

Formulating a development programme for a biosimilar medicinal product

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Summary

The legal route for approval of similar biological medicinal products in the EU has been clarified. The challenge now is to determine the exact nature of the non-clinical and clinical programme required to gain regulatory approval.

One of the first decisions that needs to be made is the choice of reference product, as the same reference product will need to be used throughout the comparability programme. Once the reference product has been selected and characterised, the next stage is to investigate whether the products are indeed comparable in terms of *in vitro* and *in vivo* effects by performing non-clinical studies.

Finally, there is the need to demonstrate safety and efficacy in the clinic. The CHMP guidelines stipulate the need to approach clinical efficacy and safety as if data from standard confirmatory and comparative efficacy/safety studies were needed. The CHMP allows for deviations from this conceptual level only if these can be justified.

However, clinical trial programmes are associated with significant costs and, moreover, considerable ethical constraints. There is, therefore, a compelling need to optimise the clinical programme so as to keep trial sizes to a minimum and to convincingly justify this approach to the regulatory authorities.

The most likely effect arising from the use of similar biological medicine is a changed immunogenicity profile compared with the reference product. This can have profound safety implications. In general, a safety database in the order of hundreds of patients will be required followed by post marketing surveillance to detect any rare serious adverse events. Altered immunogenicity is by far the most important safety consideration. Immunogenicity studies, therefore, should represent a pivotal part of any comparability programme.

The requirements are complex and manufacturers involved in the development of similar biologicals are well advised to seek third party advice and ultimately to seek scientific advice from the CHMP.

Introduction

At last the legal route for approval of similar biological medicinal products in the EU has been clarified. Specifically, Directive 2004/27/EC¹ has, at a stroke of the pen, dispatched the much-disputed term “essential similarity” into the annals of history. In its place are two new terms: “generic medicinal products” and “similar biological medicinal product”.

The need to differentiate between “generic medicinal products” and “similar biological medicinal products” arises from the view that analytical methodology is not sufficiently discriminating to detect subtle differences in the structure and conformation of complex proteins or in their impurity profiles. In fact the challenge is not so much that the methodology is inadequate but in selecting the appropriate methodology and judging the

significance of any observed differences. Even the physicochemical differences associated with the changes to Eprex that led to the development of pure red cell aplasia could have been detected had an HPLC assay been run for a longer period to enable detection of extractables from the rubber stopper^{2,3}. Clearly it is very difficult to prove a negative and even if extensive state-of-the-art methodology is applied, the regulatory authorities will still require toxicological and clinical data in order to demonstrate that a biosimilar medicine has a safety and efficacy profile comparable to the reference product.

Commission Directive 2003/63/EC (Annex Part 2 (4))⁴ outlines the approach to be followed for biosimilar medicinal products, stipulating that the exact data requirements should be determined on a case-by-case basis in accordance with relevant scientific guidelines.

Guidelines have been issued by the CHMP^{5,6,7}. While these are very general, more specific draft guidelines have been released for consultation covering recombinant erythropoietin⁸, recombinant granulocyte-colony stimulation factor, recombinant human somatropin¹⁰ and recombinant human insulin¹¹. These guidelines all stipulate the need for clinical data although, in most cases, it will not be necessary to repeat all the safety and efficacy studies if the applicant can demonstrate that it is possible to demonstrate similarity on the basis of physico-chemical properties.

Choice of reference product

One of the first decisions faced is the choice of reference product, which will need to be the same throughout the comparability programme. It is also critical that the reference product is sourced from within the EU, as it may otherwise not be possible to demonstrate conformance with the product approved for marketing within the EU. For reference products not approved via the Centralized Procedure, it is even possible for variation between member states, in which case it is advisable to consistently source the reference product from the same EU member state. There are a number of other factors that will need to be considered in making the choice of reference product; these will include:

- the patent status, not just in terms of the molecular entity but also there may be patents covering formulations, delivery devices and processes;
- the extent of physicochemical and biological similarity - a biosimilar approach will only be possible if few or no differences exist and the same generic name can be applied to both the biosimilar and reference product;
- the remaining period of data exclusivity, which will determine when a submission can be filed and when the product can be marketed;
- the current clinical perception of efficacy and safety relative to competitor products;
- the relative market share of the reference product;
- the price of the reference product relative to competitor products;
- the potential for future clinical problems (or advantages);
- the potential for competition from other manufacturers and innovations.

The biosimilar medicine will need to be administered according to the same dosage, route of administration and dosing regimen as the reference compound. This might impact market acceptability and even safety and/or efficacy.

Non-clinical data requirements

Once the reference product has been selected and characterised, the next stage is to investigate whether the products are indeed comparable in terms of *in vitro* and *in vivo* effects.

The value of *in vitro* studies and “emerging technologies” is highlighted in the CHMP Note for Guidance⁵ and revised draft⁷. A broad range of such studies is suggested, including

methods such as receptor-binding studies and cell-based assays (including those that may be used as bioassays for quality control).

The value of in vivo non-clinical studies for the assessment of biosimilar medicines is often limited; particularly if studies on the reference product do not show much evidence of toxicity or where neutralising antibodies are readily formed. Furthermore, species specificity may restrict the available options in terms of suitable species.

The original draft CPMP non-clinical and clinical comparability guideline acknowledged the limited usefulness of non-clinical studies in the assessment of clinical safety. However, this reference was dropped from subsequent versions of the guideline^{5,7}, which place more emphasis on comparative in vivo non-clinical studies. The new draft guidelines⁷ require that the studies be “comparative in nature and should be designed to detect differences in response --- and not just responses per se.” The current guideline⁵ also stipulates comparison at several different doses; however, this statement has been dropped from the draft revised guideline. The requirement for a comparative study, particularly if different doses of reference product are required, poses serious practical difficulties since generally only formulated reference product will be available, making studies at high dose impractical. In any case the effect of formulation on safety and efficacy can be profound and the value of performing studies using formulations other than those used for the marketed reference product is questionable as differences in formulation may impact higher order protein structure, which may translate into a changed efficacy and safety profile.

The guidelines^{5,7} further require that the duration of non-clinical toxicity studies should be sufficiently long to allow detection of any differences. A requirement to take into account the intended duration of use of the product has, fortunately, been dropped from the revised guideline, as this could have been interpreted as requiring long-term data, which hardly seems relevant. In reality, for biologicals, a comparative study of longer than four to twelve weeks is generally not likely to be practical and this is recognised in the product specific guidelines, which generally specify the need for just four weeks data in one relevant species, which could be the rat. Epoetin represents an exception, since owing to its extended duration of action and the potential for development of pure red cell aplasia, a longer term repeat dose toxicity study of at least three months is required⁸.

It should be stressed that the design and aim of the non-clinical study will differ considerably from that used in a standard pre-clinical programme. In particular, the study will need to be designed to demonstrate similarity and will need to be appropriately powered for that purpose, although demonstration of formal statistical equivalence is not expected. Secondly, any observed toxicity needs to be judged in relation to immunogenicity, pharmacokinetics and pharmacodynamic effects and therefore these need to be investigated in parallel and preferably in the same study.

Studies on irritation at the injection site are also likely to be required, as these may be influenced by changes in the impurity profile and formulation. Mutagenicity studies, animal reproduction and carcinogenicity studies will not be required, the latter two categories are in any case often impractical and have even not been generated for the originator product.

Clinical data requirements

Changes in protein structure may impact the clinical effect in a number of ways. For example, changed glycosylation patterns and changes in the conformation of the protein or its impurity profile may impact on pharmacokinetics, potency and/or immunogenicity. As there is no certainty that all such changes can be detected, clinical trials will generally be required.

Since clinical programmes are associated with significant costs and, moreover, considerable ethical constraints, there is a compelling need to optimise the clinical program so as to limit

trial sizes to a minimum. Thus an efficient clinical program needs to be formulated and justified to the regulatory authorities. In preparing such justification, there are a host of factors that will need to be considered. These include:

- The physicochemical and biological similarity to the reference medicinal product
- The relationship between the pharmacodynamic effect, the clinical effect and the administered dose
- The existence of suitably validated surrogate markers and their relationship to dose and resulting drug tissue levels
- The statistical burden for proof of efficacy at the 95% confidence level in terms of the acceptability of the equivalence margin, the need for assay sensitivity, the variability in terms of the common standard deviation, and the required power of the study
- The potential for immunogenicity and the potential impact of neutralising antibodies.

Phase 1

As for any clinical development programme, the biosimilar programme will commence with a Phase 1 study, which will generally need to be completed before advancing to confirmatory efficacy and safety studies. Specific considerations relevant to proteins are to be covered in a guideline under preparation on the clinical investigation of therapeutic proteins.

The purpose of Phase 1 is to demonstrate equivalent pharmacokinetics, particularly in terms of AUC and C_{max} but also elimination characteristics are important. It is critical that these studies are carried out on the formulation intended for marketing and EU sourced reference product. Generally, in order to demonstrate bioequivalence for small molecules, the AUC and C_{max} need to be within 80-125% of the reference product. A broader margin of 75-133% may be acceptable if this can be justified, for example, if assay variability proves to be a constraining factor. However, these margins may not be appropriate for biosimilars and will need to be decided on a case-by-case basis taking into consideration, the route of administration, the therapeutic window and the precision and sensitivity of the available assays. Thus the choice of equivalence margin will always need to be justified.

The Phase 1 study may also be useful in examining comparative pharmacodynamic effects, e.g., blood glucose for insulin, IGF1 for human growth hormone, progenitor cells for erythropoietin, and anti viral effect or other pharmacodynamic markers for interferons. The draft guidelines advise that: "Combined PK/PD studies may provide useful information on the relationship between exposure and effect. The selected dose should be in the steep part of the dose response curve" and that "studies at more than one dose level may be useful.

Generally the Phase 1 study will be conducted as a cross-over study, however, this may not be appropriate for therapeutic proteins with a long half-life due to the potential for carry-over effects or where there is the potential to form antibodies against the protein. Generally, the dose recommended for the reference product should be used, however, it may not be possible to detect plasma levels unless higher doses are used. There may also be the need to recruit more than 30 subjects if the variability is high, as may be the case if there is the need to rely on a biological rather than an HPLC or immunological assay method.

Confirmatory efficacy and safety studies

If a biological medicinal product demonstrates similar physico-chemical and biological properties and displays similar *in vitro* and *in vivo* effects to the reference product one might expect similar efficacy. However, experience with biosimilar medicinal products is limited and it is difficult to be certain of this, particularly for the more complex proteins. Thus comparative clinical trials demonstrating equivalent efficacy will generally be required although a comparative PK/PD study may be adequate if sufficient is known of the biological medicinal product and an acceptable surrogate marker exists, as is the case for insulin.⁷ The

revised draft guidelines⁷, recognise that in some circumstances an equivalence trial may not be feasible, in which case alternate designs will need to be discussed with the competent authorities.

Use of surrogate markers is clearly one way of reducing the number of patients and shortening the duration of the trial, but surrogate markers need to be validated and their use as a primary end-point needs very careful consideration and should be discussed in advance with the regulatory authorities. In addition to showing equivalence regarding efficacy, there may also be the need to demonstrate equivalence or at least non-inferiority in terms of dosage, particularly in situations where a clear inter-dependence between dose and efficacy exists e.g. for epoetin and insulin.

“Equivalence limits” will have to be defined *a priori* and justified. Generally, the equivalence margin should be defined in terms of a clinically meaningful endpoint and will need to be sufficiently narrow as to ensure that any potential differences will not be of clinical significance. It will also be necessary to demonstrate that the effect of the test product is distinguishable from that of placebo. In order to make this judgement, there is the need to know the effect of the reference product against placebo. This may be established following a comprehensive literature search or, when ethically acceptable, by using a placebo control.

The number of patients required to demonstrate equivalence will depend on the variability of the endpoint (common standard deviation). In order to estimate the requisite number of patients, the statistician will need have an estimate of the common standard deviation. This is often difficult to obtain from the literature and may require a pilot study. Finally the sponsor will need to decide on the power of the study; this is usually set between 80 and 90%, depending on how the sponsor wants to balance the risk of a failed trial against the need for increased numbers of patients. The trial size will also be influenced by the allocation of patients between the two groups. Equal distribution requires the least number of patients but the sponsor may wish to increase the proportion of patients receiving the biosimilar product in order to increase the safety data base and/or to reduce the cost of purchasing reference product. Consequently clinical trials sizes will vary considerably.

The situation becomes more complicated where a biological medicine is used for multiple indications. The current CHMP non-clinical and clinical comparability guideline⁵, requires that “efficacy and safety has to be justified, or if necessary, demonstrated separately for each of the claimed indications.” However, this discussion has been dropped from the draft revised version and is now only discussed under the product specific guidelines, which indicate that for e.g. somatropin¹⁰, epoetin⁸ and G-CSF⁹, results from one study can be extrapolated to other indications if this can be justified by the applicant.

Safety

The most likely effect arising from the use of similar biological medicine is a changed immunogenicity profile compared with the reference product. This can have profound safety implications in terms of hypersensitivity reactions or by breaking tolerance to self-antigens and inducing the formation of auto antibodies as has recently been observed with respect to the pure red cell aplasia seen following formulation changes to Eprex¹².

The size of the requisite safety database will vary depending on a variety of factors eg:

- The duration of usage
- The potential for risk
- The patient population being treated
- The level of risk associated with use of the reference product
- The rarity of the disease.

Clearly this will vary from product to product but, in general, will equate to the number of patients required to demonstrate comparable efficacy. However, where the potential for serious adverse effects exist (eg, epoetin), at least twelve month's data in 300 patients are likely to be required in line with the current ICH requirements for new chemical entities for long term use¹³. Nevertheless, as rare, yet serious, adverse reactions may only emerge after extensive exposure and 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.

Immunogenicity

Altered immunogenicity is by far the most important safety consideration. The effect of changing the formulation and/or container in the case of Eprex has already been alluded to. There is also evidence that manufacturing changes can impact the antigenicity of interferons without any physico-chemical evidence of a difference¹⁴. The potential for immunogenicity is highly influenced by the patient population being less of an issue in immuno-compromised patients. The route of administration will also affect immunogenicity with the sc route being associated with the greatest immunogenicity.

In general safety studies should include comparative antibody testing, which generally should be performed at screening, and at appropriate intervals thereafter until the end of the study. It is generally not possible to compare results with historical or literature data as results are highly dependent on the assay used.

Of key importance is the need to distinguish between neutralising and non-neutralising antibodies. Neutralising antibodies are of particular concern as the appearance of neutralising antibodies (NAbs) has been reported in several studies to be associated with reduced clinical efficacy or autoantigenicity^{12, 15, 16}.

Immunogenicity studies, therefore, represent a pivotal part of any comparability programme.

Scientific advice

Any manufacturer involved in the development of similar biologicals is well advised to seek third party advice and ultimately to seek scientific advice from the CPMP.

While CHMP scientific advice is not binding, applicants will be expected to adhere to the advice unless able to offer strong justification for deviation. 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, not only to present both an achievable and credible program, but moreover to justify any proposed reduction in the data package by drawing on available quality, preclinical and literature data. Therefore, CHMP scientific advice should only be requested following extensive groundwork. In this respect it may be worthwhile to consult with national agencies prior to consulting the CHMP.

References

1. 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*).
2. Boven K, et. al. "The Increased Incidence of Pure Red Cell Aplasia with an Eprex Formulation in uncoated stopper syringes." *Kidney. Int.* 2005 June, **67**, (6), 2346-53
3. Boven K, et. al. "Epoetin-Associated Pure Red Cell Aplasia in Patients with Chronic Kidney Disease : Solving the Mystery" *Nephrol. Dial Transplant* 2005 May, **20**, Suppl. 3iii, 33 – 40.
4. Commission Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community Code relating to medicinal products for human use.

5. CPMP/3097/02 Note for Guidance on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues (CPMP adopted December 2003).
6. CPMP/437/04 Guideline on Similar Biological Medicinal Products (released for consultation November 2004)
7. EMEA/CPMP/42832/05 Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues (released for consultation May 2005)
8. CPMP/31329/05 Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues containing Recombinant Granulocyte-Colony Stimulation Factor (released for consultation June 2005).
9. CPMP/94528/05 Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues containing Recombinant Human Growth Hormone (released for consultation (released for consultation May 2005).
10. CPMP/94526/05 Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues containing Recombinant Human Erythropoietin (released for consultation June 2005).
11. CPMP/32775/05 Annex Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Drug Substance - Non Clinical and Clinical Issues containing Recombinant Human Insulin (released for consultation (released for consultation May 2005).
12. Casedevall N. ,” Pure Red Cell Aplasia and anti-erthropoetin antibodies in patients treated with epoetin.” *Nephrol. Dial transplant* 2003 Nov, 18 Suppl 8 viii 37 –41.
13. Schellens H, *Nature Reviews* Vol 1, June 2002.
14. Durelli L, Verdun E, Barbero R et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: Results of a 2-year prospective randomised multicentre study (INCOMIN). *Lancet*. 2002;359:1453-1460.
15. Firtkkila M, for the EVIDENCE Study Group. The EVIDENCE study: Direct comparison study of IFN beta-1a three times weekly (Rebif®) and once weekly (Avonex®) in RRMS. *Mult Scler*~: 2001;7(Suppl 1):594. Abstract P305.
16. Simon JH, Jacobs LD, Campion M, et al, for the Multiple Sclerosis Collaborative Re-search Group. Magnetic resonance studies of intramuscular interferon beta for re-lapsing multiple sclerosis. *Ann Neurol*. Simon JH 1998;43:79-87.