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Perception And Realities of Clinical Safety of BioSimilars :

EU & US Perspectives: Part 1

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This article is Part 1 of a two-part paper appraising the clinical safety of known EU-approved biosimilar therapeutic protein medicines pre-approval and post-approval, and compares and contrasts with the long awaited overarching FDA biosimilars guidances, finally issued in February 2012. The paper aims to provide assurance of the safety of as yet unapproved potential biosimilars including the recombinant monoclonal antibodies (mAbs), insulins, heparins, and interferons. Biosimilar medicinal development, perception of general risk, interchangeability, substitution and other implications during acute or chronic use, first/second line, or adjunct therapy, are addressed here. Part 2 will be published in next month's issue.

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

Biological medicines constitute a major share of pharmaceutical expenditure in the EU, the US and globally. It is one of the fastest growing sectors of the industry, corresponding to more than 15% of the total pharmaceutical market and more than US €100 billion in sales.[1]

Biosimilars are of course a new paradigm in drug development, and are currently in a similar position to the early days of the acceptability of generic medicines. The stakeholders of biosimilars are not only the patient but also the pharmaceutical industry, the regulator, and the physician. Besides the regulatory burden, peer acceptance by medical leaders is an aspect that continues to be discussed in individual cases.[2] This view appears to be ratified by slow penetration of EU national markets, surveys in the EU and US, articles and lectures by opinion leaders, and a lack of interest in the deeper understanding of biosimilars by some medical journals and associations.[2] Small molecule generics, such as narrow therapeutic range medicines, can still experience a barrier to acceptance due to risk of subpotency or adverse drug reactions (ADRs) on overdosing, although generic pharmacy level substitution is widely adopted with a decision made nationally or regionally, and not by the EU Commission, as with biosimilars.

The fact that biosimilars are biological substances mostly endogenous to the human body, or analogues of the same, is perceived positively by the patient (as they are considered to be "natural") and yet cautiously by the regulator and the prescriber; the regulator is driven by concern for unexpected risk (eg, ADRs that may be immunogenicityconnected), and the prescriber by the best therapeutic outcome of an expensive treatment (physicians tend place more importance on effecting a cure than on ADRs, if the ADR can be managed); patients rate side-effects (the corresponding lay term for ADRs) as their main concern before electing to taking any medicine.[2]

In this article, first the concerns of the prescriber are expressed in context, and then the current scientific and regulatory issues are analysed with a view to showing the awareness of the EU and US regulators of all the factors which need to be addressed in a robust and thorough drug development programme to guarantee the safety and effectiveness of a biosimilar product within a highly scrutinised framework. In fact, experience in biosimilars has generated databases of valuable new comparative information related to the originator's medicines, providing regulators and developers with deeper insights into biologics.

The EU

The EU Commission, the EMA and the Committee for Medicinal Products for Human Use (CHMP) have established a legal and regulatory framework of directives, regulations and guidelines providing guidance to industry that has permitted 13 European approvals (see Table 1) involving only seven sponsored development programmes (interestingly, all German, except for one Austrian) for these new medicines.[3] The regulatory burden is substantial, both logistically and economically, but the reward is a portion of more than US$100 billion in sales, above US$25 billion in each of oncology or immunology and inflammation, and more than US$15 billion in diabetes.[1] Unlike unbranded generics, there is also the challenge of market penetration of EU countries, where originator companies monopolise the market and further protect their interests through a new generation of analogous molecules.

Following the patient and the regulator, the perceptions of the third stakeholder, the physician, is variable and depends on region (US, east-EU or west-EU); disease, for example, metastatic cancer *vs* early stage, oncology *vs* immunomodulatory diseases, monotherapy *vs* combination adjunct therapy, localised *vs* systemic. The fourth stakeholder is the payer or health technology assessment (HTA) body, which is an added complexity that involves many national, regional or hospital controls and approvals to permit the listing of biosimilars, and to take decisions on pricing at the retail and hospital levels across Europe. The approval process at the HTA level can take many months to more than a year.[2]

The US

It remains to be seen how major regions other than the EU, such as the US, accept biosimilars. The first concrete signs from the FDA are that, for some drugs, alternatives to huge EU biosimilar development pathways are possible, such as that exemplified by enoxaparin sodium,[4] a low molecular weight heparin (LMWH) classified as a biosimilar in the EU.[6] The FDA approved enoxaparin through an abbreviated new drug application (ANDA) pathway, remarkably, with an AB interchangeable rating (the US term for substitution) with a minimum of pharmacokinetic (PK) requirements to extrapolate to efficacy and safety, whereas 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 2011 concept paper.[6]

The 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 FDA considered to be a highly complex but well-characterised polysaccharide. The extensive EU guideline on LMWHs was considered by the FDA but not applied. Immunogenicity was also resolved based on the decision on "sameness", established by the Quality data. This precedent, even though enoxaparin was not a protein, was described by senior FDA staffers in a New England Journal of Medicine (NEJM) paper in August 2011, in what may be viewed as a policy paper.12 This overall concept of fingerprinting, using the FDA's five criteria and its prior experiences, would be further uniquely adopted by the FDA in its pragmatic approach to approval of biosimilars, based on a rich FDA 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.[12] The same paper provides examples where the EU experience was evaluated by the

FDA; for instance, senior FDA staffers said of the mAb CHMP/EMA guidance: "The guideline thus suggests an increasing alignment with the totality-ofthe-evidence approach favoured by the FDA."

In confirmation, the FDA itself restates, in the current 2012 Scientific Considerations biosimilars guidance, that it will consider "the totalityof-the-evidence" in its evaluation.[13] This has been, in fact, the European practice for the past five years during biosimilars assessments by the CHMP/EMA, with only four failed biosimilars submissions between 2006 and 2011:

- Alpheon (interferon alfa), BioPartners GmbH – negative opinion CHMP, June 2006
- Insulins (3 products, Short, Intermediate, Long), Marvel Life Sciences –withdrawn 16 January 2008
- Epostim (epoetin alfa), Reliance Genemedix – withdrawn March 2011
- Biferonex (interferon beta-1a) (developed as a biosimilar before the guidelines, submitted as a new biologic), BioPartners GmbH – negative opinion CHMP, February 2009 – withdrawn May 2009.

Also, the FDA would 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".[13] Neither efficacy nor benefit is emphasised by the FDA, as both are already implicit in the continued licence of the originator medicine.[13,14,15] These aspects are similarly brought to our attention by the CHMP/EMA guideline on biosimilar mAb development10 which is in effect a retrospective and reflective position document, actually illustrating the EU concept of biosimilars development well, not only for mAbs. The EU mAb guideline describes a mAb development scenario in an oncology setting but its principles can be applied more widely to immunomodulatory mAbs and other molecules. The FDA has drawn parallels to it in the 2011 NEJM paper[12] (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: "Scientific Considerations", "Quality Considerations" and "Questions and Answers" (regulatory aspects)[13,14,15] which, although offering certain new features compared with the EU required programme of biosimilar drug development (described below), present a similar wide scope of drug development requirements to the EU CHMP/EMA. Apart from many references to the possibility of a "targeted"[13] and "abbreviated"[13,14,15] drug development programme, it is not obvious from the FDA guidance's that such drug development would be curtailed, although this would be anticipated from the FDA's progressive enoxaparin sodium landmark decision, a new paradigm. It was therefore surprising, when reviewing the guidance's, 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 the FDA, the actual US development agreed on may well be curtailed compared with EU requirements, based on FDA consultation at the individual therapeutic review division level. The FDA divisions can be viewed almost in the same way as competent authorities are in Europe, each with its own history, philosophy, review and approval practice, and so decisions would be on a case-by-case by product and division, but these guidances[13,14,15] would provide an overarching perspective as for the European biosimilars framework defined by overarching CHMP/EMA guidelines.[16-21] Of course it is assumed that, on a therapeutic divisional consultation, various other FDA offices would be involved, especially at the advice meetings, review and approval stages, and that the New Acting Associate Director for Biosimilars in Office of New Drugs, Dr Leah Christl, and other future FDA oversight mechanisms would assist with the coordination and consistency of FDA guidance across the therapeutic divisions.

Under the newly-planned biosimilars user fee programme, the FDA would be authorised to spend user fees on its biosimilars activities related to the review of submissions.[22] This would include activities related to biosimilar biological product development meetings and investigational new drug (IND) applications. It would also include development of the scientific, regulatory, and policy infrastructure necessary for review of biosimilar biological product applications, such as regulation and policy development related to the review of biosimilar biological product applications, and the development of standards for products subject to review and evaluation. The FDA plans to offer a series of at least five separate meetings within around a one-year period with a biosimilar applicant, relating to review of an application, guidance for additional clinical and analytical tests, and reviewing the results of those tests.

The timeliness of this initiative fits with current demands, as the FDA has apparently received (as of December 2011) 31 pre-IND meeting requests for biosimilars which reference 11 products, and has held around 21 pre-IND meetings with sponsors.2 Also, around seven IND applications for biosimilar development programmes have been opened.[2]

Current Positive Trends

Proposed major considerations in a safety evaluation by any stakeholder intending to use a biosimilar are described below, based on five years of approved EU biosimilars,3 and experience of EU development and CHMP consultation; this will be compared with the relevant aspects of the new FDA biosimilars guidances. The analysis begins with a clarification of the ultimate goal of achieving interchangeability.

Interchangeability providing assurance of efficacy without compromising safety: The issue of interchangeability concerns the risk to the patient of new ADRs on switching a treatment to the biosimilar equivalent. Additionally, the possible risk of compromising treatment potency is an interchangeability issue. In a worst-case scenario the switch can elicit an immunogenicity response such as a hypersensitivity reaction. All the evidence pre- and post-approval findings

Table 1: EU biosimilar marketing authorisation approvals				
International nonproprietary name (INN) of substance	**Marketing authorisation holder (MAH)**	**Date of EC approval**	**Brand name**	**Reference product**
Somatropin *(Both developed as biosimilars before guidelines)*	Sandoz GmbH	12 April 2006	Omnitrope	Genotropin
	BioPartners GmbH Drug substance sourced from Korean LG Life Sciences	24 April 2006	Valtropin	Humatrope
Epoetin alfa	Sandoz GmbH	28 August 2007	Binocrit	Erypo/Eprex
	Hexal GmbH	28 August 2007	Epoetin alfa HEXAL	Erypo/Eprex
	Medice Arzneimittel Pütter GmbH & Co KG	28 August 2007	Abseamed	Erypo/Eprex
Epoetin zeta	STADA Arzneimittel GmbH	18 December 2007	Silapo	Erypo/Eprex
	Hospira UK Ltd	18 December 2007	Retacrit	Erypo/Eprex
Filgrastim	Ratiopharm GmbH	15 September 2008	Ratiograstim	Neupogen
	Teva Generics GmbH	15 September 2008	TevaGrastim	Neupogen
	CT Arzneimittel GmbH	15 September 2008	Biograstim	Neupogen
	Sandoz GmbH	6 February 2009	Zarzio	Neupogen
	Hexal GmbH	6 February 2009	Filgrastim HEXAL	Neupogen
	Hospira UK Ltd	8 June 2010	Nivestim	Neupogen

with approved biosimilar drugs (or those known by the author to be being developed) suggest there are no new untoward effects and efficacy is not compromised in any way.

There are different understandings of what interchangeability means. Interchangeability decision cannot be ruled by the CHMP/EMA or EU Commission, only at national level in the EU: From an EU perspective, there is no guidance from the EU Commission, but the 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."[23]

Interchangeability can be decided by the FDA, but prerequisites are postponed: From a US perspective, it appears that interchangeability in practical terms means 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 pharmacy level.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) (Biosimilars Act §7002(b)(3), amending 42 USC §262(i)), defines the term "'interchangeable' or 'interchangeability', in reference to a biological product that is shown [to be a 'biosimilar']," 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."[13,15]

Some future FDA approved "biosimilars" are foreseen as not being interchangeable with the FDA-licensed biological RMP but, surprisingly, the conditions are not laid down for industry in the current guidances!

Approval of interchangeability is, after all, the desirable goal of biosimilars. In February 2012, the FDA's position was expressed in the Q&A guidance in the context of the 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)15 And, "...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).[15]

That is, the current guidances cover general common requirements for both non-interchangeable and interchangeable tiers of biosimilars, but unfortunately without giving any specifics of what would be needed to ridge to obtain approval for industry's real objective of the authorised interchangeable biosimilar!

Interchangeability by other stakeholders: The European Generics Association (EGA), with more than four of its 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."[24]

The World Health Organisation (WHO) defines interchangeability as referring to "the medical practice of switching one medicine for another that is equivalent, in a given clinical setting."[15]

Furthermore, the WHO states: "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."[25]

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 serious unexpected 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. The FDA's clear statements below are elucidating.

Interchangeability and further scientific and regulatory facts: The FDA expresses its viewpoint in its Scientific Considerations guidance that *"slight differences in rates of occurrence of adverse events between the two products ordinarily would not be considered clinically meaningful differences."*[13, Line 296] Furthermore, that *"lower immunogenic or other adverse events would not have implications for the effectiveness of a protein product."*[13, Line 687]

Additionally, in a post-marketing scenario the 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."[13, Line 811]

As the biosimilar usually has the same composition with identical excipients to the originator, and in practically all cases the presentations are solution forms, the introduction of risk with the DP is minimal. With the Valtropin EU approval in 2006,[26a] *the CHMP/EMA also took the milestone decision to approve a yeast-based somatropin*[8] *cell expression system, compared to an E. coli-based reference medicinal product (RMP) of Humatrope.*[26b] *Valtropin was produced in Saccharomyces cerevisiae (yeast) cells. The previously marketed somatropins were expressed in either E. coli (eg, Humatrope, Genotropin, Nutropin) or in mammalian cells (Saizen), making the Valtropin yeast-cell process unique among growth hormones. Omnitrope's somatropin drug substance (also approved in April 2006) was produced in an E. coli (bacterial) host.*[26a,26b]

This precedent of a new fermentation expression system was endorsed by the CHMP/EMA four years later in the mAbs guideline.[10] *The FDA provides a similar flexibility when, apart from covering many aspects of new manufacturing implications, in its Quality Considerations biosimilar guidance it says: "Therapeutic protein products can be produced by microbial cells (prokaryotic, eukaryotic), cell lines of human or animal origin (eg, 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."*[14, Line 366]

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 on 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 fermentation upstream and downstream processes and derived impurities are completely aligned.

Some biosimilars sponsors additionally have significant experience with manufacturing the DS and DP, and medical use, in other regions of the world. Yet the FDA in its Quality biosimilar guidance considers that the risks associated with a new manufacturer, the biosimilar sponsor, are greater than those of the originator.[14]

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, changes in pharmaceutical forms, presentations, devices, ownership, manufacturing site and equipment, testing methods and specifications, etc, 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 be under CHMP/EMA scrutiny.[19]

Interestingly, the FDA also 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, according to its Q&A (regulatory) guidance.[15] *For instance, albumin may be omitted as excipient,*[15, Line A. I.3] *or the FDA 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 for solution for injection RMP.*[15, Line A. I.4]

When the medicinal product is titrated according to treatment response (eg, epoetin, insulin) rather than given at a fixed dosage (eg, somatropin in GH-deficient children, mAbs) in the EU, equivalence should be demonstrated not only with regard to treatment response but also with regard to dosage. This is best achieved by defining a combined primary endpoint that also includes the dosage.

Interchangeability illustrated by human growth hormones: *Although* their development programmes were very different, both Valtropin and Omnitrope's involved switching of the RMP arm to the test biosimilar medicinal product (BMP) arm during the open extensions phase of the clinical Phase III studies. Some other EU biosimilars also furnished data of the RMP arm switched to the test BMP data, for instance Abseamed (epoetin alfa) where the switch took place during weeks 29-56.[26c]

Thus when in April 2006 the EU Commission authorised (approved) for marketing the first two biosimilars, Omnitrope and Valtropin, this meant that both

are biosimilar to Genotropin, Humatrope, NutropinAq, Norditropin, Saizen and Zomacton. This means that the data support "interchangeability" among these. This is different to the ANDA concept of "sameness" by which the FDA approved enoxaparin sodium, which can only interchange for Lovenox and not other LMWHs. This also illustrates the concept of "biosimilarity".

The approvals were based on comprehensive comparisons against two different RMPs: Genotropin for Omnitrope, and Humatrope for Valtropin. Comparative clinical efficacy, bioavailability and safety data, notably the most sensitive patient population of prepubertal 5-13 year old children, based on long-term multicentre 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 summaries of product characteristics (SmPCs).

Growth rate measured by height velocity, and 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 of the 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.13, Lines 577, 723, 758, 787 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 that 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 situation where there was more than one possible RMP, which is not the case with biosimilar mAbs candidates, but is found for other future biosimilar candidates such as insulins,[7] interferons,[5] etc.

Interchangeability illustrated by human insulins: The most complex case of unapproved biosimilars has been the human insulins, which is not well recognised as being an intricate challenge among regulators or industry. There are actually three products, and not one, used together in medical practice, namely a "soluble" short-acting, "isophane" long-acting (these being used as a free combination), and "biphasic", a mixture of the short and long products. Patients can be switched from free to fixed combination during clinical use or maintained on one or other option; also, the soluble may be added to the biphasic inpatient hyperglycaemia peaks. The isophane and biphasic are also unique among biosimilars or future candidates as they are both suspensions and not solutions, therefore complicating the biosimilar development of insulins further.

For the physician or HTA body, the normal clinical-use scenario of insulin is most important as all three products are then in use, which would entail a Phase III study evaluating efficacy and safety against the RMP, which would alternatively be rh-insulin soluble, (and suspensions of) isophane and biphasic pharmaceutical forms sourced from alternative manufacturers Eli Lilly, Novo Nordisk and sanofi aventis. However, for the EU regulator a product bioequivalence study per *individual* product is pivotal to approvals instead, such as Phase I PK studies or PD glucose "clamp" studies, which assumes that insulininduced glucose suppression is a surrogate marker of diabetes mellitus.

Biosimilars developers should not underestimate the need to ensure the design of the development programme has the acceptance of the HTA body and physician; sale and profitability are not guaranteed on approval of a biosimilar. An effective market penetration strategy is required. Adequate clinical, not just PK or PD, data are desirable. For instance, prescribers would have more confidence in biosimilars if clinical Phase III data are available; this is particularly the case for use of a biosimilar in chronic treatment. In addition, although surrogate endpoints can be objective and reached more quickly, physicians also want confirmation of biosimilar effectiveness through evidence of clinical endpoints.

There may also be competition from delivery device/product combinations. In addition, price erosion through HTA bodies' demands and tenders will influence profitability. Robust marketing efforts are required to counter the aggressive detailing of prescribers by originators.

Choice of reference medicinal product

The importance of choosing an acceptable RMP cannot be underestimated, and is clarified in the following.

Impact of the RMP: The safety profile of the RMP is defined by the SmPC (EU) or the PI (US) of the comparator, the RMP selected when more than one originator is marketed, which is the case with the r-somatropins or rhu-insulins, r-insulin analogues or LMWHs or r-interferons-alpha or r-interferons-beta. Furthermore, the comprehensive battery of structural and analytical pharmaceutical comparability chemical, biophysical, biochemical, bioassay/bioidentity tests of the BMP *vs* RMP not only defines the identity, integrity and potency connected with efficacy of the product, but also its impurity profile, stability, microbiology (sterility, endotoxins, preservative) and other aspects of safety.

Selection of the RMP: The FDA has made some important concessions regarding the RMP:

1 The FDA's decision to accept an RMP from another major regulated region is far-reaching,[13, Line 74,9] to "scientifically justify the relevance of these comparative data to an assessment of biosimilarity"[15, Line A. I.8] and the EU would generally qualify for an FDA-acceptable RMP as it complies with ICH regulatory standards. The FDA states in its Q&A guidance: " [The precondition is also that] *as a scientific*

matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the US-licensed reference product."[15, Line A. I.8]

So the FDA would need bridging EU *vs* US RMP scientific data as proof of comparability, as well as all information on manufacturing sites and licence holders which could be relevant.

Accepting a foreign RMP is a forward-looking milestone compared with Europe where the RMP must be purchased in the EU, according to the so-called *acquis communautaire* legality, to render the studies pivotal, otherwise all effort is wasted and the studies would be scientific findings that would only be supportive. Canada has a provision also allowing a non-Canadian RMP.[27]

2 As in Europe, where more than one RMP is available, comparability studies against a single one will suffice for approval.[13, Line 198]

3 The USPI will identify a biosimilar: *"Labeling of a proposed product should include all the information necessary for a health professional to make prescribing decisions, including a clear statement advising that: This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s). This product (has or has not) been determined to be interchangeable with the reference product."*[13, Line 821]

To conclude on the RMP, the FDA has made a significant advance and set an excellent international precedent by being prepared to accept comparative data from a non-US RMP (such as the EU) as pivotal. This will allow an EU–US development programme to be conducted, thus making savings in time and resources. In cases where the biosimilar has already been approved in Europe, bridging studies can be agreed on with the FDA. Where a full new programme is envisaged, an appropriate strategy is to consult the FDA after the European development has been ratified by the CHMP/EMA, which represents 30 national competent authorities (27 EU countries, including the veterans with the largest markets, Germany and France, and newer EU Eastern European members such as Poland, Hungary, Czechoslovakia, Romania and Bulgaria, and three EEA countries). The FDA position represents a single progressive authority and an abbreviated development and submission would be within reach, and probably require fewer studies. But the FDA is likely to have some significant demands in terms of the details of some of the studies.

Recognising but not overstressing immunogenicity

It is well known that immunogenicity is a major concern for the regulator for biologics and is addressed in several EU guidelines.28 The FDA, too, addresses the issue in some detail.7, Line 522 Regarding operational aspectsof testing, the EU 2007 immunogenicity guideline on proteins and the2010 immunogenicity guideline on mAbs, both multidisciplinary qualitynonclinical / clinical in coverage, are suitable.

The methodology used for immunogenicity testing is critical, and this is emphasised in particular by the FDA, which has a dedicated guidance,[29] whereas the EU has a general guideline covering quality, nonclinical and clinical, and a class-specific guidance for mAbs.[28] The scientific merit of the findings depend on it.

The FDA in its 2012 guidance on Scientific Considerations13, Line 533 emphasises its 2009 guidance on analytical validation methodology,[29] which needs to be robust. The clinical requirements depend on *"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"*, and require the study to be conducted in the *"most sensitive"* population, just as with the CHMP/EMA. The FDA guidances overlap with the scope of the CHMP/EMA but can go even further if the clinical consequence is severe, such as anaphylaxis, or, 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."*

The regard for the risk of immunogenicity is high by the EMA pre- and post-approval and would be monitored during formal antibody response to protein or mAb studies, and also as part of observational studies. The fascinating and developing theme of the European experience of mainly clinical safety aspects of biosimilars, and comparisons with the emerging FDA regulatory framework and guidances, will be further discussed in Part 2 of this paper.

Conclusions

Biosimilars development requires a highly specialised cross-disciplinary team effort. A substantial body of pharmaceutical, *in vitro*, *in vivo*, toxicology/toxicokinetic, PK, PD, PK/PD, and clinical efficacy and safety data – matching a chosen RMP with the intent of interchangeability – has been gathered in the EU.

A judicious choice of methods and thorough immunogenicity investigations, and carefully validated methods, are incorporated in demanding clinical studies. The FDA guidances, too, describe a comprehensive programme, as well as frequent consultations with the agency. But the FDA proposes a "stepwise" and risk-based "targetedapproach, the concept being the FDA's 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."*[13, Line 475]

Also, experience shows such systematic studies can lead to new, previously unexplored data on impurities, immunogenicity in special patient populations, the properties of the RMP, comparability aspects and so on.

This is providing fresh insights into therapeutic proteins such as quality characteristics and immunogenicity properties. Originator companies do not always publish information on immunogenicity, either keeping it proprietary or because it is not available.

The MAA package has undergone rigorous review by 30 reputable national authorities, led by a harmonised CHMP and EMA, with European perspective and oversight. Therefore, assurance of the safety of the biosimilar is high at the time of launch. Monitoring continues in parallel with changes of the RMP under an EU risk management plan. And for thoroughness, there is an EU post-authorisation requirement to capture safety data across different indications. The FDA has comparable demands on pharmacovigilance pre- and post-approval. This will be a focus of Part 2 of this paper.

A well thought out, well executed development programme in sensitive populations is critical for success. Extrapolation from one usage to another can be justified but is not a given. Indications not studied have been 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 paper, published in next month's issue of *Regulatory Rapporteur*.

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