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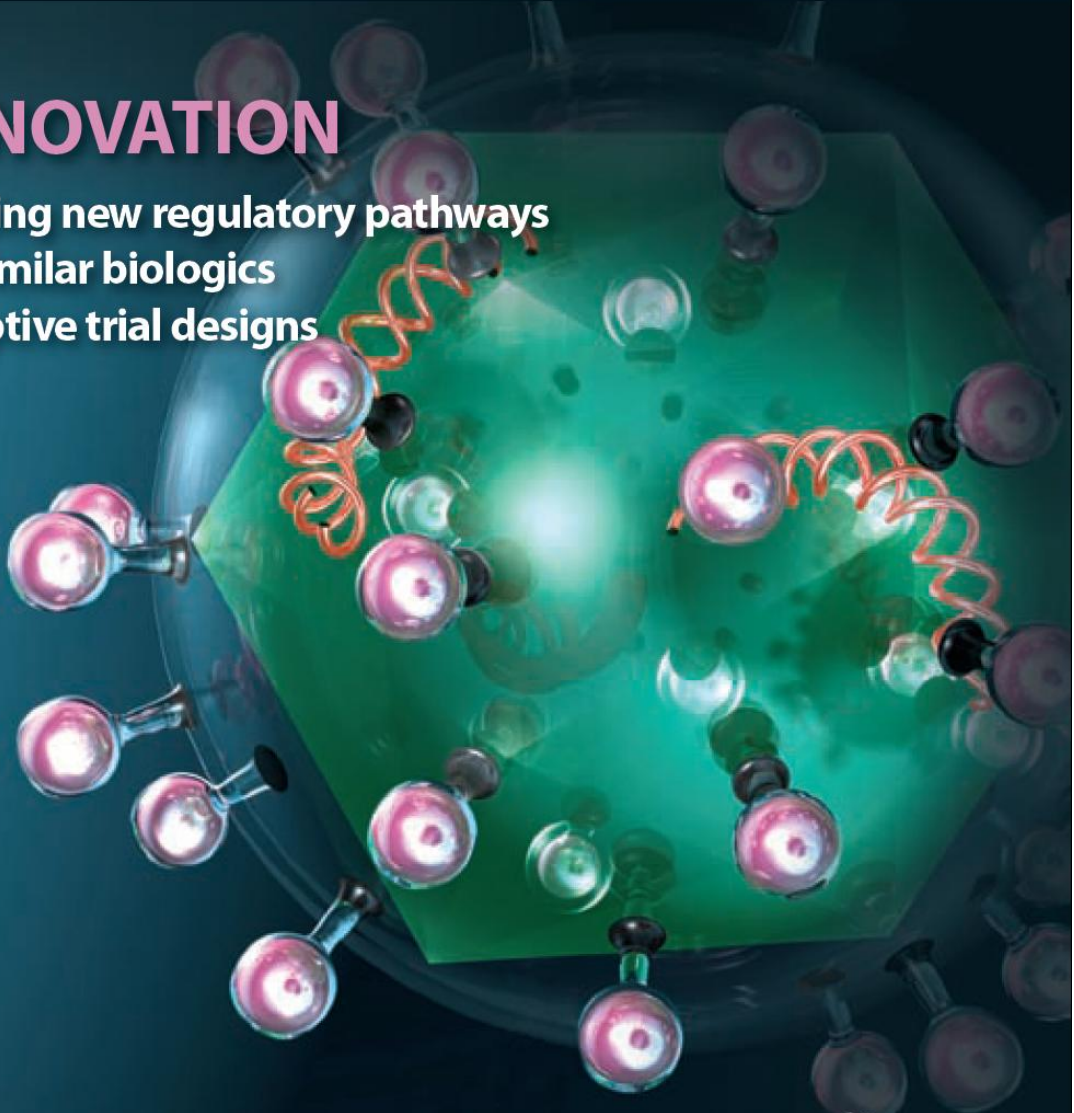
## INNOVATION

Forging new regulatory pathways  
Biosimilar biologics  
Adaptive trial designs

PLUS

Social media – pushing the envelope?  
Clearer guidance for EU clinical studies  
Interview: Christer Backman, CMD(h)

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# Inspiration, innovation and regulation



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The subject of this month's focus is innovation, which should be a concept familiar to most of us. Since the EU led the way by opening up the approval process for a follow-on biologic product, or biosimilar, 13 have been successfully brought to market. However, the US FDA has been slower on the uptake with these products, and although the final legislation to make this a possibility is in place, these follow-on products are not considered to be interchangeable with the originator product. Even so, even in the EU, it's not all plain sailing. Our focus article by Hoss Dowlat explains why even a simple development programme for a biosimilar is, while necessary, a significant financial burden for many companies.

This could make a biosimilar pipeline less attractive for many small companies, deterred by the significant costs of the clinical development needed to show similarity to the originator for these products, not to mention the post-approval RMP (risk management plan) requirements, compared to their standard (chemical) generic counterparts. That said, patient safety must – entirely reasonably – be at the forefront of our considerations.

Innovative approaches to the conduct of clinical trials are increasingly taking centre stage, as we hear from William Sietsema. Of course, this is a key design feature of a clinical study and the significant benefit of any adaptive trial must be carefully considered in the context of the integrity of the trial and the validity of the resulting data. To quote the EMA/EFPIA March 2010 workshop on this topic, the development time saved by adaptive designs may be at the expense of the period of "thinking time" that traditionally bridges the end of Phase II and start of Phase III development. Increasingly, based on the EMA's 2007-2008 survey, adaptive designs appear to be the focus of EU Scientific Advice requests and, similarly, all 15 of the FDA's reviewing divisions have received adaptive design proposals! This is clearly a concept that we as RA professionals need to come to terms with quickly!

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Regardless of design, clinical trial approval must always be sought, and in the EU the detailed guidance on requests to competent authorities for approval of initial clinical trial applications and subsequent amendments has undergone re-working of late, and now provides clearer and more harmonised guidance for applicants. Odette Dunkley provides us with a neat summary of the key changes in this new version of the guidance. Clearly, while the additional transparency and harmony brought by this update is very much welcomed by those of us who have struggled with multinational trial approvals, more extensive changes – for instance, a centralised approval process for all EU member states, along the lines of that desired by many sponsors – would only be possible by re-opening the Clinical Trial Directive itself. This would be a complex and lengthy activity, making the desire of the European Commission to work within the confines of the current legislation understandable.

Last, but by no means least, has there been a greater technological advance relative to our field since the introduction of eCTD? As we hear from Alan Minsk, the growing availability and widespread use of social media has very much slipped under the regulatory radar to some extent thus far. It seems as though the US FDA has acknowledged the issues that present themselves owing to the likes of YouTube and other such sites as we steadily appreciate the impact of free communication on medicinal products and devices in open fora on our responsibilities as developers of those therapies. It would come as no great surprise if this is an area of focused attention for regulators over the coming years; regions outside the US, where direct-to-consumer advertising is not always allowed, are not immune to global communications via the web and therefore efforts at a global level – matching the global availability of information on the internet – may be needed to ensure patients, wherever they may be, have access to information of a similar nature and standard. Any changes could be a natural extension of global risk management practices, the current approach to which is nicely summarised by Angela Miller in her meeting report in this issue.

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# The current status of biosimilar biologics – Part 2: Practical considerations in international development through European lessons learned

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Biosimilars; Reference Medicinal Product (RMP); Biocomparability;  
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Management Plan; Safety data; Immunogenicity.

## Abstract

*Biotech products coming off patent afford a window of opportunity to obtain a marketing approval for a “follow-on” by a new product developer. If the supporting data are sufficient to authorise interchangeability or substitution then the new product is defined as a similar biologic or “biosimilar”. Europe is leading the way in defining the regulatory pathway for biosimilars. This article – the second in our two-part series on the biosimilars landscape – shares lessons learned from successful European development and approvals that can provide strategic insights to guide future biosimilar development plans.*

## Challenges in the development of biosimilars

The European approval of biosimilar products require a substantial and robust pharmaceutical development package of information, possibly larger than the Reference Medicinal Product (RMP), primarily due to the requirement for an extensive battery of biocomparability tests.

A clinical equivalence study is also normally required, but can be waived where a pharmacodynamic (PD) surrogate measure correlated with clinical effect can be justified through CHMP/EMA Scientific Advice. A precedent was set by Zarzio (filgrastim, granulocyte colony stimulating factor G-CSF), which relied on four comparative pharmacokinetic (PK)/PD studies in 146 healthy volunteers as a basis of approval, but post-approval follow-up commitments – to conduct three Phase IV clinical safety studies in patients – had to be fulfilled.<sup>1a</sup> No clinical efficacy study in patients was conducted prior to approval of Zarzio, unlike the biosimilar competitor Tevergastim,<sup>1b</sup> and there was no patient exposure in PK/PD studies. Sponsors should be aware that such a lack of clinical data may be unacceptable to physician opinion leaders constraining marketing. The perceived risk by some users is considered greatest for the use of G-CSF in healthy volunteers for bone marrow transplantation. Furthermore, the Zarzio development predated the G-CSF 2006 guidance and any pivotal PK/PD design should be confirmed by CHMP/EMA scientific advice.

For Valtropin, (somatropin, recombinant human growth hormone (rhGH)), the pivotal study monitoring paediatric growth was a noninferiority,<sup>2</sup> randomised, 12-month double-blinded phase, followed by a 12-month unblinded (open) extension phase of 149 prepubertal children 6-10 years old, in which the children were either switched from Humatrope to Valtropin or continued on Valtropin. The study also demonstrated equivalence<sup>2</sup> of the adjusted mean ratio of the primary height velocity with a 95% confidence interval. For Omnitrope, the key study was a nine-month, open label, parallel design study in 89 prepubertal children aged 5-13 years old, followed by an extension phase with a switch from comparator to Omnitrope.<sup>3</sup> In both cases the adult indication was approved as well, by extrapolation from the paediatric study.

In spite of guidances for somatropin, erythropoietin, G-CSF, interferon, insulin and other biosimilars, most applicants still seek official CHMP/EMA Scientific Advice for their biosimilar products to ensure they have properly interpreted the guidelines or, where they consider deviation from the guidelines, the deviation can be justified to allow an innovative or a more efficient programme.

The first biosimilar consultations with CHMP/EMA occurred in 2000, when very little was known about the data requirements for this new class of “generic” medicines and no regulations were in place. The first guidances were issued in 2004–05, arising out of EU Directive 2003/63/EC amending Directive 2001/83/EC. Later, the far reaching Directive 2004/27/EC, a new amendment of 2001/83/EC, provided the current European legal framework. In 2006, those guidances were expanded based on the data and experience of the first somatropin biosimilar approvals and Scientific Advice processes.<sup>4</sup> The next biosimilars in the EU – erythropoietin and G-CSF – were approved in 2007–2008 based on published guidances and Scientific Advice. There have been 13 EU approvals up to July 2010.

## Reference medicinal product comparator

The requirement to repeat studies against Reference Medicinal Product (RMP) comparators that are sourced from different regions (even if the RMP is manufactured by the same company with the same pharmaceutical form, strength, presentation and route of administration) significantly increases the time and cost of biosimilar development. This requirement applies in Europe as of 2009 – with no suggestion of change – as well as in Japan (where an RMP is called a “precedent biotechnology drug”).

## Europe

Regional regulatory authorities continue to insist that the RMP be sourced within that region, eg, an EU biosimilar filing must use a comparator manufactured in the EU or the European Economic

Community (Norway or Iceland, and not Switzerland). An agreement among regional authorities worldwide on a common RMP, irrespective of where the biologic product is sourced, would save time, resources and expense, and allow biosimilar products to be approved more quickly, without duplication of effort and data.

The regulatory challenge is how to prove that one biologic is the same as another with the identical drug substance from region to region, even if the biosimilar is assumed to have identical pharmaceutical form, composition, manufacturing formulation and presentation, and even to prove that the RMP is manufactured by the same company. The expectation is that the RMP's manufacturing process and production facility in different regions would have to be identical, and only the MAH has that confidential information. There are also potential differences in impurities, potency, packaging and other factors that can affect safety and efficacy.

Where comparative data against an RMP sourced from outside the region are generated, they can only be considered supportive, rather than pivotal, in the EU. In one recent case, an applicant completed a two-year clinical study of its biosimilar product for the EU, during which time the specific pharmaceutical presentation of the RMP used in the study was discontinued in the EU. The sponsor had to purchase the RMP from the US to ensure the same packaging and maintain the study's blinding. Despite the fact that there was explicit FDA documentation proving that the US RMP was identical to the EU RMP previously used by the trial sponsor, the data for the US product were not considered pivotal by CHMP/EMA<sup>5</sup> and the clinical data had to be reanalysed to exclude the results from the US-sourced RMP.

In view of the major expense and short shelf-life of biologics, stockpiling the RMP for a long study is not practical. This example demonstrates just one of the difficulties faced by biosimilar trial sponsors trying to meet the requirements of regional RMP sourcing.

### Canada

Health Canada will not make it mandatory that reference biologic drugs have to be approved and marketed in Canada. There are alternative means of obtaining credible and valid information about a reference product for a Subsequent Entry Biologic (SEB) submission according to Health Canada. Criteria for a reference drug include a drug that has been widely used and as a result has significant information on its safety profile and quality attributes for the SEB, is approved in a jurisdiction that has similar processes and procedures for drug approval as Health Canada, and can be tied to a product authorised for sale in Canada. Any safety risk concerns that may be associated with use of non-Canadian reference products are minimised because SEBs will be approved based on their own clinical trial data.

Surprisingly, South Africa is less conciliatory and requires a nationally approved reference product.<sup>6</sup>

### World Health Organisation

WHO recommends that the acceptability and suitability of using a reference biotherapeutic product (RBP) licensed or resourced in other countries will depend on:

- Whether the RBP was marketed for a significant duration and has a volume of use such that its licence is supported by a substantial body of data regarding safety and efficacy

## Only through a risk management plan involving pharmacovigilance measures – often utilising a registry – can there be adequate control of unexpected outcomes, particularly for narrow therapeutic range biologics

- If the other jurisdiction has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products, and post-marketing surveillance activities.

Therefore, a European RBP would qualify. However, the acceptance of an RBP for evaluation of a similar biotherapeutic product (SBP) in a country does not imply approval for use of the RBP by the national regulatory body (NRB) of that country.

### Manufacturing considerations

It is critical to ensure that manufacturing changes to the product at the drug substance (DS) or drug product (DP) stage do not impact comparability with respect to potency, safety or efficacy by verifying these against the RMP, which has a proven record of patient use.

The increased sophistication of state-of-the-art chemical and biological testing methodologies, combined with the power of spectroscopic techniques, has permitted an accurate assessment of comparability following manufacturing changes to the drug substance, such as the raw materials for fermentation, the master cell bank or the drug product. These advances have reduced the burden of additional testing, generally requiring limited or no clinical or nonclinical bridging studies on making the change, for example. The knowledge gained by investigating changes of DS or DP in approved biologics has formed the basis of the regulatory authorities' current guidance regarding biosimilar comparisons with RMPs. A thorough and extensive investigation of comparability continues to be an absolute requirement.

Numerous biochemical, biophysical and immunochemical tests are required to ensure the identical primary structure and to compare the secondary and tertiary structure/conformation of the biosimilar against the RMP. Relevant tests must be repeated if any changes are implemented. Every study should be performed with comparisons to internal and international (eg, National Institute for Biological Standards and Control, European Pharmacopoeia or United States Pharmacopoeia) reference standards, if available, and the RMP.

If the molecule can be compared using stress conditions – such as temperature, oxido-reductive, osmotic and pH stresses – using current sophisticated analytical methodologies, the resulting data can be very useful because they represent excursions from normal storage conditions. At a minimum, however, fresh and aged batches of drug product should be compared. Changes in manufacturing processes would trigger the need for such comparability studies; the extent would depend on a risk-based assessment of changes including those in materials, scale-up, work-up, purification, controls in process and at release/stability, impurities and packaging.

### Clinical safety considerations

Biosimilar approvals also require an adequate safety database, which can vary widely depending on the biologic's indication and nature. The available population for the safety data that form the basis of approval is usually limited, so the database must be supplemented by postmarketing data. Establishing therapeutic equivalence through bioavailability and clinical criteria alone is not adequate to ascertain safety. A clinical therapeutic setting, which allows more extensive exposure, is necessary to capture potential safety signals such as those associated with immunogenicity issues.

Only through a risk management plan (section 1.8.2 of the EU Common Technical Document, CTD) involving pharmacovigilance measures – often utilising a registry – can there be adequate control of unexpected outcomes, particularly for narrow therapeutic range biologics. The risk management plan must be designed carefully and presented to the CHMP for its acceptance to properly mitigate risk. Scientific Advice can also be sought for the plan.

In Europe, some biologics coming off patent were previously approved by National or Deconcentration or Mutual Recognition Procedures, rather than the Centralised Procedure. As a result, EU regulatory expertise on biological products, such as experience with pharmacovigilance, is spread across assessors of multiple authorities. In the US, many approved protein products such as therapeutic proteins and monoclonal antibodies have been reviewed and approved by the FDA's Center for Biologics Evaluation and Research (CBER), under the Public Health Service (PHS) Act, giving CBER a significant depth of knowledge about biologics safety. Whereas, interestingly, hormones (r-insulin, rhGH, menotropin), enzymes (hyaluronidase) and peptides were approved under the Federal Food, Drug, and Cosmetic Act (FFDC Act), (as for small molecules) by FDA's Center for Drug Evaluation and Research (CDER). Furthermore, since 2003, responsibility of the review and approval of therapeutic proteins and antibodies has been transferred to CDER. While sponsors can benefit from CDER's and CBER's exceptional insights into biologic therapies, this expertise has not yet been leveraged by FDA to approve biosimilars.

It remains to be seen how future biosimilars approved in the US would be "substitutable/interchangeable" for the innovator biologic, just as generic drugs are "AB" rated in the "Orange Book", a US drug registry. This is not yet the case in the US, even though several biologics – including recombinant and natural hyaluronidases, recombinant salmon calcitonin, glucagon and somatropin (rhGH, Omnitrope) – have been approved under an abbreviated new drug application (ANDA) 505(b)(2) pathway since 2006, but are not therapeutic equivalents.

In Canada, qualifying as a SEB is not a declaration of pharmaceutical and/or therapeutic equivalence to the reference biologic drug.

In South Africa a stronger position is taken, as it is explicitly stated that "they [biosimilars] cannot be considered interchangeable with the reference product or products of the same class."<sup>6</sup> Equally, automatic substitution (ie, the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) cannot apply to biosimilars.

"Such an approach ensures that treating physicians can make informed decisions to ensure that treatment is in the interest of patients' safety."<sup>6</sup>

### Immunogenicity as part of clinical safety

Under current regulations in Europe, interchangeability or substitution is not regulated by the EMA after a successful Centralised Procedure in the EU, but the ultimate decision is still controlled by each country's national healthcare system.<sup>7</sup>

One of the concerns about switching from an existing therapy to a biosimilar is the issue of immunogenicity, which – for some human versions of proteins, such as epoetin – has been associated with inducing autoimmune neutralisation of endogenous epoetin. Any change in a biologic product, whether an innovator product or a biosimilar, has the potential to impact immunogenicity, which must be rigorously tested and constantly monitored. Clinical consequences are:

- Development of neutralising antibodies (binding) against the product with impact on pharmacokinetics, requiring dose adjustment to keep plasma levels stable
- Reduced efficacy, or reduced duration of response (due to neutralising antibody)
- Increased adverse drug reactions by infusion or subcutaneous administration, hyperimmune reactions or delayed hypersensitivity (due to precipitating or cross-reacting antibody).

Immunogenicity-derived toxicity is route-dependent. Hypersensitivity reactions are a particular risk for the subcutaneous route of administration. One example of this phenomenon is epoetin alfa, which was contraindicated from December 2002 to May 2006 for subcutaneous (but not intravenous) administration in the EU for patients with chronic renal failure, due to the increased frequency of anti-erythropoietin, antibody-induced, pure red cell aplasia.<sup>8</sup>

EMA, CHMP and the Biosimilar Medicinal Products Working Party have produced two current guidance documents on immunogenicity: one on proteins and one on monoclonal antibodies.<sup>9</sup>

CDER reviewing divisions currently raise the question of immunogenicity prior to an NDA submission as a matter of policy as a submission screening issue, and involve CBER-trained chemistry reviewers, now within the Office of Biotechnology Products of CDER, with particular attention to determination of assay cut-off points and related assay method development.<sup>10a, 10b</sup>

The most significant challenge is to identify the potential safety signals arising from each biologic's immunogenicity when subject to specific manufacturing, packaging and formulation variables. This can only be accomplished with post-approval marketing pharmacovigilance experience in a wider population. Predicting immunogenicity effects using a database that is limited at the time of approval requires collective agency experience, as well as good scientific and empirical reasoning.

The WHO recommends that the manufacturer will need to justify its antibody testing strategy including the sensitivity, selection, assessment, and characterisation of assays, identification of appropriate sampling time points including baseline, sample volumes and sample processing/storage as well as selection of statistical methods for analysis of data.

### Conclusion

As with generic small molecules, there is the opportunity to have several MAHs/sponsors/applicants for the same biologic drug substance – each with a profitable market share – because of

the strong contribution biologics make to human health. Such competition offers the possibility of affordability in a category of medicine that is presently out of the reach of some patients. Biologics coming off patent in the near future include recombinant interferons, interleukins and monoclonal antibodies – each with its own unique challenges to developing new biosimilars. In Europe, determining a biosimilars pathway for development of several monoclonal antibodies coming off patent is, in particular, the subject of frequent Scientific Advice consultation by applicants with the CHMP/EMA. However, any company venturing into this field must carefully plan its development strategy. Experience with the approval and medical use of biosimilars is limited worldwide, and there are inherently high regulatory and legal hurdles, and also barriers for gaining acceptance by healthcare bodies (the “fourth hurdle”), professionals and patients.

Europe has established precedents for biosimilar approvals, and has the broadest regulatory experience, although still limited market penetration nationally. Other major ICH regions, such as the US, are taking significant measures before their regulatory frameworks facilitate approval of true biosimilars, while Japan, Canada, Australia and many others have made advances in 2009 and 2010.

It is clear that biosimilars are an exciting new frontier reminiscent of the early days of “generic” small molecule medicines. However, each biosimilar presents its own unique scientific and regulatory challenges that must be addressed and overcome if it is to fulfil its potential to increase the availability and reduce the cost of biological therapies for patients around the world.

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