic substitution of a Similar Biotherapeutic Product (SBP) for a Reference Biotherapeutic Product (RBP) should be made on a national level taking into account potential safety issues with the product or class of products. Decisions on interchangeability should be based on appropriate scientific and clinical data and are beyond the scope of this document."[40]

What would be acceptable to the prescriber, the patient or the healthcare provider? And what about the pharmaceutical sponsor? Is it a question of efficacy or safety? What is

most important is to achieve the same therapeutic dose for the biosimilar as the originator. Is there concern about a suboptimal dose, or the expectation that the drug substance (DS) must be identical and not similar, not appreciating what is meant? Is there a risk that there will be a suspected unexpected serious adverse reaction (SUSAR) arising from the DS or drug product (DP) manufacturing?

This has not been seen to date, after five years of pharmacovigilance. Common sense needs to prevail. FDA's clear statements below are illuminating.

Interchangeability and Further Scientific and Regulatory Facts

FDA expresses its viewpoint that "slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences."[41] Furthermore, that "lower immunogenic or other adverse events would not have implications for the effectiveness of a protein product."[42]

In a postmarketing scenario, FDA envisages spontaneous reports of "the identification of adverse events associated with the proposed product that have not been previously associated with the reference product."[43]

As the biosimilar usually has the same composition, with identical excipients as the originator, and in practically all cases the presentations are solution forms, the introduction of risk with the DP is minimal. With the EU's approval of Valtropin in 2006,[44] CHMP/EMA also made a milestone decision to approve a yeast-based somatropin[8] cell expression system, compared to an *E. coli*-based reference medicinal product (RMP) of Humatrope.[45] Valtropin was produced in *Saccharomyces cerevisiae* (yeast) cells. The previously marketed somatropins were expressed in either *E. coli* (e.g., Humatrope, Genotropin, Nutropin) or in mammalian cells (Saizen), making the Valtropin yeast-cell process unique among growth hormones. Omnitrope's, (also approved in April 2006), somatropin drug substance was produced in an *E. coli* (bacterial) host.[46,47]

This precedent of a new fermentation expression system was endorsed by CHMP/EMA four years later in the mAbs guideline.[48] FDA provides similar flexibility by stating: "Therapeutic protein products can be produced by microbial cells (prokaryotic, eukaryotic), cell lines of human or animal origin (e.g., mammalian, avian, insect), or tissues derived from animals or plants. It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant."[49]

Even using the same cell expression system, there can be new protein-derived impurities, for example, using *E. coli*. These new impurities are allowable in a biosimilar as long as they are qualified and depending upon their comparison with the rest of the impurity profile of the RMP. Of course, new process impurities are also present and may be associated with immunogenicity. The FDA and CHMP/EMA guidance on fermentation upstream and downstream processes and derived impurities are completely aligned.

Some biosimilar sponsors also have significant experience with manufacturing the DS and DP and medical use in other regions of the world, reducing the risk to safety.

Yet FDA considers that the risks associated with a new manufacturer, the biosimilar sponsor, are greater than those of the originator.[50]

Furthermore, it should not be forgotten that the RMP itself is being developed by the originator during its lifecycle, with changes in the DS and DP process, pharmaceutical forms, presentations, devices, ownership, manufacturing site and equipment, testing methods and specifications all adding to the safety risk. Batch-to-batch variability in both the test BMP and RMP should be monitored; in fact, "drug shift" of the RMP is a new concern that will come under CHMP/EMA scrutiny.[51]

Also, most interestingly, FDA shows considerable flexibility when it explicitly defines allowable differences in formulation or presentation when the dosage form (pharmaceutical form) of the biosimilar is the same as the RMP's, according to its Q&A (regulatory) guidance.[15] For instance, albumin may be omitted as an excipient,[52] or the agency would allow a prefilled syringe or an auto-injector biosimilar instead of a solution for injection RMP, or a solution for injection for a powder instead of a solution for injection RMP.[53]

Interchangeability Illustrated by Human Growth Hormones

Although their development programs were very different, both Valtropin and Omnitrope involved switching the RMP arm to the test biosimilar medicinal product (BMP) arm during the open extensions phase of the clinical Phase 3 studies. Some other EU biosimilars also furnished data on switch of the RMP arms to the test BMP data, for instance Abseamed (epoetin alfa), where the switch took place during weeks 29–56.[54]

Therefore, when in April 2006 the commission authorized (approved) the first two biosimilars, Omnitrope and Valtropin, this implied "biosimilarity" to Genotropin, Humatrope, NutropinAq, Norditropin, Saizen and Zomacton. This means that the data support interchangeability among them. This is different from the ANDA concept of sameness by which FDA approved enoxaparin sodium, which can only interchange for Lovenox and not other LMWHs.

The RMPs were different: Genotropin for Omnitrope, and Humatrope for Valtropin. Comparative clinical efficacy, bioavailability and safety data, notably the most "sensitive" patient population of prepubertal 5- to 13-year-old children, based on long-term multicenter studies, were the basis of approval. As a result, the two approved biosimilar products had different label claims for specific indications and pharmaceutical characteristics originating from their respective RMPs. Although they had indications in common—children with growth failure due to an inadequate secretion of normal endogenous growth hormone and replacement therapy in adults with pronounced growth hormone deficiency and associated safety profiles—there were also many differences in the SmPCs.

Growth rate measured by height velocity. immunogenicity and ADRs were the clinical endpoints in prepubertal children, although PK (exogenous hGH levels) and PD (IGF-1 and IGFBP-3) bioequivalence studies in healthy volunteers were conducted separately as proof of efficacy. These data together demonstrated equivalence and bridged to allow products to carry all four or five label claims of the marketed products for children, as well as extrapolating to claim the adult indication(s) (child and adult onset) based on body mass changes and not height.

Similar to the CHMP/EMA, the FDA guidances allow extrapolation of indications.[55] Immunogenicity was investigated using validated assays, and the results were comparable. Also, there was no change of immunogenicity or efficacy in terms of growth height velocity for the patients who were switched, confirming the safety of Valtropin.

These first somatropin biosimilar approvals involved studies uniquely in children, whereas all subsequent work has required adults. Also, somatropins demonstrated a case of more than one possible RMP, which is not the case with biosimilar mAbs candidates, but is found for other as yet unapproved biosimilar candidates such as insulins,[56] interferons,[57] etc.

Interchangeability Illustrated by Human Insulins

The most complex case of unapproved biosimilars has been the human insulins, which present an intricate challenge to regulators and industry. There are actually three products, and not one, used together in medical practice, namely a "soluble" short-acting product, an "isophane" long-acting product (these being used as a free combination) and a "biphasic" mixture of the short and long products. Patients can be switched from free to fixed combination during clinical use or remain on one or the other option. The soluble may also be added to the biphasic in patient hyperglycemia peaks. The isophane and biphasic insulins are also unique among biosimilars or future candidates as they are both, complicating development.

Alternative manufacturers of RMP are Eli Lilly, NovoNordisk and Sanofi Aventis. For the CHMP/EMA, a product bioequivalence study per *individual* product is pivotal to approvals instead, such as Phase 1 PK studies or PD glucose "clamp" studies, which assume that insulin-induced glucose suppression is a surrogate marker of diabetes mellitus. Additionally, a 12-month Phase 3 immunogenicity and safety study is essential to EU Commission approval.

Recognizing but Not Overstressing Immunogenicity

Comparative immunogenicity is a major concern for the regulator of biologics and is addressed in several EU guidelines.[58,59] FDA, too, addresses the issue in some detail.[60]

The methodology used for immunogenicity testing is critical, and this is emphasized in particular by FDA, which has background literature [61] and a dedicated guidance,[62] whereas the EU has a general guideline covering quality, nonclinical and clinical aspects of immunogenicity,[63] and a class-specific guidance for mAbs.[64]

FDA, in its February 2012 guidance on scientific considerations,[65] emphasizes the 2009 guidance on analytical validation methodology,[66,67] which needs to be robust. The clinical requirements depend upon "the severity of consequences and the incidence of immune responses" but it is "only important to demonstrate that the immunogenicity of the proposed product is not increased."

FDA requires the study to be conducted in the "most sensitive" population, just as CHMP/EMA does. The FDA guidances overlap with the scope of the CHMP/EMA guidance but can go even further if the clinical consequence is severe, such as anaphylaxis. If the immune response to the reference product is rare, two separate immunogenicity studies may be necessary: "(1) a premarket study powered to detect major differences in immune responses between the two products and (2) a postmarket study designed to detect more subtle differences in immunogenicity."

Conclusions

Biosimilar development requires a highly specialized, cross-disciplinary team effort. A substantial body of pharmaceutical, *in vitro*, *in vivo*, toxicology/toxicokinetic, PK, PD, PK/PD and clinical equivalence data are gathered in the EU, matching a chosen reference product with the intent of interchangeability. A judicious choice of endpoints and methods and thorough immunogenicity investigations, with carefully validated methods, are part of demanding clinical studies.

Overall, success requires a well-thought-out, well-executed clinical program in sensitive and homogenous populations. Extrapolation from one usage to another can be justified but is not a given. Indications not studied were allowed for somatropins, filgrastims and erythropoietins. But the new indications are associated with distinct patient populations, doses and regimens. This complicates the options on design and range of studies chosen to support the label claims in connection with safety aspects of the biosimilar development. This issue is illustrated with examples of mAb development in Part 2 of this series.

The FDA guidances describe a very comprehensive program, too. But FDA proposes a "stepwise" and risk-based "targeted" approach, based on its willingness to reduce the burden of nonclinical and clinical testing to essentials. For instance, "The scope and magnitude of clinical studies will depend on the extent of **residual uncertainty** about the biosimilarity of the two products after conducting structural and functional characterization and possible animal studies. The frequency and severity of safety risks and other safety and effectiveness concerns for the reference product may also affect the design of the clinical program."[68]

Such systematic comparative studies in Europe have led to completely new, previously unexplored data and insights on impurities, immunogenicity in special patient populations, the properties of the RMP, comparability aspects and so on.

The MAA package has undergone rigorous review by 30 advanced national regulatory authorities, led by a harmonized CHMP and EMA perspective and oversight. Therefore, assurance of the safety of the biosimilar is high at the time of launch.[69,70,71] Monitoring continues in parallel with the changes of the RMP under an EU risk management plan.[72] And for thoroughness, there is a European postauthorization requirement to capture safety data across different indications. FDA has comparable demands for pharmacovigilance pre- and postapproval. This will be a focus of Part 2 of this series.

References

1. IMS Health data, December 2010, not including advanced therapies (ATMPs).
2. Private communications and presentations by companies marketing biosimilars at European Generic Association Annual conferences 2009-2012.
3. Ibid.
4. HA Dowlat. "Biosimilars Breaching Borders: How FDA and EMA Find Common Ground." *Regulatory Focus*, March 2012; Table 1.
5. Op cit 2.
6. US Food and Drug Administration. Generic Enoxaparin, Questions and Answers. www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm. Accessed 8 May 2012.

7. European Medicines Agency. *Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins,* EMEA/CHMP/BMWP/118264/2007 (19 March 2009).
8. Ibid.
9. S Kozlowski, J Woodcock, K Midthun, RB Sherman. "Developing the Nation's Biosimilars Program." *New England Journal of Medicine.* 2011:365(5);385-8.
10. Ibid.
11. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER. February 2012).
12. Ibid.
13. Ibid.
14. *Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (issued jointly by CDER and CBER. February 2012).
15. *Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (issued jointly by CDER and CBER. February 2012).
16. *Guideline on similar biological medicinal products containing monoclonal antibodies* (Draft). EMA/CHMP/BMWP/403543/2010. (18 November 2010).
17. Op cit 11.
18. Op cit 14.
19. Op cit 15.
20. Op cit 11.
21. Ibid.
22. Op cit 14.
23. Op cit 15.
24. European Medicines Agency. *Guideline on similar biological medicinal products.* CHMP/437/04. 30 October 2005.
25. Concept paper on the revision of the guideline on similar biological medicinal product, EMA/CHMP/BMWP/572643/2011 (17 November 2011).
26. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues.* EMEA/CHMP/BWP/49348/2005.
27. Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMA/CHMP/BWP/617111/2010 (7 February 2011).
28. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*. EMEA/CHMP/BMWP/42832/2005 (June 2006).
29. Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues. EMA/CHMP/BMWP/572828/2011 (22 September 2011).
30. US Food and Drug Administration. *Biosimilars User Fee Act* of 2012. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM287749.pdf. Accessed 8 May 2012.
31. Op cit 2.
32. Ibid.
33. European Medicines Agency. Q&A document EMEA/74562/2006 (Rev.1 22 October 2008).
34. Op cit 11.
35. Op cit 15.
36. Ibid.
37. Ibid.
38. European Generic Medicines Association. *EGA, Biosimilar Handbook*. Sage Publications (2011).
39. Op cit 15.
40. World Health Organization. "Guidelines on evaluation of similar biotherapeutic products (sbps)." WHO, expert committee on biological standardization Geneva, 19-23 October 2009.
41. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER. February 2012).
42. Ibid.
43. Ibid.
44. European Medicines Agency. EPARs: Valtropin H-C-602-en6; Scientific Discussion, non-inferiority, children as sensitive model, equivalence model: pp13, 15, 17, 19, 27.
45. European Medicines Agency. EPARs: Omnitrope H-C-607, 060706en6. Scientific Discussion.
46. Op cit 44.
47. Op cit 45.
48. Op cit 16.
49. *Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product* (issued jointly by CDER and CBER. February 2012).
50. Op cit 14.
51. Op cit 27.
52. *Draft Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (issued jointly by CDER and CBER. February 2012).
53. Ibid.
54. European Medicines Agency. EPARs: Abseamed H-727-en6; Scientific Discussion.
55. European Medicines Agency. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER. February 2012).
56. European Medicines Agency. *Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin.* EMEA/CHMP/BMWP/32775/2005, 22 February 2006.
57. Current product-specific European guidelines on biosimilars 5-11): Guideline on similar biological medicinal products containing interferon beta. EMA/CHMP/BMWP/652000/2010 (15 December 2011).
58. *Guideline on immunogenicity assessment of biotechnology derived therapeutic proteins*. EMA/CHMP/BMWP/86289/2007,
59. *Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use,* 18 *November* 2010.
60. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER. February 2012). Line 522: 'immunogenicity'.
61. AR Mire-Sluis, *et al*. "Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products." *Journal of Immunological Methods*.. 2004:289(1-2); 1-16.
62. US Food and Drug Administration, CDER and CBER. *Guidance: Assay Development for Immunogenicity Testing of Therapeutic Proteins (CMC).* December 2009 (Draft).
63. Op cit 58
64. Op cit 59

65. *Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (issued jointly by CDER and CBER. February 2012).
66. Op cit 61.
67. Op cit 62.
68. Op cit 65.
69. H Dowlat. "The importance and impact of the EU RMP and US REMS to risk–benefit assessments." *Regulatory Rapporteur*. 2011:8(2) February 2011, 20-23.
70. H Dowlat, 'The current status of biosimilar biologics – an international perspective: Part 1', *Regulatory Rapporteur,* Vol 7, No 9, September 2010, 24-27.
71. H Dowlat. 'The current status of biosimilar biologics: Part 2: practical considerations in international development through European lessons learned', *Regulatory Rapporteur*, Vol 7, No 10, October 2010, 8-11.
72. Op cit 69.

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