Drug safety 3

Safety and efficacy of biosimilars in oncology

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Biosimilars are considered to be one of the solutions to combat the substantially increasing costs of cancer treatment, and its imminent introduction is expected to expand affordability worldwide. However, biosimilar monoclonal antibodies provide many challenges compared with first-generation biosimilars, growth factors, and hormones, because they have shown only a modest clinical effect, and are often used in combination with other more toxic therapies, making it difficult to design studies that allow appropriate efficacy and safety assessments compared with the original products. The value of comparative clinical trials for showing clinical equivalence of biosimilars that demonstrate a high degree of similarity in physical, chemical, structural, and biological characteristics with the original product is increasingly being questioned, and advances in analytical methods that provide robust non-clinical data might reduce the need for extensive clinical comparisons. In this Series paper, the third of three papers on drug safety in oncology, we review the safety and efficacy of biosimilars in oncology, assessing biosimilar monoclonal antibodies in relation to first-generation biosimilars, the issues surrounding interchangeability and extrapolation of biosimilars to other disease and patient indications, and reassessing the safety approval pathway in light of 10 years worth of biosimilar experience.

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This is the third in a Series of three papers about drug safety

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Introduction

The term biosimilars was first introduced in 2006 in the European Union (EU) to describe biological medicines developed as copies of innovative biologicals (or reference products) after expiry of their data protection and patents.[1] Biological medicines are derived from living cells, and consist of nucleic acids or proteins, or both. Most biologicals in clinical use are proteins consisting of aminoacids and often glycan structures. For the production of non-glycosylated proteins, microbial host cells such as *Escherichia coli* are commonly used, whereas mammalian cells such as CHO cells are used for the production of glycoproteins.[2]

Glycosylation is the main cause of heterogeneity among therapeutic proteins such as monoclonal antibodies, the main class of biopharmaceuticals. Heterogeneity not only reflects the natural variation of these molecules, but also reflects the heterogeneity of the production process.[3] This heterogeneity contributes to the batch-to-batch variation that is typical in the manufacture of biologicals. Impurities and product modification derived from host cells, such as deamidation, oxidation, and aggregation, during production and storage, add to batch variations. Characteristics of biopharmaceuticals also show a change over time as their manufacturers improve their production methods during the lifecycle of the product.[4]

The classic generic approach for the authorisation of copies of small-molecule drugs is impossible to use.[5] A generic drug is authorised if it is shown to be chemically identical to the original drug and bioequivalent by comparing pharmacokinetics. However, heterogeneity and batch-to-batch variation make it impossible to show one biological medicine to be structurally identical to another.

The European Medicines Agency (EMA) was the first regulatory agency to issue a comprehensive set of regulations[6] for the marketing authorisation of biosimilars. In contrast to generics, biosimilar regulations require comparative preclinical and clinical data because of uncertainties regarding the level of characterisation achievable, and the possible clinical consequences of differences in physical–chemical characteristics, such as amount of impurities.[7]

Additionally, comparative immunogenicity data are required, because immunogenicity is considered the most important safety concern with biologicals in the EMA regulations. This emphasis on immunogenicity was based on a major incident[8] with an epoetin in Europe at the time when the necessity for an EMA biosimilar regulatory pathway was discussed. A reformulation by the originator company of an epoetin alpha, requested by the European regulatory authorities, caused the induction of neutralising antibodies.[8] These antibodies cross-reacted with endogenous erythropoietin, resulting in aplasia of pure red cells in more than 200 patients through a blockade in red blood cell differentiation. This incident is still often used as an argument for the need of clinical trials to test biosimilars, because the safety and efficacy of biologicals are assumed to not be predictable from physical–chemical characterisation alone.[9,10]

In this Series paper, we investigate whether there is a genuine need for comparative clinical data to assess similarity in the efficacy and safety of biosimilars. The emphasis will be on biosimilars in oncology, because filgrastim and epoetins were among the first generation of biosimilars marketed for approval. Furthermore, as anticancer biosimilar monoclonal antibodies are expected to enter the market soon, they will pose new challenges for showing similarity in safety and efficacy compared with the original products. Moreover, their modest clinical efficacy, insufficient pharmacodynamic markers, and their common use in combination therapies, complicate the design of clinical trials and analysis of their results.[11]

First-generation biosimilars

The regulatory pathway for biosimilars introduced in Europe a decade ago has been the example for other regulatory bodies, including the US Food and Drug Administration (FDA) and WHO, in the regulation of biosimilars. WHO's guideline is the standard for developing countries where many are introducing regulatory pathways for biologicals and biosimilars on the basis of European principles.[12]

Biosimilar development started as an activity by a few companies introducing relatively simple molecules such as growth hormones, epoetins, and filgrastims in the EU and other markets in developed countries. However, the number of manufacturers developing biosimilars has expanded in the past decade.[13] Many biotechnology companies are active in this field, especially in upcoming economies in Asia and Latin America, and most of the established multinational pharmaceutical companies have their own biosimilar programmes, often in collaboration with biotechnology companies in Asia.[13] As a result, the number of biosimilars being introduced worldwide is increasing.[13]

Researchers at Hexal—based in Holzkirchen, Germany, with its parent company Sandoz, which is itself a subsidiary of Novartis (Basel, Switzerland)—pioneered the current approach in developing a biosimilar. The approach has two phases: in phase 1, the process to produce a highly similar product is developed;[14] and in phase 2, the similarity is shown in preclinical models and clinical trials. The first important step in phase 1 is to analyse the reference biological product in depth, not only regarding its physical–chemical characteristics but also its biological activities.[14] These analyses include multiple batches of the reference biological product, sampled sometimes for several years. This detailed analysis shows the extent of heterogeneity, which is the most specific attribute of biologicals, the variation between batches, and also how the reference product has changed over time. All these analyses establish the range of biological and structural properties that the biosimilar candidate needs to meet. Next, a manufacturing process is developed to produce a highly similar molecule.[14] This starts with transforming host cells by introducing the gene coding for the identical sequence of the reference product. In the case of monoclonal antibodies, the host cells will be mammalian cells. The transformed cells are selected on the basis of quality of production of the desired protein, stability of production, and whether the product has the right biological and structural properties. Then the large-scale production conditions and the methods to isolate, purify, and concentrate the final product from the culture media are developed. State-of-the-art and highly sensitive analytical tools are used to monitor whether the product meets the specifications set by the analysis of the reference product. The manufacturing process is optimised by a highly iterative method, meaning that the process is adapted on the basis of the findings of the analytical tools (physical and chemical among others) until the product has the same molecular structure as the originator product.[15]

After a highly similar product is established, similarity needs to be shown in non-clinical (mainly biological) and clinical studies. Design of these studies is often made in consultation with regulatory bodies such as the EMA or FDA. These agencies follow the principle that the higher the level of similarity in structural and in in-vitro characteristics, the less clinical evidence is needed to show clinical similarity.[16,17] Regulatory agencies consider that the knowledge generated by connecting and integrating data from all methods is much greater than the sum of the data generated by individual methods, referred to as the totality of evidence. Although clinical trials are needed for biosimilar approval, the purpose is to show similarity to the reference product and not to show safety and efficacy in all indications, because these indications have already been shown for the reference product.[18]

Biosimilars in oncology

Since 2006, more than 20 biosimilar products have been introduced in the EU.[19] Filgrastim and epoetin alpha biosimilars, used as supportive therapy in oncology, were among the first, and there is now a decade of experience with these products. Moreover, biosimilars in the EU are, for the great majority, hormones and growth factors intended for substitution therapy. They were developed as copies of the original products that were themselves copies, or better biosimilars, of natural proteins. Thus, the biosimilar approach was highly likely to succeed with these first biosimilars.

Most biosimilars introduced in the near future will be monoclonal antibodies, especially for the treatment of cancer, for which the costs have been increasing substantially during the past years, but also for chronic inflammatory diseases. The potential health effect of more affordable alternative products is therefore high.[20] Biosimilar monoclonal antibodies, which are often disease modifying, also provide some additional challenges compared with first-generation biosimilars, which are used for substitution—either switching to a biosimilar after the patient has started with the reference product, or substitution of the biosimilar for the reference product by the pharmacy from the outset—and exert general and physiological functions. For some anticancer monoclonal antibodies with only a modest clinical effect, showing clinical bioequivalence is complicated. Anticancer monoclonal antibodies are often used in combination with other more toxic therapies, making it difficult to design studies that allow the identification of differences in safety that—if they exist—will be minor. Even in the case of monoclonal antibodies that have shown efficacy as monotherapies, such as trastuzumab or rituximab, these agents are used more commonly in combination with chemotherapy

backbones, complicating the decision with regard to the most appropriate indication and patient population in which to perform trials to show biosimilarity.[21–23] Other monoclonal antibodies have very diverse indications, making extrapolation of their safety and efficacy to other indications challenging.

There is no scientific definition of a biosimilar. It is a regulatory designation and therefore the future availability of biosimilars in oncology is dependent on agencies such as the EMA and FDA. They define a biosimilar as a biological medicine that is similar in quality, safety, and efficacy to a product already on the market in their territories. However, the EMA and many other regulatory agencies are moving away from double-blind equivalence trials and large post-marketing safety studies as the standard to show clinical similarity because regulatory agencies are realising that comparative clinical trials are not sensitive enough to show possible differences in safety and efficacy.[24,25] Therefore, there is now increasing emphasis on physical–chemical characterisation and on in-vitro biological assays to show similarity between the biosimilar and the reference product.

Safety of biosimilars in oncology

Oncology biosimilars will be mainly disease-modifying monoclonal antibodies for which the current regulatory approach is either impossible or too expensive. This regulatory approach is a modification of the generic pathway for small molecules, adapted to the more complex and heterogeneous characteristics of biologicals. When considering how to assess the safety of biosimilars, it is important to realise the specific characteristics of biologicals. Biopharmaceuticals are generally safe drugs, mostly acting extracellularly by binding to a specific ligand or receptor on the cell membrane. They are either excreted or catabolised, or both, into aminoacids, sugars, and other natural products, and recycled. Unlike small molecules that enter cells and sometimes interfere with internal metabolism, biologicals do not exert such toxic effects. Instead, systemic adverse effects of biopharmaceuticals are most often the pharmacodynamic effects of the drug, and are therefore closely related to the potency of the biopharmaceutical.[26,27]

Biopharmaceuticals are generally injected, and skin reactions are the most frequent side-effect. These reactions are typically mild and non-specific. Some reactions are caused by the formulation or, rarely, by pharmacological and immunological effects.[28] Immunogenicity is considered the main safety issue for biopharmaceuticals.[29] Nearly all biopharmaceutical products are immunogenic. Although many factors modulate the immune response, the primary causes are product related. Besides the intrinsic immunogenicity of the protein, product-associated factors, such as aggregations and host-cell proteins, are responsible for the immunogenicity. Because the intrinsic immunogenicity between the biosimilar and the original product will be identical, differences in immunogenicity can result only from differences in physical–chemical charateristics. In other words, if there are no relevant differences in physical–chemical characteristics, the probability of differences in immunogenicity between the biosimilar and the original product is low.[30,31]

Immunogenicity generally leads to a transient and low concentration of binding antibodies with no clinical consequences. Sometimes persistant and high concentrations of neutralising antibodies inhibit efficacy; this effect is seen mainly with monoclonal antibodies, not receptor constructs.[32] With some monoclonal antibodies, association between infusion reactions and immunogenicity is high.[33] In rare cases, biologicals induce antibodies that cross-neutralise an endogenous factor with serious clinical consequences, as discussed in the case of epoetin. So, unless there is no alternative treatment, and the use of the reference drug is associated with infusion reactions or induced antibodies that might cross-react with an essential physiological factor, there is no reason for a post-marketing commitment for immunogenicity studies if there is no relevant difference in quality between the biosimilar and the original.

Efficacy and safety are reflections of the product's potency. If the biosimilar has the same potency as the original, it can be assumed to be clinically equivalent to the original. For some products for which no validated in-vitro assay or preclinical model is available, comparative human data might be necessary. A comparative dose response in vitro or in vivo is also much more sensitive to detect clinically relevant differences than a clinical study with a clinical endpoint at a dose that is in the linear part of a dose–response curve.

Naming, substitution, interchangeability, and extrapolation

The regulatory pathway for biosimilars is a modification of the generic pathway for chemically synthesised small molecules. When authorised, the generic is considered identical with the original product, is designated with the same international non-proprietary name (INN) as the original product, is considered completely interchangeable, and can be substituted with the originator product. However, the consequences of biosimilarity for naming, extrapolation, interchangeability, and substitution are less straightforward, and are important issues for the safety of biosimilars.

Originator companies are advocating for distinctive INNs for biosimilars for reasons of traceability in case of safety problems with a biosimilar. However, some experts see this as a strategy to frame biosimilars as different and risky.[34] In reality, incidents with marketed biopharmaceuticals are extremely rare, and for many years different innovative biopharmaceuticals with

identical INNs (eg, insulin, somatotropin, interferon β-1a) have been used without issue. Furthermore, traceability has proven complicated even in situations in which the products involved had separate INNs. In general, safety issues with biopharmaceuticals are batch related. Therefore, registering the batch applied to an individual patient by the barcode on the packages of the products is preferred.

Some technical issues hamper the use of the INN system for biosimilars. An INN is only issued by WHO on request, so there is no legal basis to force a biosimilar manufacturer to use a different INN. An INN is given to a defined chemical structure. Biopharmaceuticals are always mixtures of process-related or naturally occurring variants showing batch-to-batch variation, making it impossible to describe a biological product as a single chemical structure.

Although interchangeability and substitution are closely linked, they have different meanings.[35] Interchangeability is a property of a product and a condition for substitution, which mostly refers to automatic substitution at the dispensing level without the physician's knowledge or consent. In many European countries, there are rules against this type of substitution to avoid difficulties in traceability in case of product-related adverse effects.[36] The EMA avoids any ruling on the interchangeability of biosimilars because of the close link to substitution, which is a national responsibility in EU countries. However, various national regulatory agencies in the EU have declared biosimilars interchangeable.[37] The FDA expects manufacturers to submit data for the interchangeability of their biosimilar as a condition to consider the product as interchangeable, and the evidentiary bar is expected to be higher than that required for regular biosimilar authorisation. Opponents of interchangeability and automatic substitution believe the burden of evidence should be on the manufacturer to provide further data for efficacy and safety, rather than relying on the absence of evidence of differences compared with the reference product. However, there is no scientific evidence for any possible biological or clinical adverse effect caused by switching a patient from an original product to its biosimilar. Although biosimilars have been used for roughly a decade in the EU, not a single adverse effect has been reported related to switching.[38]

As more biosimilars enter the market, there is a theoretical and unkown risk associated with repeated switching between several similar biological products with subtle differences in glycosylation or other post-translational modifications, and this risk remains a concern for some clinicians. One argument against this potential concern is the natural effect of molecular drift in the reference product itself over time due to evolutionary changes in the manufacturing processes.[4] In this regard, many of the reference biologicals on the market today would technically be considered similar to the product when it was initially approved, yet this has never been shown to cause a safety problem (with the exception of the reformulation of epoetin alpha, which involved a major manufacturing change by the originator company).

Nevertheless, regulatory agencies need to respect the concerns of clinicians and their patients with regard to physician control, rather than pharmacy control, over the specific biological product administered. In this regard, the designation of interchangeability, which should be inherent in the designation of biosimilarity unless there are scientific reasons to believe otherwise, does not obviate incorporation of physician notification if the pharmacy plans to substitute a biosimilar product, and adoption of such a strategy might help to alleviate some of the concerns in the community.

The regulatory pathway for biosimilars is intended to offer an abridged procedure for developing biopharmaceuticals to allow efficient development and reduced pricing. Extrapolation of safety and efficacy between indication populations is a way to simplify the development process and truncate requests for marketing authorisation. Without possibility for extrapolation, there is no incentive to develop a biosimilar.[39] Most regulatory authorities agree that biosimilars do not need to show safety and efficacy for every indication as the reference product. They allow extrapolation but it needs to be justified scientifically. Considering this scientific justification for extrapolation, regulators have emphasised that the indications tested and extrapolated should have comparable patient populations, that the pathogenesis of the two diseases should be similar, and biologicals should have the same mode of action or receptor interaction, or both in each indication. In theory, there might be a scientific rationale to believe that the mechanism of action of the biological might differ between disease states, or that patient populations might differ in a clinically meaningful way that could affect sensitivity to treatment, or that extrapolation might not be feasible, and additional trials might be required; however, current regulatory processes appear to accept the present situation.[40]

CT-P13: the first biosimilar monoclonal antibody

In 2014, the infliximab biosimilar CT-P13 became the first biosimilar monoclonal antibody to be approved by the EMA.[41] Infliximab is a tumour necrosis factor inhibitor, a class of drugs for which other biosimilars are in the pipeline. Pivotal clinical trials were done in patients with a rheumatological disease, and the European regulators of the EMA allowed extensive extrapolation to other indications.[42,43] This product has been introduced in various European countries. In some countries, the discount has been up to 70% from the original product and the biosimilar has completely replaced the orginal product in the market.[44,45] The assessment of CT-P13 by the EMA is revealing because it shows the increasing confidence of the regulators in

using physical–chemical characterisation and (in vitro) pharmacodynamic markers to show clinical similarity between the biosimilar and the reference product.

Many immune-mediated inflammatory diseases, such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel diseases, are mediated in part by the cytokine tumour necrosis factor. Although the pathogenetic details are probably distinct, tumour necrosis factor appears to constitute a common final pathway in all these disorders.[46,47] Indeed, with the approval of tumour necrosis factor inhibitors for Crohn's disease and rheumatoid arthritis more than 15 years ago, these types of drugs were the first biologicals ever licensed for inflammatory diseases mediated by the immune system. Since then, in view of the multiple indications and their price, blockers of tumour necrosis factor, such as adalimumab, etanercept, and infliximab, have become top selling drugs for many years,[48] with certolizumab pegol and golimumab being recent additions.[49]

Preclinical assessments of CT-P13 provided sufficient evidence that this new agent indeed fulfils the criteria of biosimilarity in all respects—namely, that it is within the range of the originator product's variability in structural, physicochemical, and immunological properties.[50] The randomised controlled clinical trials of CT-P13 provided convincing evidence of biosimilarity in terms of efficacy, safety, and immunogenicity for rheumatoid arthritis and ankylosing spondylitis,[51,52] and for other infliximab and etanercept biosimilars.[53,54]

In line with its general regulations on biosimilars, CT-P13 was approved by the EMA not only for the treatment of rheumatoid arthritis and ankylosing spondylitis, but also for all other indications for which the originator infliximab is licensed. This extrapolation of indications elicited opposition from the inflammatory bowel disease community,[55] which was rejected by the EMA.[40] Indeed, arguments from the European Crohn's and Colitis Organisation are debatable because they were based, to a large extent, on some differences in antibody-mediated cellular cytotoxicity between the originator and biosimilar agent. Meanwhile, it is not evident that the European Crohn's and Colitis Organisation had available cytotoxicity data for all batch variants of the originator products; nevertheless, these batch variants were used consistently for many years, possibly even without knowledge of every variation. Moreover, all monoclonal antibodies against tumour necrosis factor are approved for Crohn's disease or ulcerative colitis, or both, in Europe and the USA, despite differences in cellular cytotoxicity mediated by the antibody. The receptor construct etanercept is not sufficiently efficacious in inflammatory bowel disease and therefore is not approved for this indication.

For some agents, the variability between batches can be quite large,[4,32] whereas for other products it can be quite low,[56] and a biosimilar product would have to fall within this respective range to determine biosimilarity. Indeed, it would be of interest to the medical community if companies would publish the results on the batch-to-batch variations of their originator products on a regular basis, rather than having to learn about these variations from those manufacturers developing biosimilars.

In 2016, two other biosimilars were approved by the EMA: a further infliximab biosimilar monoclonal antibody, SB2 (approved in April, with same disease indications as infliximab—ie, ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis),[53] and a biosimilar tumour necrosis factor receptor construct for etanercept, SB4 (approved in January for adults with moderate to severe rheumatoid arthritis, psoriatic arthritis, non-radiographic axial spondyloarthritis, and plaque psoriasis).[54]

Biosimilar monoclonal antibodies in oncology

The approval of biosimilar monoclonal antibodies for inflammatory diseases that are mediated by the immune system heralds their inevitable introduction into the field of oncology, in which several therapeutic monoclonal antibodies are facing patent expiry in the near future. In this regard, a proposed biosimilar of the HER2-targeted monoclonal antibody trastuzumab, Myl-1401O, is in late-phase clinical development. Results were recently reported from the phase 3 HERITAGE trial that compared Myl-1401O versus trastuzumab in combination with a taxane, in 500 patients with HER2-positive metastatic breast cancer receiving first-line treatment.[57] The primary endpoint, overall response rate, at week 24 was equivalent between groups (70% for Myl-1401O *vs* 64% for trastuzumab), and the hazard ratio (1·09) was within the predefined equivalence margin. Safety was also comparable between groups, and no significant change in cardiac function from baseline to week 24 was detected. Several other proposed trastuzumab biosimilars have completed pharmacokinetic analyses, and have moved, or will be moving, into comparative clinical trials.[58–62] Although there are questions regarding whether response is the most appropriate and sufficient endpoint to measure similarity between a biosimilar and a therapeutic agent with a demonstrated survival advantage, clinical testing for trastuzumab biosimilars is rapidly moving forward. It is most likely that one of these molecules will be the first biosimilar monoclonal antibody to gain regulatory approval for use in the treatment of cancer. Several proposed biosimilars of the anti-CD20 monoclonal antibody rituximab are also in clinical development.[63]

Discussion

Following the lead of the EMA, the recent recommendation by the FDA Arthiritis Advisory Committee for the approval of CT-P13 to include all indications of infliximab

further illustrates the increasing confidence of regulatory agencies in biosimilar safety. The FDA briefing document noted that the assessment of biosimilarity rests on the totality of evidence, and indicated that the data provided were sufficient to address the scientific considerations needed to justify extrapolation to other conditions for which infliximab is approved, beyond rheumatoid arthritis and ankylosing spondylitis in which clinical trials have been done.[64] The fact that CT-P13 is a therapeutic antibody, rather than a small-molecule hormone or growth factor, and will be used in the fields of arthritis and gastroenterology, rather than oncology, further underscores this growing confidence in biosimilar safety by regulatory agencies.

The EMA and FDA guidelines advocate similar progressive step-wise approaches to the identification of biosimilarity that can be tailored to each individual candidate.[16,17,64] The first step involves comprehensive characterisation of the physicochemical and biological parameters of the candidate biosimilar compared with the reference product using the most appropriate and relevant in-vitro assays. The requirement for subsequent non-clinical and clinical studies can then be tailored on the basis of remaining uncertainties, which might depend on the degree of similarity observed in previous steps and the extensiveness of known characteristics of the reference product. In other words, the more that is known about the reference product regarding structure, mechanisms of action, pharmacokinetic, and pharmacodynamic markers, the greater the chance that non-clinical studies and pharmacokincetic or pharmacodynamic analyses can sufficiently demonstrate comparability. Thus, robust non-clinical data might reduce the requirement for extensive (and expensive) clinical comparability studies.

Potential savings in cost and time associated with the manufacture of biosimilars derive from the ability to build on the foundational discovery and development efforts performed for the reference product and the assessment of its variations, not from reduced concern for efficacy and safety that could undermine patient care. The process leading to approval of a candidate biosimilar is rigorous, requiring clinical investigation in the most sensitive patient populations and strong scientific justification to support extrapolation to other indications. To demand confirmatory trials in all possible indications would waste valuable patient, staff, and monetary resources for no substantial gain, and such requirements should be avoided unless extrapolation cannot be justified on the basis of mechanism of action and existing data. There needs to be wider recognition that the use of clinical comparability studies to assess efficacy with therapeutic antibodies is complicated, with limited sensitivity, and unlikely to detect minor differences in activity or adverse events. Further, advances in the development of more sensitive analytical methods will make the in vitro-characterisation more accurate and comprehensive, raising the possibility that eventually—at least in some cases—clinical confirmation might not even be necessary.

The greatest concern with biosimilars is their potential for immunogenicity. However, even in this regard, a common sense approach to testing is called for—the characterisation of immune responses does not need to be performed across every potential indication or patient population. Rather, immunogenicity should be assessed in settings in which the underlying immune response could be expected to vary, such as with the concomitant use of immunomodulatory drugs. With approximately 400 million patient days of experience with biosimilars in Europe, no serious safety signals have arisen to date.[65]

Conclusion

Current regulatory requirements for biosimilars were introduced at a time when some in the field were claiming it was impossible, if not outright dangerous, to introduce an abridged regulatory process to streamline the development and marketing approval of such molecules. However, more than 10 years of experience has now shown that these regulations have led to the introduction of 20 safe and effective biosimilars, with substantial associated cost savings. Further, these regulations have spurred an interest into the study of such issues as the effects of manufacturing changes and the natural drift in the molecular composition of reference biologicals, factors contributing to immunogenicity, the pros and cons of interchangeability, and technological advances for the characterisation of biologicals.

However, biosimilar developers still face barriers to entry, including development costs, particularly with regards to clinical trials. Other challenges include a regulatory emphasis on similarity rather than on safety and efficacy, coupled with an over-reliance on the use of comparative clinical trial data. Finally, current regulations define general scientific criteria for extrapolation or interchangeability, but might benefit from increased clarity to prevent the possibility of either being denied without sound scientific rationale.[40,66]

Biosimilars have the potential to substantially affect patient care by reducing costs and increasing the availability of therapeutic biological agents. This potential should provide further incentive to streamline regulatory processes and expedite approvals as long as efficacy, safety, and quality can be maintained. Perhaps the greatest hurdle to integrating biosimilars in the clinic will be the acceptance of biosimilars by physicians and patient consumers, particularly in health-care systems such as the USA where clinicians and patients retain more control over choice between available therapeutic agents, as opposed to health systems in Europe, where single-payer systems are used. Maintainence of transparency in the review process and balance of scientific rigour with efficiency will be essential to maximise end user confidence.

Search strategy and selection criteria

We did a systematic search with no specific date parameters of MEDLINE using the following terms: "biosimilars", "similarity", "bioequivalence", "immunogenicity", "biopharmaceuticals", "regulations", "substitution", "interchangeability", "extrapolation", and "biogenerics". We restricted our search to reports written in English, and selected peer-reviewed publications of clinical significance. We included other sources such as the EMA and FDA websites using the search terms "similar" and "biosimilar draft guidelines", as well as position papers, question and answers, and the Generics and Biosimilars Initiative website. We generated the final reference list on the basis of originality and relevance to the broad scope of this Series paper.

Contributors

RMR, HS, and JSS were responsible for the primary design of this manuscript, including identifying references, writing the preliminary drafts, collating co-author comments, and revising subsequent drafts. MD reviewed the manuscript and provided critical comments. All authors reviewed and approved the final submitted manuscript.

Declaration of interests

RMR has participated in advisory boards on biosimilars for Amgen, EMD Serono, Sandoz, Hospira, and Coherus, all outside the submitted work. HS has participated in advisory boards for Merck-Serono; has received lecture or travel fees, or both, from Chemo-Mabxience, Medigen, Mexican Organisation of Pharma Companies, Brazilian Organisation of Pharma Companies, and Libbs; and has received salary from WHO Utrecht Center for Affordable Pharmaceuticals, all outside the submitted work. JSS has received grants and personal fees from Abbvie, Lilly, Merck Sharp & Dohme, Pfizer, and Roche; and personal fees from Amgen, Astra, Astro, Celgene, Chugai, GlaxoSmithKline, ILTOO, Janssen, Novartis-Sandoz, Samsung, Sanofi, and UCB, all outside the submitted work. MD has received personal fees from Teva, Amgen, and Merck Sharp & Dohme, all outside the submitted work.

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