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Confronting the  
challenges in  
developing a biosimilar  
medicinal product

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# S21 Confronting the challenges in developing a biosimilar medicinal product

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## SUMMARY

While development of generic medicines is easy, development of similar biological medicinal products is certainly not. Biologicals are more complex than small molecules although there is a spectrum of increasing complexity which in reality blurs the differentiation between biological and non biological products.

As with the development of any drug, some non-clinical testing will be required prior to regulatory approval to move to the clinic. Current requirements focus on the need for intensive *in vitro* testing generally coupled with a 28 day study in one species, usually the rat.

Just as for standard generic medicines there is a requirement for bioequivalence type studies to be performed in either healthy volunteers or patients. However EU regulatory guidelines on biosimilars, focus heavily on the need to also demonstrate similar levels of efficacy. In certain circumstances it may be acceptable to substitute confirmatory clinical trials with pharmacodynamic studies, but usually equivalence trials in patients will be necessary and these are fraught with difficulties.

By far the most relevant concern in substituting one biological medicinal product for another is the potential for increased immunogenicity. Thus

monitoring safety, and particularly immunogenicity, is a critical part of any development programme for a biosimilar. As the exact data requirements will vary on a case-by-case basis, any manufacturer involved in the development of biosimilar proteins is well advised to seek third-party advice and ultimately to consider scientific advice from the Committee for Medicinal Products for Human Use (CHMP).

Biosimilar medicinal products are here to stay and the discussion of what can and cannot be considered as biosimilar is with us for the foreseeable future.

## **INTRODUCTION**

The term “biogeneric” has proved to be one of the most controversial terms in the pharmaceutical industry. The orthodox view is that there can be no such beast as proteins are far too complex and heterogeneous to be treated as generics; for proteins the process defines the product. Thus a product from a different process has to be considered as a different product. To circumvent the objection to this term, a plethora of other terms was applied until the European Union fixed on the name “similar biological medicinal product”.

In the USA the term “follow on protein” is widely used but there is no consensus and there is also no regulatory framework in place to handle the majority of potential “follow on proteins”. Thus the discussion that follows focuses on the situation in the European Union.

“Biogenerics” first came to the forefront of regulatory discussion when the EU Commission failed to adopt a positive CHMP opinion for the first “biogeneric”, Omnitrope (somatotropin). The rationale for this negative decision by the EU Commission was that the legal basis for approval under Article 10iii of Directive 2001/83 (well established use)<sup>1</sup> was inappropriate in that well established use was intended to apply to simple molecules such as aspirin and not to complex proteins where there could be no certainty of similarity.

## **LEGAL BASIS FOR A BIOSIMILAR MEDICINAL PRODUCT IN THE EU**

The situation in the EU has now become much clearer from a regulatory perspective at least. Two relevant amendments have been made to Directive 2001/83 since 2001. Firstly Directive 2003/63<sup>2</sup> set out the requirements for demonstrating the similar nature of two biological medicinal products even before the concept “similar biological medicinal product had been embodied in the EU regulatory framework; this happened a year later with Directive 2004/27<sup>3</sup>, which substantially amended Directive 2001/83. Directive 2004/27

dispensed with the concept of essential similarity, replacing this with the terms “generic medicinal product” and “similar biological medicinal product”.

Generally for standard generic medicinal products, as stipulated in Article 10 of Directive 2001/83/EC (as amended), there is no need to provide results of “*pre-clinical tests and of clinical trials*”. The Article however then goes on to state that: “*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in the Annex and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided*”.

So why are biological medicinal products singled out? In fact the differentiation into standard generics and what are termed “similar biological medicinal products” is partly political and partly scientific. Clearly biologicals are more complex than small molecules. However there is a spectrum of increasing complexity. With modern techniques, small peptides such as glucagon and insulin can, arguably, be almost as well characterised as small molecules. However, full characterisation of the more complex proteins such as monoclonals and clotting factors remains a challenge. The definition of a biological substance in Commission Directive 2003/63/EC takes into account the issue of increasing complexity and defines a biological substance not merely as “*a substance that is produced by or extracted from a biological source*” but goes on to add “*and that needs for its characterisation and the determination of its quality a combination of physicochemical- biological testing, together with the production process and its control*”. In other words if a biologically extracted substance can be characterised to the extent of a small molecule, it would no longer be a biological substance according to this definition. Thus one can reasonably question whether small peptides actually fall within the EU medicine definition of a biological substance. The ultimate decision as to what is or is not a biological is left to the regulators and if challenged, the courts. So far no one has challenged the regulatory interpretation and for now any recombinant protein or peptide no matter how simple will be classed as a biological medicinal product. In fact even non proteins such as low molecular weight heparin are being categorised as biologicals.

## **EU REGULATORY GUIDELINES**

As already mentioned, the manufacturer of a similar biological medicinal product will be required to provide the “*results of appropriate pre-clinical tests or clinical trials*”. The question is how much data are actually required? A plethora of CHMP guidelines helps to address this issue. These include an overarching guideline (EMA/CHMP/437/04)<sup>4</sup>, guidelines covering quality (EMA/CHMP/BWP/49348/05)<sup>5</sup> and non clinical and clinical issues (CHMP/3097/02)<sup>6</sup> and guidelines covering recombinant erythropoietins (EMA/CHMP/94526/05)<sup>7</sup>, recombinant somatropin (EMA/CHMP/94528/05)<sup>8</sup>, recombinant granulocyte-colony stimulating factor (EMA/CHMP/31329/05)<sup>9</sup>, and recombinant human insulin (EMA/CHMP/32775/05)<sup>10</sup>. Additionally concept papers have been published covering recombinant alpha-interferon (CHMP/ BMWP/7241/06)<sup>11</sup> and immunogenicity assessment (CHMP/BMWP/246511/05)<sup>12</sup>.

The guidelines are by necessity general, since in fact no two cases are likely to be the same. Continual advancements in analytical technology mean that it is unwise to apply the guidelines too rigidly and it is hoped regulators will take a pragmatic approach. For example, modern analytical technology enables resolution down to the atomic level using 2D NMR, while mass spectrometry coupled with High Performance Liquid Chromatography (HPLC) allows masses to be determined to within one Dalton. Furthermore immuno- and chemo-luminescence assays are capable of detecting impurities at sub pico-gram levels. Therefore, it is often not a question of whether differences can be detected but rather whether detected differences matter. The quality guideline (EMA/CHMP/BWP/ 49384/2005)<sup>8</sup> does not require the biosimilar product to be identical to the reference product. Minor structural differences such as variability in post-translational modifications may be acceptable but must be justified. Additionally, differences in impurity profile will need to be justified. Furthermore, these differences may impact on the extent of non-clinical and clinical data needed. In fact a spectrum of difference may be encountered, from simple proteins expressed by the same host cell where no difference is discernible at all, to complex proteins having different glycosylation and impurity profiles and potential differences in higher order structure. Proteins that differ with respect to the amino acid sequence fall outside the boundaries of what might be considered biosimilar.

In principle the concept of biosimilarity could apply to any similar biological medicinal product. However in practice a number of factors will dictate whether or not a protein can be handled from a regulatory perspective as a biosimilar. These include the complexity of the protein and the extent to which it can be

adequately characterised. The overarching guideline (EMA/CHMP/437/04)<sup>4</sup> singles out clotting factors, proteins extracted from animal or human tissue and gene and cell therapy as falling outside the scope of what could currently be considered to be biosimilar. Monoclonal antibodies, too, are currently not likely to be accepted through the biosimilar route.

## THE NEED FOR NON CLINICAL TESTING

As with the development of any drug, some non-clinical testing will be required prior to regulatory approval to move to the clinic. It is important to undertake both the non clinical and clinical programme using reference product sourced from the European Economic Area (EEA). It will otherwise be virtually impossible to prove that the reference product is indeed the product approved for sale within the EEA.

The original draft guidance acknowledged that non clinical studies could be of limited usefulness in the assessment of clinical safety but this statement was dropped from the final guidance, which placed far more focus on the need for non clinical data. With the revision of the guideline a more pragmatic view appears to have prevailed and there appears to have been a shift away from the need for comparison at several different doses and for the duration of testing to take into account the intended duration of use. Current requirements focus on the need for intensive *in vitro* testing generally coupled with a 28 day study in one species, usually the rat. The intention is for the sponsor to maximise the data obtained from such a study so as to obtain pharmacokinetic, pharmacodynamic, toxicity and immunogenicity data from a single study. Questions such as the need to study both sexes, the need for satellite groups for assessment of toxicokinetics and recovery, the number per group are not addressed in either the overarching or product specific guidelines and are left for the sponsor to discuss with the regulatory authorities on a case-by-case basis.

## PHASE 1 STUDIES

As is the case for standard generic medicines there is a requirement for bioequivalence type studies to be performed in either healthy volunteers or patients. These studies will however differ from the standard generic in that both pharmacokinetics and pharmacodynamic endpoints will generally need to be examined.

The note for guidance on bioequivalence studies (for small molecules) (CPMP/EWP/QWP/1401/98)<sup>13</sup> states that “*AUC is the most reliable reflection*

of the extent of absorption” and this is true for biosimilar products as well. Maximum plasma concentration is singled out as another important parameter to monitor, and clearance and elimination half life should be explored. While for small molecules an equivalence margin for AUC of 80-125% and exceptionally 75-133% is stated as acceptable, the margin for biosimilars needs to be defined and justified on a case-by-case basis. Issues to consider in such a justification include variability of potency within reference product batches, the clinical need for tight control of plasma levels and the performance of the available analytical detection methods.

Batch-to-batch variability and deviation from the labelled strength seen with the reference compound can most certainly confound bioequivalence studies. For example, the European Pharmacopoeia monograph for epoetin allows a potency range of 80-125%. Limits of detection and assay variability can also impact the design of the bioequivalence trial, for example there may be the need to dose at supra-normal levels in order to enable reliable measurement of drug plasma levels, as has been the practice with studies on interferon beta. The presence of endogenous protein might also interfere with the determination of drug plasma levels; such is the case with insulin – necessitating trials in patients or utilisation of special designs such as the glucose clamp. These factors will also impact sample size and bioequivalence trials may need to recruit anything from twenty to hundreds of subjects.

As mentioned earlier, pharmacodynamic endpoints will also need to be explored during Phase 1. It may be possible to combine these trials with the bioequivalence trial or there may be the need for these studies to be conducted as separate studies. In order to discern any difference that may exist it is critical for the dose to be within the steep part of the dose response curve. This may sound obvious but in fact the therapeutic dose of some proteins may fall within the asymptotic area necessitating pharmacodynamic studies to be conducted at levels lower than the therapeutic dose or the use of several doses. The choice of endpoints depends on the protein. For proteins such as insulin and filgrastim, the endpoints such as glucose levels and absolute neutrophil count directly relate to the therapeutic effect. On the other hand, for somatropin and interferon, the relationship between endpoints such as IGF1 levels and antiviral activity do not correlate precisely with the intended clinical effect. Thus for insulin and filgrastim pharmacodynamic endpoints could be accepted as surrogates for clinical effect while for somatropin and interferon beta this would not be acceptable.

## THE REQUIREMENT FOR CONFIRMATORY EQUIVALENCE TRIALS

While inherent differences in efficacy between similar proteins are not generally encountered, the EU regulatory guidelines on biosimilars, focus heavily on the need to demonstrate similar levels of efficacy. Usually when equivalence is seen using several bioassays and through pharmacokinetic and pharmacodynamic studies, differences in clinical effect are highly unlikely and if they do occur are likely to be associated with the presence of neutralising antibodies. Changed glycosylation pattern or higher order structure may also impact efficacy but generally this effect should become apparent in the preclinical or phase 1 testing.

In certain circumstances it may be acceptable to substitute confirmatory clinical trials with pharmacodynamic studies. However this will only be acceptable if the pharmacokinetics and pharmacodynamics are well understood, an acceptable surrogate marker exists and a clear relationship between dose and therapeutic response can be established and is well understood

Generally equivalence trials in patients will be necessary; these are fraught with difficulties such as the need to establish an equivalence margin that will be acceptable to the regulatory authorities and the need to demonstrate assay sensitivity. These issues will be discussed later.

The first point to consider in designing a clinical programme for a biosimilar, is the choice of the primary endpoint, which will need to be clinically relevant, easily measurable, ideally have low inter and within subject variability and above all be acceptable to the regulators. Surrogate markers may be acceptable but will need to be justified if not validated. For some proteins such as interferon beta for the treatment of multiple sclerosis there is no good understanding of the structure activity relationship necessitating the use of endpoints such as relapse rate, which would require thousands of patients in order to have any hope of demonstrating an adequate level of similarity. As such interferon beta is not a good candidate for development as a biosimilar.

Another key question is how similar does similar have to be? This is addressed by setting an 'equivalence margin' which needs to be defined *a priori* and justified in terms of the clinical and practical relevance of the permissible difference in efficacy between the biosimilar and reference products. When justifying the equivalence margin to regulatory authorities there is the need to take into consideration a number of factors. Generally the agreed margin should be tight enough to ensure no clinically relevant difference from the reference product and the regulators will certainly like to see the margin as tight as possible. However practical constraints such as the common standard deviation

for the selected endpoint, batch-to-batch variability of the reference and test products and the potential to recruit adequate numbers of patients will also need to be taken into consideration. The common standard deviation is a critical factor in the sample sizing of the equivalence trial and if not available from the literature will need to be obtained through a pilot study. As mentioned earlier accepted batch-to-batch variability for the reference product can be high, as much as  $\pm 20\%$  or more and this needs to be taken into account in the setting of the equivalence margin and/or a correction factor may need to be introduced. One other critical consideration is that the equivalence margin will need to be sufficiently tight to exclude any anticipated placebo effect. This will need to be based on a review of historical and literature data.

As for all equivalence designs, assay sensitivity will need to be ensured. This requires a comprehensive literature review to demonstrate that the selected endpoint is capable of detecting a significant clinical difference if such exists.

Exact patient numbers will naturally depend on the selected endpoint and will require statistical advice. Factors that impact patient numbers include the tightness of the equivalence margin, the variability of the endpoint, the power, the confidence interval (which should be 95%) and the adoption of uneven randomisation. Uneven randomisation will increase the number of patients required, for example if 1:1 randomisation requires 120 patients, 1:2 randomisation might require 135 patients and 1:3 randomisation, 160 patients. However there may well be good reasons to adopt an uneven randomisation as this will cut the cost for purchase of expensive comparator drug product, and increase the safety data base for the test product.

The situation becomes more complicated where a biological medicine is used for multiple indications. The CHMP non-clinical and clinical comparability guideline<sup>6</sup> addresses this, stating that “*efficacy and safety of the medicinal product claimed to be similar has to be justified, or if necessary, demonstrated separately for each of the claimed indications*”. From the European Public Assessment Reports published to date<sup>14, 15</sup>, it seems that such justification has been possible at least with somatropin, which is the only category of biosimilar to be approved to date. However there will be the need to construct a robust justification based on all available literature.

## **IMMUNOGENICITY AND SAFETY**

The greatest, if not the only, concern in substituting one biological medicinal product for another is the potential for increased immunogenicity. Since similarity to the reference protein in terms of pharmacokinetics, pharmaco-

dynamics and clinical efficacy will have been demonstrated, it is unlikely that any unexpected adverse reactions will arise other than due to immunogenicity. The immunogenicity of a protein is sensitive to factors such as alteration of higher order structure leading to exposure of hidden epitopes, changed glycosylation patterns, and differing impurity profiles. These concerns are real not theoretical, for example Raut *et al.*<sup>16</sup> reported that the introduction of a pasteurisation step in production of plasma derived factor VIII exposed a hidden epitope resulting in increased immunogenicity while the European Public Assessment Report for Omintrope<sup>14</sup> reports that initial high levels of host cell proteins were associated with high levels of anti-somatropin antibodies which were resolved when the purity was improved. Similarly the emergence of pure red cell aplasia associated with the subcutaneous administration of Eprex is believed to have been caused by the adjuvant effect of leachates from the rubber stopper<sup>17</sup>.

Immunogenicity is more pronounced when proteins are administered subcutaneously and less when the intravenous route is employed. The impact of antibodies can be quite varied: they may impair bioavailability or change plasma clearance leading to reduced or increased plasma levels. If antibodies bind to the active moiety they will impair potency. An immune response can also precipitate a hypersensitivity reaction and even autoimmune syndromes, where antibodies to the exogenous protein interact with endogenous proteins such as was seen with the pure red cell aplasia associated with the use of subcutaneous administration of erythropoietin.

Thus monitoring safety and particularly immunogenicity is a critical part of any development programme for a biosimilar. The number of patients that will need to be exposed will depend on the level of risk considered acceptable and the rarity of the disease. This will vary from product to product but, in general, it will be in the order of hundreds of patients. For chronic therapies, at least six months' data in at least several hundred patients are likely to be required in line with the current International Conference on Harmonisation (ICH) guidelines. Clearly immunogenicity will need to be monitored using a sensitive and specific assay to detect binding antibodies. If binding antibodies are detected, their neutralising capacity will need to be assessed using a validated bioassay.

As rare, yet serious, adverse reactions may only emerge after extensive usage, there is the need to monitor safety profiles post marketing; this is likely to require post marketing commitments or even pharmacovigilance registries, and periodic safety update reports (PSUR) reporting as for a new product.

## **SCIENTIFIC ADVICE**

As discussed, exact data requirements will vary on a case-by-case basis, therefore any manufacturer involved in the development of biosimilar proteins is well advised to seek third-party advice and ultimately to consider scientific advice from the CHMP.

It is important to appreciate that the advice emanating from the CHMP will be very much based on the data and justification provided in the applicant's briefing document. It is, therefore, of critical importance to present both an achievable and credible programme and to rigorously justify any reduction in the data package by drawing on all available quality, preclinical and literature data. If this is not done, it is quite probable that the CHMP will make what might appear to the applicant to be excessive demands and, while not binding, applicants will be expected to comply. Therefore, CHMP scientific advice should only be requested following extensive groundwork and with an understanding of the likely impact of the advice.

## **PARTNERING WITH A CRO**

Clearly, development of a biosimilar medicinal product requires not only considerable resource but also expertise in a variety of disciplines including drug development, regulatory, statistics and medical knowledge. It is therefore likely that those developing biosimilar medicinal products will need to work with a CRO and the choice of CRO could make the difference between success and failure. It is therefore important for any sponsor to meet with the team and to understand the capabilities and experience of the CRO. It is equally important to get the scope of the project right and in that respect bringing in the right expertise early is critical. Developing a biosimilar medicinal product is complex; however there is no reason why, with the right partner, this cannot be successfully achieved.

## **CONCLUSION**

Development of generic biological medicinal products represent a huge challenge.

The ultimate decision as to what is or is not a biological is left to the regulators and they will need to be conservative in their views. Thus all recombinant proteins are likely to be classed as biologicals as are non proteins such as low molecular weight heparin.

While a plethora of CHMP guidelines exists, no two cases are the same and consequently these guidelines cannot be definitive. Thus it is left to the sponsor to develop a suitable programme and the best way to approach this is to undertake a risk analysis of how differences in structure and impurity profile might impact on safety and efficacy.

The regulatory guidelines appear to focus on potential efficacy differences. Designing adequate equivalence trials is challenging and often requires expert advice and consultation with the regulatory agencies. However by far the most relevant concern is the potential for increased immunogenicity. Monitoring of safety, and particularly immunogenicity, is a critical part of the development programme for any biosimilar. However as rare, yet serious, adverse reactions may only emerge after extensive usage, there will also be the need to monitor safety profiles post marketing.

Clearly biosimilar medicinal products are here to stay and the discussion of what can and cannot be considered as biosimilar is with us for the long-term, as patents and data exclusivity periods for more and more complex biological products expire, making for an ever more interesting debate.

## REFERENCES

1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use *Official Journal L 311, 28/11/2001 p. 67 – 128*.
2. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use *Official Journal L 159, 27/6/2003 p. 46– 94*.
3. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use *Official Journal L 136, 30/4/2004 p. 34–57*.
4. CHMP/437/04 Guideline on Similar Biological Medicinal Products.
5. EMEA/CHMP/BWP/49348/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (CHMP adopted February 2006).
6. EMEACHMP/94528/05 EMEA/CHMP/42832/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (CHMP adopted February 2006).
7. EMEA/CHMP/94526/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant Erythropoietins (CHMP adopted March 2006).
8. EMEA/CHMP/94528/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Somatropin (CHMP adopted February 2006).

9. EMEA/CHMP/31329/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor (CHMP adopted February 2006).
10. EMEA/CHMP/32775/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues – Guidance on Similar Medicinal Products containing Recombinant Human Insulin (CHMP adopted February 2006).
11. CHMP/BMWP/9437/06 Concept Paper on Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process – Non-Clinical and Clinical Issues (Released for consultation February 2006) (Replaces Guideline CPMP/3097/02).
12. CHMP/BMWP/246511/05 Concept Paper on Guideline on Immunogenicity Assessment of Therapeutic Proteins (Released for consultation in 2006).
13. CPMP/EWP/QWP/1401/98 Note For Guidance on the Investigation of Bioavailability and Bioequivalence (Adopted July 2001).
14. European Public Assessment report for Omnitrope INN: *Somatropin* – Published 25/04/06.
15. European Public Assessment report for Valtropin INN: *Somatropin* (Rev. 1) – Published 29/08/06.
16. Raut S, Di Giambattista M, Bevan SA, *et al.* Modification of factor VIII in therapeutic concentrates after virus inactivation by solvent-detergent and pasteurisation. *Thromb Haemost.* 1998 Oct; **80**(4): 624–31.
17. Villalobos AP, Gunturi SR, Heavner GA. Interaction of polysorbate 80 with erythropoietin: a case study in proteinurfactant interactions *Pharm Res.* 2005 Jul; **22**(7): 1186–94. Epub 2005 Jul 22.