

Perception And Realities of Clinical Safety of BioSimilarars : **EU & US Perspectives: Part 2**

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Hoss has an acute business sense and is a successful negotiator with Regulatory Agencies EU/US/ROW. He is internationally minded, flexible, versatile and multilingual (English-French-German). He has extensive experience with European, EMA and FDA submission procedures, US/EU Scientific Advice, and with eCTD-NDA/BLA//MAA or IND/CTA conversions. He is a pioneer in international Biosimilar approvals leading one of the first of two European Biosimilar Marketing Authorizations MA, unprecedented approvals, in April 2006. Also, he has substantial Orphan Drugs experience.

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This article continues from Part 1 (see Regulatory Rapporteur, April 2012) in appraising the clinical safety of known EU-approved biosimilar therapeutic protein medicines pre-approval and postapproval, comparing current EU regulations with three new FDA biosimilars guidances issued in February 2012: “Scientific Considerations”, “Quality Considerations” and “Questions and Answers” (Regulatory). This second article examines the implications of pharmacovigilance and safety attributes being influenced by the particular patient population studied. Careful planning of clinical development is highlighted with safety in mind.

Keywords

Guidance; US FDA; European Medicines Agency (EMA); Committee for Medicinal Products for Human Use (CHMP); Reference medicinal product (RMP); Biosimilar medicinal product (BMP); Interchangeability; Monoclonal antibody (mAb); Somatropin; Filgrastim; Epoetin; Insulin.

Introduction

The purpose of this two-part paper is to provide insights into the new paradigm of biosimilar medicines based on approval and medical experience post-approval. It proposes a framework for the understanding, development and acceptance of a new generation of biologic medicines, “biosimilars”, in the US¹⁻⁴ and worldwide.

In 2012, the knowledge gleaned by regulators and industry permits a degree of confidence in biosimilars authorised in the EU by the European Commission after nearly six years of pharmacovigilance, providing reassurance in the regulatory process leading to approval. Further aspects of safety are explored in the discussions which follow, describing in depth the development and regulatory approval criteria for biosimilar medicines in Europe and the US. At the same time, this paper is an attempt to dispel false perceptions which are contrary to the established safety and efficacy of biosimilars.

Addressing perceptions of risk

Is there really a difference in risk in starting treatment with an originator biologic and then switching to an EU-approved biosimilar, or starting treatment with a biosimilar instead of the originator biologic medicine? Should the patient in the first case be maintained on the originator medicine, despite the fact that the biosimilar has been approved in Europe?

Any concerns regarding subpotency are allayed by the fact that the pivotal studies are all equivalence trials at present, or at a minimum non-inferiority studies in line with the new US guidances.¹⁻³ And safety is proven by a battery of quality (chemistry, manufacturing and control, CMC), nonclinical and clinical tests typically including a complex, 12-month clinical immunogenicity investigation using systematic antibody assay testing (with rigorous validations of screening, confirmatory, cross-reacting, and neutralising antibodies), and positive efficacy confirmed, in direct comparison with the European reference medicinal product (RMP). Not only is the biosimilar medicinal product (BMP) meticulously compared with the RMP for similarity, but every point of difference (every peak on the analytical spectrum or any impurity) is carefully and critically assessed in the context of benefit–risk. Clearly, the degree of scrutiny of the European regulator, led by the highest level regulatory and scientific authority, the CHMP, could not be more rigorous, and is consolidated by the combined experiences of 30 EU member states.

It is hoped that the perceived “risks” of biosimilars will change as these compounds are better understood. A monoclonal antibody (mAb), being costly, might not be used as an adjuvant in oncology in unsupported healthcare systems, but a biosimilar may afford that opportunity. Even the use of a G-CSF, filgrastim, as an adjuvant in oncology to reduce neutropenia, has increased greatly in some EU countries such as the UK due to cost savings, offering major advantages to patients.⁵

Surveys have shown that a mAb biosimilar might be perceived as less risk in palliative treatment, or in an

adjuvant setting compared with an acute life-saving scenario, or in a metastatic setting compared with the cost of an originator product.⁵

In some poorer European countries, for example in Eastern Europe, biosimilars fulfil an unmet medical need. In developing countries worldwide the biologic medicine might be affordable only on the introduction of the biosimilar, and in these circumstances the biosimilar would constitute a first entry to market.

Pharmacovigilance

A European risk management plan (RMP_{PV})⁶ which includes a risk minimisation and pharmacovigilance plan is an essential part of a marketing authorisation application (MAA) approval of biologics, during both the lifecycle of the RMP and the biosimilar, to predict, mitigate and contain risk.^{6,7} Risk can be affected by exposure, route of administration, by indication, and by severity.

The biosimilar RMP_{PV} includes safety specifications consisting of a summary of important identified risks, including safety pharmacology and toxicology for important potential risks and missing information obtained from clinical studies, immunogenicity testing (in the patient population that carries the highest risk of an immune response and immune-related adverse reactions), and evidence of its symptomology, spontaneous adverse event reporting, and scientific literature. The summary needs to be updated following changes to the originator’s RMP_{PV}.

It can be assumed that an FDA risk evaluation and mitigation strategy (REMS)⁶ would only be relevant where the originator product already has a REMS, although this is speculation, and will depend on the FDA’s future experiences. Components of a typical FDA REMS are a communication plan; patient selection; web-based materials and a medical scientific liaison; elements to assure safe use; an implementation system; a patient or physician survey; and clear communication of risk through the Patient Counselling Information.

Notably, and unexpectedly, according to the FDA guidance a biosimilar that does not qualify for interchangeability will be viewed as a “new active ingredient”; as such it will be also be subject to the FDA’s paediatric requirements.³ In fact this would be triggered at the time of filing an investigational new drug (IND) and would require the preparation of a paediatric investigation plan (PIP). In the EU, a biosimilar is exempt from a PIP.

However, once approved, a biosimilar must follow changes in the approved RMP such as those summarised in the originator’s product information (the EU summary of product characteristics (SmPC) and the US package insert (PI)). However, in Europe it can additionally follow a separate lifecycle development pathway in principle, although there is nothing on this in the regulations or guidelines at present. That could mean new pharmaceutical forms, new indications or new target populations. This principle is present in the Canadian biosimilars guideline,⁸ but not in the US or EU guidances.

The mAb guideline of November 2010 reflects four years of CHMP/ EMA experience of biosimilars and therefore lays down the best principles, and attempts to reduce the burden of nonclinical testing.⁹ It also makes

explicit the requirement to select the most sensitive and homogeneous populations (an aspect which for study allows extrapolation of indications). But justification that immunogenicity can be predicted in the other claimed populations based on the studies forming the basis of approval is an important condition. Sensitive and homogeneous populations are aspects which the CHMP/EMA repeatedly raise in scientific advice. The FDA emphasises sensitivity in its guidances but does not directly mention homogeneity. Why this is omitted is not known.

Clinical efficacy aspects

A decrease in potency or lack of efficacy on marketing a medicine is a pharmacovigilance issue and to date there is no evidence of this, after five years of EU medical experience of marketed biosimilars.⁵

The most sensitive patient population, a homogeneous patient population, and clinical endpoint are chosen in the pre-approval studies to be able to detect product-related differences, if present, and, at the same time, to reduce any confounding patient- and disease-related factors to a minimum in order to increase precision of analysis and maximise response. This also reduces the variability and thus reduces the sample size needed to prove equivalence, and can simplify interpretation.

Patients with different disease severity and with different previous lines of treatment might be expected to respond differently, and it may remain uncertain whether such differences would be attributable to the consequence of patient- or disease-related factors rather than to differences between the biosimilar and reference product. This is very relevant to mAbs.

The FDA, as with the CHMP/EMA mAb guideline,⁹ accepts that: “A sponsor can use endpoints that are different from those in the reference product’s clinical trials”¹, Line 711

The FDA cautions that appropriate subjects need to be selected, and advises the exclusion of “patients (who) have different co-morbidities and disease states (eg, immuno-competent or immuno-suppressed) and receive different concomitant medications”. It adds: “In general, using similar study populations is essential for supporting the constancy assumption that is critical to interpreting the non-inferiority finding in a one- or two-sided comparative test.”¹, Line 723

It is also worth noting that the FDA places a high degree of importance on clinical pharmacology studies as evidence of comparative efficacy, and does not consider a need to prove benefit. This is in line with the opinion of the CHMP/EMA. The FDA places importance on safety determined by the immunogenicity study, and describes features that are very similar to CHMP/EMA expectations, among which is a 12-month minimum study. The FDA expects an efficacy study to be conducted only when necessary, and outlines some basic study statistical criteria including the alternatives of equivalence and noninferiority designs. Noninferiority with a primary variable of efficacy has not been allowed in the EU as a basis of any approval to date, as far as the author is aware. It may be acceptable

for safety studies such as immunogenicity studies. However, the FDA allows both alternatives.

The FDA recommends that sponsors consider the use of population pharmacokinetics (PPK) to explain observed differences in safety and effectiveness that may occur due to variability in pharmacokinetics (PK)¹, Line 700 According to the guidance: “PPK methods are an efficient way to quantitate the influence of covariates (eg, age or renal function) on PK and, in some cases, [pharmacodynamics] PD.”

Paediatric assessment under the US Pediatric Research Equity Act (PREA) will be triggered for noninterchangeable biosimilars at the time of IND filing, although at that time it may not be known to which of the two tiers of biosimilars the product will belong! “Section 505B(n) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a “new active ingredient” for purposes of PREA, and a pediatric assessment is required unless waived or deferred.³

An interchangeable biosimilar product is not considered to have a “new active ingredient” for the purposes of PREA, therefore a paediatric assessment of the interchangeable product is not required.

Clinical safety aspects

Selection of subjects: In the same way as efficacy, homogeneity and sensitivity aids in providing data that are easier to interpret. In addition, selecting the most sensitive population is important in immunogenicity.

The inclusion of patients from non-European countries is generally acceptable for EU biosimilars as long as there are no ethnicity or other concerns in connection with intrinsic (genetics, metabolism, etc) and extrinsic (diet, habitat, etc) factors.

The FDA allows non-US studies but cites its guidances on foreign studies and ethnicity.¹ But the likelihood is that EU studies or studies conducted elsewhere in support of an EU biosimilar will be acceptable.

In Europe, knowledge of efficacy and safety of the reference biologic in a particular region may be necessary in order to prospectively define an equivalence margin. Stratification and appropriate subgroup analyses are normally expected in the EU if patients from different regions of the globe are included. Diagnostic and treatment strategies should be comparable in order to prevent the influence of extrinsic factors.

It is advisable to use the same definitions for safety parameters as those used for the reference biologic in its original development programme (if known) where no homogeneous or harmonised definition exists (eg, measurement of cardiotoxicity in the case of mAbs).

It is necessary to reflect on the normal clinical setting and also on how re-treatment of patients would be handled, and to systematically measure safety of repeat exposure of patients, eg, oncological indications where patients undergo several treatment cycles.

Physicians’ perceived risk of use of a biosimilar was demonstrated in the EU by the reluctance of some to use

Zarzio G-CSF in healthy subjects for stem cell mobilisation, as the approval was based solely on healthy volunteer studies and not patients.⁵ Medical uses of filgrastim G-CSF in the EU include dose intensification of chemotherapy (patients); prophylaxis of febrile neutropenia; treatment of febrile neutropenia; and stem cell mobilisation (healthy subjects), so some physicians felt the risk of subjecting a healthy person to a new treatment which was unproven in a Phase III clinical study was too high. A significant proportion of physicians cannot easily relate to the objective value of bioequivalence clinical pharmacology studies, even PK studies.

The pivotal clinical study (efficacy) or immunogenicity study (safety) can be extended as a post-authorisation follow-up study to a full treatment cycle, where relevant and feasible.

Where possible, patients previously treated with the reference biologic are excluded, to avoid negatively influencing interpretation of the safety data, and also decrease sensitivity for detecting differences. This can be particularly important in measuring meaningful antibody response to the biosimilar.

There is an EU post-authorisation requirement for obtaining further indication-specific safety data for the reference biologic to capture data on safety across different licensed indications.

The current mAbs being developed as biosimilars come in a range of pharmaceutical forms: powders for solutions or for concentrates, solution concentrates, ready-to-use solutions, or alternative presentations such as vials, prefilled syringes, or cartridges (to fit pen devices). There is therefore the risk of increasing the extent of new chemical or biological impurities or bioburden through filtration or lyophilisation steps, and introducing new impurities through drug/packaging interaction. However, most biosimilars closely match the originator excipients, packaging components and process to curtail problems.

The FDA is flexible on allowing new formulations and presentations of the biosimilar compared with the RMP, as noted earlier, as long as certain conditions are fulfilled, among which is the same pharmaceutical forms.^{3, Q/A. 1.4.}

Examples of mAb and infusion proteins illustrating the considerations for multiple indications regarding safety: A biosimilar can be expressed from different yeast, *E. coli*, rodent or mammalian cell species which have different associated immunogenicities. For instance, process changes from chimeric (stem, -iximab) to humanised (stem, -zumab) to fully humanised mAbs (stem, -umab) have progressively decreased risk of immunogenicity. Patients with human anti-mouse antibody (HAMA) or human anti-chimeric antibody (HACA) titres may elicit allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic mAbs.

Examples of the indications, doses and regimens of rituximab, infliximab and etanercept¹⁰ illustrate the complexity of the use of the mAb and fusion proteins with particular clinical safety concerns, as well the challenge of selecting the appropriate patient populations for sensitivity and homogeneity for PK, PD and clinical efficacy and safety studies to support extrapolations to groups not investigated with the biosimilar.

Product-specific examples:¹⁰

MabThera (rituximab). MabThera, an r-IgG1, is a rituximab concentrate for solution for infusion. It has three approved but diverse indications, each with different pharmacovigilance programmes noted within section 4.8 of the EU SmPC: Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and rheumatoid arthritis (RA). Only RA has an additional contraindication of cardiovascular disease. The size of the safety database depends on the condition treated and the nature of the biologic.

The doses and regimens are different, eg, for NHL it is 375 mg/m² body surface area per cycle, for up to eight cycles, while for RA it is 1,000 mg by intravenous (IV) infusion followed by a second 1,000 mg IV infusion two weeks later. The infusion rate can be from 50–400 mg/h and has an influence on adverse reactions. Infusion-related reactions are very common in RA patients given rituximab. Therefore, as this example shows, there are many variables in any biosimilar clinical development programme that will impact both efficacy and safety.

Remicade (infliximab). A Remicade vial contains 100 mg of infliximab powder for concentrate for solution for infusion. Remicade is indicated (second line treatment) for adults with active RA, Crohn's disease, ulcerative colitis in paediatric 6–17 year olds, psoriatic arthritis or plaque psoriasis (skin) in adults; doses are either 3 mg/kg or 5 mg/kg by IV infusion with diverse regimens. Therefore, distinctly different pharmacovigilance programmes are involved.

Enbrel (etanercept). This is a recombinant human tumour necrosis factor TNF inhibitor receptor p75 Fc fusion protein, a powder and solvent for solution for injection. Etanercept is in principle a "new generation" derivative of mAb infliximab maintaining the Fc moiety, but is a smaller molecule which represents the first fusion protein biosimilar candidate coming off patent, and has essentially the same indications as infliximab except for Crohn's or colitis. The recommended dose of Enbrel is 25 mg administered twice weekly or 50 mg administered once weekly by subcutaneous injection.

The subcutaneous route raises the risk of dermally triggered serious hypersensitivity reactions compared to the IV infusion route which in itself can induce infusion reactions. The IV, however, represents higher exposure. So each route and pharmaceutical form has associated safety risks. The FDA requires the subcutaneous route to be studied as it is associated with the highest risk of immunogenicity.

Post-approvals Reports

There is virtually no specific clinical European public assessment report (EPAR) information on post-approval clinical activities of biosimilars.¹¹

A 2009 variation concerns an update of the SmPC following the completion of a class safety review by the EMA's pharmacovigilance working party (PhVWP) and the CHMP. As a result, the CHMP requested to update section 4.4 of the SmPC to include more information on pure red cell aplasia (PRCA) in patients with hepatitis C treated with interferon, ribavirin and epoetin, and section 5.1 to include

additional data on the Cochrane meta-analysis and the effects of epoetins in cancer patients.

In 2010 there were updates to the Retacrit epoetin zeta label and the RMP_{PV} version 8.0 concerning allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery. The marketing authorising holder (MAH) submitted data from a Phase III study comparing efficacy and safety (including immunogenicity) of a subcutaneous test BMP with RMP in patients with renal anaemia, to support an extension of the current indication to the use of epoetin zeta as an alternative to blood transfusions in adult patients about to undergo major orthopaedic (bone) surgery where there is a potentially high risk from blood transfusion complication. The original approval was for IV administration, as at that time the subcutaneous route was contraindicated in the EU, so the addition of a subcutaneous route of administration in the indication of “anaemia associated with CRF on haemodialysis and patients on peritoneal dialysis” and “severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing analysis” was recent.

In the cases of G-CSF Zarzio and Filgrastim Hexal, the update of section 4.8 of the SmPC required the inclusion of the terms “Graft versus Host Disease (GvHD)” and “pseudogout” as undesirable effects, as well as an update of section 4.4 to include a statement on traceability. The inclusion of GvHD was requested by the CHMP following the assessment of the periodic safety update report (PSUR 3) and the additional changes were proposed by the MAH to bring the product information in line with the RMP. There were also amendments to reflect a core (class) SmPC change.

The Omnitrope marketing authorisation was renewed after five years based on the CHMP opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and it therefore considered that the benefit–risk profile of Omnitrope continues to be favourable. During the renewal procedure, changes were made to the Product Information to bring it in line with the RMP Genotropin.

Conclusions

As increasing medical experience is gained with biosimilars approved under the scientific and regulatory rigour of the European Commission and its regulatory instrument, the EMA, it is hoped that the medical community and the patient will rapidly appreciate that biosimilars can be safely used in medicinal drug treatment strategies. At present, the adoption of biosimilars is relatively slow due to various hurdles after European approval, including health technology assessment (HTA) body requirements, physician acceptance, patient acceptance and various lobbying interest groups. But this situation must change because of escalating drug costs, and because many new approvals of biologics including therapeutic proteins can fulfil unique medical needs.

Several important considerations have been put forward and appraised in this two-part paper. It is apparent that the EU regulatory framework offers reassurance of the equivalent safety and effectiveness of biosimilars, albeit very demanding in the data package forming the basis of approval. The FDA system gives the first signs of offering a scope which overlaps with EMA requirements, although there is the hope and desire that the FDA may relax some of the current study demands of the CHMP/EMA as part of an international programme, based on the FDA’s intended “stepwise” and risk-based “targeted” approach.¹² This might impact on future EU biosimilars development by triggering a reconsideration of CHMP/EMA guidelines, as we have seen happen for anticoagulant low molecular weight heparins (LMWHs), each a complex mixture of oligosaccharides (eg, enoxaparin, dalteparin, and tinzaparin).¹³ The FDA surprisingly approved enoxaparin sodium in 2010 under an abbreviated new drug application (ANDA), namely, a generic pathway.

The cooperation of the EMA and FDA in 2010/2011 has been exceptional and covers MAA/NDA/biologics license application reviews, clinical safety, scientific advice, joint good manufacturing practice (GMP)/good clinical practice (GCP) inspections and all facets of drug development and approval.¹⁴ It will be interesting to see how the new 2011 so-called “biosimilars cluster” consultation forum between the two major regulatory agencies will progress and impact international development of biosimilars to the continuing highest EU standards.

References

1. FDA. Draft Guidance for Industry on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (issued jointly by CDER and CBER, February 2012).
2. FDA. Draft Guidance for Industry, Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (issued jointly by CDER and CBER, February 2012).
3. FDA. 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).
4. FDA contact points on biosimilars: (a) the Biosimilars Program Staff at the Center for Drug Evaluation and Research (CDER)’s Office of New Drugs at 301-796-0700; or, (b) if the reference product for a proposed biosimilar product is regulated by the Center for Biologics Evaluation and Research (CBER), contact the Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 301827-1800 or by email to ocod@fda.hhs.gov. For general questions related to FDA’s implementation of the BPCI Act, contact Sandra Benton at the CDER’s Office of Medical Policy at 301-796-2500.

5. Private communications, presentations and surveys by companies marketing biosimilars and other stakeholders.
6. Hoss A Dowlat. 'The Importance and Impact of the EU RMP and US REMS to risk-benefit assessments', Regulatory Rapporteur, Vol 8, No 2, February 2011.
7. European Parliament and of the Council, Directive 2010/84/EU and Regulation 1235/2010/EU, Pharmacovigilance (Effective new requirements from 2012); and EudraLex – Volume 9, Pharmacovigilance Guidelines (updates expected 2012).
8. HWC Canada. Information and Submission Requirements for Subsequent, Entry Biologics (SEBs), Canadian Guidance (Draft) Health and Welfare Canada, 2009-03-27 draft; also, Q&A 2009-03-27.
9. EMA. Guideline on similar biological medicinal products containing monoclonal antibodies (Draft), EMA/CHMP/BMWP/40354/3/2010 (18 November 2010).
10. EMA. EPARS: Mabthera, Remicade, Enbrel.
11. EMA. EPARS: Postapproval. Retacrit Epoetin, G-CSF Zarzio, Filgrastim Hexal, Omnitrope.
12. S Kozlowski, J Woodcock, K Midthun and R B Sherman (FDA). 'Developing the Nation's Biosimilars Program', NEJM, 365;5, 385-8, 2011.
13. US approval of anticoagulant Lovenox and CHMP/EMA reaction: (a) FDA. Generic Enoxaparin, Questions and Answers, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm>; (b) EMA. Concept paper on the revision of the guideline on nonclinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins, EMA/CHMP/BMWP/522386/2011 (21 July 2011).
14. EMA/705027/2010 Directorate (June 2011), Interactions between the EMA and US FDA September 2009–September 2010; also check FDA Office of International Programs, Europe Office staff located at the FDA headquarters Maryland, US, at the EMA in London, UK and at the EFSA, located in Parma, Italy: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OfficeofInternationalPrograms/ucm243678.htm>