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How Similar Should Be A Biosimilar!!!

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ABSTRACT

The imminent patent expiration of many biopharmaceutical products will produce the possibility for generic versions of these therapeutic agents (i.e. biosimilars). However, there are a number of issues that will make approval of biosimilars much more complicated than the approval of generic equivalents of conventional pharmaceuticals. These issues center on the intrinsic complexity of biopharmaceutical agents, which are recombinant proteins in most cases, and the heterogeneity of proteins produced by different manufacturing processes. The increased occurrence of antibody (Ab)-mediated pure red cell aplasia (PRCA) associated with change in the formulation of one particular epoetin-α product highlights the potential for increased immunogenicity of recombinant proteins with different formulations, or those manufactured by different processes. The subsequent production of 'biosimilars' has aroused interest within the pharmaceutical industry as biosimilar manufacturers strive to obtain part of an already large and rapidly growing market. The potential opportunity for price reductions versus the originator biopharmaceuticals remains to be determined, as the advantage of a slightly cheaper price may be outweighed by the hypothetical increased risk of side effects from biosimilar molecules that are not exact copies of their originators. This review focuses on the issues surrounding biosimilars, including quality control, clinical efficacy and side effects.

Keywords: Biosimilars, Follow-on-biologics, Biopharmaceuticals, Biogenerics

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INTRODUCTION

Reducing health costs is a major issue in many countries, so the introduction and use of generic drugs is extrapolated. The generics may be introduced when the patent of an innovative drug expires. With classic drugs, normally produced by chemical synthesis, only limited data for marketing approval application are needed compared with the original drug[1]. The generic manufacturer has to submit the data proving their drug to be pharmaceutically identical in terms of bioequivalence to the RLD. The clinical trials required for the approval of new products to prove safety and efficacy are not required in conventional generics. The introduction of a generic also stimulates innovation because the innovator aims to improve their products, which can be protected by new patents. This continuous cycle of price drop and better drugs is good for patients.

The similar procedure cannot be extrapolated to therapeutic proteins for a number of reasons[2]. Protein drugs are produced by living cells. They generally are large, complex molecules that mostly also show heterogeneity. This heterogeneity is the result of natural processes in the host cells that modify proteins during their production to protect them during transport through the different cell compartments.

Manufacturing therapeutic proteins is a complicated process, and all steps of the production and purification process influence their biologic and clinical properties. The different steps need to be carefully monitored by sophisticated analytical tools and by using many in-house standards. Most of the analytical methods need to be adapted for each specific product. In addition, most production processes, especially those for the first products for which the patents will expire, have undergone important and continuous improvements based on increased experience in manufacturing.

The features of a particular biopharmaceutical are the result of the basic characteristics of the molecule such as amino acid sequence and three-dimensional structure as well as the specific production, purification, formulation, and storage conditions. To produce a biopharmaceutical of required quality constantly, a company needs experience and the in-house standards to apply the methods used to analyze the structure of a given product.

It is inconceivable, in the majority of cases, that another manufacturer, on the basis of the patent or published data, is able to manufacture a protein pharmaceutical that can be assumed similar enough to the original innovative product that only a limited documentation of physical chemical characteristics would be sufficient to show equivalence. In most cases only limited data are

available in Pharmacopoeial monographs and scientific reports. Moreover, even the most sophisticated analytical tools are not sensitive enough to fully predict the biologic and clinical characteristics of the product.

Because the generic approach is not applicable to protein drugs, the term biogenerics is considered misleading. Other terms have been used over the years such as multisource products, off-patent biotechnology products, and second entry biologicals[1]. The FDA is using the term "follow-on biologics"[3]. "Similar biologic medicinal product" is the official terminology in the European Union (EU), but "biosimilars" has become the preferred terminology both in scientific and regulatory discussions.

Biosimilars chasing biologics

According to the European Medicines Agency (EMA), "biological medicinal products" (referred to as biopharmaceuticals in this review) are medicinal products containing biotechnology-derived proteins as active substances[4]. Sales of biopharmaceuticals currently amount to over $30 billion in the United States alone[5]. This figure is increasing, as other complex biological medicines are being manufactured and marketed to help in the treatment of many diseases. A case in point is the treatment of anemia associated with chronic kidney disease. The advent of recombinant human erythropoietin (epoetin) has minimized the need for blood transfusions, revolutionizing the treatment and management of this chronic condition. The four main biopharmaceuticals accounting for the majority of sales are epoetin, insulin, growth hormone (GH), and granulocyte colony stimulating factor (G-CSF), but several others like cytokines, antibodies and hormones are also available[6]. Biopharmaceuticals make up a large proportion of new medicines and many are being developed using the same technology that is used to produce vaccines. Advances over the last quarter of a century in recombinant DNA technology have allowed the large-scale manufacture of biologically engineered proteins within living cells[7]. Many of the patents to these products are now close to expiring or have already expired[2], such as for Humulin®, Intron A®, Procrit®/Eprex®, and Neupogen®, and manufacturers of so-called copycat pharmaceuticals are attempting to expedite the production of follow-on biopharmaceuticals, termed biosimilars.

Biosimilars are fundamentally different from generic chemical drugs. Important differences include the size and complexity of the active substance, and the nature of the manufacturing process. Unlike classical generics, biosimilars are not identical to their originator products, and therefore should not be brought to market using the same procedure applied to generics. This is

partly a reflection of the complexities of manufacturing, and safety and efficacy controls of biosimilars when compared to their small-molecule generic counterparts.[8,9,10]

Some of the issues that concern all stakeholders include testing for similarity and comparability of the biosimilars with the originator products, as well as guidelines for long-term pharmacovigilance programs and assessment of potential complications arising from both short and long-term use.

Biopharmaceuticals are usually recombinant protein molecules manufactured in living cells.[7,11] Manufacturing processes for biopharmaceuticals are highly complex and require hundreds of specific isolation and purification steps[9]. It is thus impossible to produce an exact copy of a biopharmaceutical, as changes to the structure of the molecule can occur with changes in the production process[12]. A protein can be modified in many ways: side chains can be added, the product can have alterations to its tertiary or quarternary structure through protein misfolding; degradation by oxidation or de-amination can also occur. As manufacturing protocols are generally proprietary knowledge of the originator company, it is impossible for a biosimilars manufacturer to duplicate the process. This makes the production of biosimilars extremely challenging as different manufacturing processes may invariably lead to structural differences in the final product. In turn, these differences may lead to differences in efficacy and, more importantly, in their ability to trigger damaging patient immune responses.[13,14]

Assessing Biosimilarity

Exact copies of synthetic, "small molecule" pharmaceuticals can be synthesized, and considered to be equivalent if they have the same chemical structure, composition, and pharmacokinetic profiles as the originator drugs.[8,15] The case for biopharmaceuticals, however, is not as simple. Using an entirely different production process, biosimilar manufacturers can only produce a molecule that is "similar" but not identical to, the originator product. A challenge for biosimilar manufacturers is to demonstrate that their products have sufficient likeness to the originator product, in addition to showing consistency of quality between different production runs from their own manufacturing facilities.[10,15,16] The maintenance of consistent product efficacy is also important in order to avoid product "overdosing" and the concomitant risks of incurring adverse events.

Biopharmaceuticals can be as large as hundreds of kilodaltons, and their molecular weights can vary by as much as 1000 daltons[16]. Various *in vitro* tests are currently used to compare the structural aspects of biosimilars with their originator molecules, including assessments of the primary amino acid sequence, charge and hydrophobic properties[9]. Determination of higher-

order structure is performed using nuclear magnetic resonance or mass spectroscopy, and predictions of immune reactivity using assays based on conformational-dependent antibodies[9]. However, *in vitro* tests cannot predict biological activity *in vivo*. Despite similarities in size and structure, there may be significant differences in biological activity. Furthermore, *in vivo* biological activity can also be affected by product formulation and packaging, in addition to cold chain handling, as these parameters can influence the presence of impurities and protein aggregates[7]. In addition, biological activity is difficult to assess adequately as few (if any) animal models are able to provide data that can be extrapolated for an accurate prediction of biological activity in humans. Ultimately, controlled clinical trials remain the most reliable means of demonstrating similarity between a biosimilar molecule and the originator product in the clinic. However, even these trials may frequently be underpowered to detect infrequent iatrogenic (induced in a patient by a physician's activity, manner, or therapy) complications. Detailed registry data may be a prerequisite.

PROOF OF SIMILARITY OF A BIOSIMILAR

Non-Clinical Studies

Before initiating clinical development, non-clinical comparative studies[17]should be designed to detect differences in response between the similar biological product and the reference medicinal product. It is important to note that design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physicochemical and biological characterization studies should be reviewed from the point-of-view of potential impact on efficacy and safety. Further dynamic studies could be attempted.

In vitro studies:

Assays like receptor binding studies or cell-based assays, many of which may already be available from quality related bioassays, should normally be undertaken in order to establish comparability in reactivity.

In vivo studies:

Animal studies should be designed to maximize the information obtained and to compare reference and similar biological medicinal products intended to be used in the clinical trials. Information on the erythrogenic activity may be obtained from the described repeat dose toxicity study[17].

Toxicological studies:

The duration of the studies should be sufficiently long to allow detection of relevant differences

in toxicity and/or immune responses between similar biological medicinal product and reference medicinal product.[17]

Non-clinical toxicity should be determined in at least one repeat dose toxicity study of at least 28 days in one relevant species. This must include toxico kinetic measurements whereby determination of antibody titres, cross reactivity and neutralizing capacity should be measured.[17]

i) Pharmacodynamics Evaluation

Pharmacodynamics should be evaluated as part of the comparative pharmacokinetic studies. The selected dose should be in the linear ascending part of the dose-response curve. The Pharmacodynamics markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product[11].There is sufficient knowledge of the Pharmacodynamics properties of the reference medicinal product, including binding to its target receptor(s) and intrinsic activity[11]. Sometimes, the mechanism of action of the biological product will be disease specific. The relationship between dose/exposure and response/efficacy of the reference medicinal product is sufficiently characterized. These reports or information must be evaluated and assessed by the marketing authorization holder in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies.

ii) Efficacy Trials

Usually comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biological and the reference medicinal product[11]. Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds. As for all clinical comparability trial designs, assay sensitivity has to be ensured. If a clinical comparability trial design is not feasible, other designs should be explored and their use discussed with the competent authorities.

iii) Immunogenicity Studies

The prime safety concerns for all biopharmaceuticals relates to their immunogenic potential[14]. Many factors can influence the immunogenic potential of a biosimilar medicinal product. The predictive value of non-clinical studies for evaluation of immunogenicity of a biological medicinal product in humans is low due to inevitable immunogenicity of human proteins in animals. While non-clinical studies aimed at predicting immunogenicity in humans are normally not required, animal models may for example be of value in evaluating the consequences of an immune response.

Factors Affecting Immunogenicity

For many proteins and peptides, a number of patients develop clinically relevant antidrug

antibodies. The immune response against therapeutic proteins differs between products since the immunogenic potential is influenced by many factors, such as the nature of the active substance, product and process related impurities, excipients and stability of the product, route of administration, dosing regimen, and target patient population[18]. The patient related factors may have a genetic basis, e.g. lack of tolerance to the normal endogenous protein, or acquired, such as immunosuppression due to the disease or its concomitant medication[19]. There is considerable inter-individual variability in antibody response in terms of different antibody classes, affinities, and specificities. Thus, data should be collected from a sufficient number of patients to characterize the variability in antibody response.

There are various potential consequences of immunogenicity such as loss or enhancement of efficacy, neutralization of a native protein and general immune effects (allergy, anaphylaxis, serum sickness). Therefore, the immunogenicity issue has become a subject of concern in the development and approval of biopharmaceuticals. An immune response to the product may have a significant impact on its clinical safety and efficacy. Although only neutralizing antibodies directly alter the pharmacodynamic effect, any binding antibody may affect the pharmacokinetics[11]. Thus, an altered effect of the product due to anti-drug antibody formation might be a composite of pharmacokinetic, pharmacological and safety changes. Antibody formation can cause increased or decreased clearance of the therapeutic protein, although the former effect is the most common. The immunogenicity of a similar biological medicinal product must always be investigated. Normally, an antibody response in humans cannot be predicted from animal studies. The assessment of immunogenicity requires an optimal antibody testing strategy, characterization of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects. It is important to consider the risk of immunogenicity in different therapeutic indications separately. The applicant should present a rationale for the proposed antibody testing strategy. Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies. An assay for neutralizing antibodies should be available for further characterization of antibodies detected by the screening assays. Standard methods and international standards should be used whenever possible. The possible interference of the circulating antigen with the antibody assays should be taken into account. The periodicity and timing of sampling for testing of antibodies should be justified. In view of the unpredictability of the onset and incidence of immunogenicity, long term

results of monitoring of antibodies at predetermined intervals will be required. In case of chronic administration, one-year follow up data will be required pre-licensing. The applicant should consider the possibility of antibodies to process related impurities.

Evaluation of the Clinical Significance of the Observed Immune Response[17]

If a different immune response to the product is observed as compared to the innovator product, further analyses to characterize the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required. Special consideration should be given to those products where there is a chance that the immune response could seriously affect the endogenous protein and its unique biological function. Antibody testing should be considered as part of all clinical trials protocols. The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. The sponsor needs to discuss possibilities to encourage the reporting of relevant adverse events, including events related to loss of efficacy.

iv) Pharmacovigilance Studies

As ever, a rigorous pharmacovigilance plan is required. For every new medicine, including biosimilar medicines, a Risk Management Plan (RMP) must be submitted[8]. The RMP describes what is known about the safety of the medicine and outlines how the manufacturer will further monitor and fill any gaps in knowledge as well as any measures needed to minimize any risk from the medicine. Attention should be paid to immunogenicity and potential rare serious adverse events, especially in patients undergoing chronic administration.[30]

IDENTIFICATION OF POTENTIAL PROBLEMS WITH BIOSIMILARS

There are 4 major points to consider about biosimilars, i.e. safety, automatic substitution, naming and labeling/prescription rules[4].

i) Safety

By definition, biosimilars will only be similar but not identical to the product they seek to copy. In biotechnological medicine, each product has a unique safety profile dependent on its mechanism of action, unique manufacturing process, and composition (including byproducts and impurities)[11]. The best example to illustrate that the safety profile of the biosimilar will not be identical to that of the reference product is that the recently approved biosimilar growth hormone Valtropin® has different precautions and warnings than its reference product Humatrope. This is a likely consequence of the different cell lines used to produce both drugs [yeasts in the case of Valtropin and Escherichia coli in the case of Humatrope®[20]].

Immunogenicity is the unique safety issue of biotechnological medicines[20]. All therapeutic proteins have the potential to induce antibody responses. Such a response may include both an initial response to therapeutic protein and later a broad response including endogenous proteins. In many cases, no clinical consequences are found but in rare cases an antibody-related reaction can be serious and even life threatening. Unfortunately, the immunogenicity of biosimilars cannot be fully predicted using preclinical or non-human studies. For this reason clinical immunogenicity studies are required before approval, however robust pharmacovigilance still remains a critical part of the process. There are various potential consequences of immunogenicity such as loss or enhancement of efficacy, neutralization of a native protein and general immune effects (allergy, anaphylaxis, and serum sickness). The complication of epoetin therapy, i.e. Pure red cell aplasia (PRCA), well known to nephrologists, was caused by the production of neutralizing antibodies directed against recombinant erythropoietin. This complication was manifested by severe epoetin resistant anemia, which required blood transfusions, immunosuppressive treatment and eventually kidney transplantation. The story of PRCA was very instructive not only for nephrologists as its outbreak occurred more than 10 years after the introduction of epoetins on the market and was most likely caused by only a subtle change in the manufacturing process[20]. Taking into consideration the complexity of the action of therapeutic proteins and the fact that most of them are relatively new drugs, it is likely that we are not yet aware of all complications of their use (especially those that may develop after a long term treatment). As mentioned before, to minimize the risk of such unexpected reactions an appropriate pharmacovigilance is mandatory. The issue of pharmacovigilance is not unique to biosimilars but without any doubt it has been highlighted and exaggerated by their arrival. Pharmacovigilance should ensure the traceability of the products. Companies and regulatory agencies shoulddistinguish one manufacturer's product from another. This is complex if biosimilars have the same International Non-proprietary Name (INN) as the innovator. Also adverse event reports are often incomplete. This holds especially true in cases of an automatic substitution. Uncontrolled substitution will confound accurate pharmacovigilance although it is obvious that occasional changes are inevitable or necessary in chronic therapy.

ii) Substitutability of biosimilars (Automatic Substitution)

The term biogeneric is not in favor with regulators since generic implies a product that has proven bioequivalence with an originator drug. Even the generic industry now accepts that this is not quite possible for biologics; instead, regulators on both sides of the Atlantic talk about proving a high degree of "similarity." Hence the term biosimilar! This is the official name given

in the EU pharmaceutical directives. The United States, having no defined regulatory path for these products, has no firm terminology. The FDA currently talks about "follow-on biologics" or "follow-on protein products" [21,22].

An approval path exists in the EU, and this is a major achievement, but biosimilars may struggle to gain acceptance and, most of all, the right to substitution[21]. According to the European Generic Medicine Association (EGA), Europe's health care systems are eager for the cost relief that biosimilar products could bring. Originator biological medicines currently account for 7 of the top 10 injectable medicines and treat conditions like diabetes and renal failure. They cost from 10,000 to 100,000 euros per person per year, while the initial pricing approvals for the first biogenerics were 20–30% below the price of the reference product[25]. Only six products (somatropin, interferon alpha, interferon beta, insulin, erythropoietin, and granulocyte-colony stimulating factor [G-CSF]) are currently susceptible to biosimilar competition in Europe, owing to patent expiration, but this first wave of products could generate savings of around 2–3 billion per year[26]. The most commonly prescribed LMWH (Low Molecular Weight Heparin) in both the United States and Europe is enoxaparin, being on the market for 12 years with global sales of 1,904 million (US$2,368 million) in 2004[27]. A huge cost saving could be attained only if biosimilar products are considered substitutable for the originators.

As effectively summarized by the title of an article published in Nature: how similar do "biosimilars" need to be[28]. How similar do they need to be in order to be considered not only equivalent but also substitutable for filling of prescriptions, a hallmark of generic drug approvals? The debate on biosimilar substitutability is still open as is the somehow related debate on whether the current INN system for medicines should be revised, to assign each biological product a distinct INN. The biosimilar industry has been advocating that a biosimilar product, with proven biosimilarity, should be entitled to the same INN as its reference product. On the other hand, the innovative industry has claimed that a distinct INN should be assigned to biosimilars, especially for the sake of traceability and pharmacovigilance[13]. The INN system was established by the World Health Organization (WHO) in 1953 to "provide health professionals with a unique and universally accepted available designated name to identify each pharmaceutical substance." The current understanding within the WHO, the European Commission, and the EMA is that the rules of the INN naming system should remain international, science-based rules. The same scientific rules should apply to all products, be they innovative products or biosimilars. The INN nomenclature should not be used to distinguish between biosimilars and other types of products.

Substitutability is considered to be beyond the scope of the existing EMA guidelines on biosimilars and a recent document, "Questions and Answers on Biosimilar Medicines," issued by the EMA states that "biosimilar and biological reference medicines are used in general at the same dose to treat the same disease. 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"[29]. The positive CHMP (The Committee for Medicinal Products for Human Use) scientific opinions on the three medicinal products biosimilar to epoetin alpha (the INN of one of them is followed by the company name), on the other hand, demonstrate that the same INN as that allocated to the reference product could be allocated to more complex biosimilar medicines.

iii) Naming

The WHO INN system aims at identifying every medicinal product. This system is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.

The INN medicinal products

The generic versions of chemical medicines are assigned the same name, as they are identical copies of the reference product. The WHO is currently deciding whether biosimilars should be assigned a different INN to that of the original biotechnological medicine[23].

iv) Labeling

From all that is written above it is clear that labels of originator and biosimilar products should be different. Physicians, pharmacists and patients should be aware of the clinical data available to support an introduction of a medicine to therapy[24]. A summary of product characteristics should be transparent and clear. Reference products should be defined. Also data for approval should be described. Furthermore unique safety data should be included and substitution advice should be provided.

CONCLUSION

The development of biosimilars is far more complicated than for conventional generic agents, and consequently their approval is likely to require much more than the demonstration of pharmacokinetic bioequivalence. In the post-PRCA era, the immunogenicity of recombinant therapeutic proteins has become a major safety concern. The situation is complicated further by the complexities of manufacturing and establishing standard process parameters, testing for

quality assurance, and packaging and distribution. Unlike generic pharmaceuticals, biosimilars are not identical to their originator products. The highly unpredictable nature of immune responses against biopharmaceuticals urges the appropriate testing of biosimilars based on sound scientific rationale and rigorous experimental evidence. The extent of biosimilar entry into the healthcare market as alternative therapeutic options remains open to speculation. Physicians, pharmacists, health care fund holders and patients will need to balance possible cost savings of biosimilar medications verses the risk of iatrogenic complications.

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