Biosimilars: the science of extrapolation

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Abstract

Despite the establishment of a specific approval pathway, the issuance of detailed scientific guidelines for the development of similar biological medicinal products (so-called ‘biosimilars’) and the approval of several biosimilars in the European Union, acceptance of biosimilars in the medical community continues to be low. This is especially true in therapeutic indications for which no specific clinical trials with the biosimilar have been performed and which have been licensed based on extrapolation of efficacy and safety data from other indications. This article addresses the concerns frequently raised in the medical community about the use of biosimilars in such ‘extrapolated’ indications, and explains the underlying scientific and regulatory decision making including some real-life examples from recently licensed biosimilars.
Introduction

Since the establishment of a specific approval pathway for similar biological medicinal products, so-called 'biosimilars', several biosimilars have been licensed and become available in the European Union (EU).\(^1\) However, despite a stringent approval process, acceptance of biosimilars in the medical community continues to be low. This appears especially true for therapeutic indications, for which no specific clinical trials with the biosimilar have been performed and which have been licensed based on extrapolation of efficacy and safety data from other indications.\(^{2-21}\)

Several learned societies have issued statements discouraging the use of biosimilars in such 'extrapolated' indications.\(^{13-20}\) The reasons for this distrust may be manifold. The frequently cited paradigm that biosimilars are “similar but not identical”, compared to the “identicality” principle of the more familiar small molecule generics, appears to be confusing and may leave physicians at unease about remaining uncertainties with respect to efficacy and/or safety of the biosimilar. In addition, clinicians tend to mainly look at clinical trial data to judge on efficacy and safety of a medicinal product, whereas the foundation of any biosimilar development is the extensive characterisation and comparison of structural and functional characteristics using state-of-the-art analytical tools. Inconsistent use of terminology and fears arising from problems reported on biologicals licensed in other regions of the world and erroneously called “biosimilars” may also contribute to the wrong perception that biosimilars in general may not be sufficiently studied and may not be safe.\(^{22}\) Finally, clinicians may just not be well informed about the scientific concept underlying the development and licensing of biosimilars.

This article specifically addresses the concerns raised about the use of biosimilars in 'extrapolated' indications and explains the underlying science and regulatory decision.
making including some real-life examples from recently licensed biosimilars. This article is an extension to a previous paper in which we explained the principles of biosimilar development in general. (21)

**The similar-but-not-identical paradigm**

Every biological displays a certain degree of variability (‘microheterogeneity’), even between different batches of the same product, which is due to the inherent variability of the biological expression system and the manufacturing process. Since biosimilar developers have to establish their own independent manufacturing process, the resulting biosimilar and the respective originator product, the reference product, can technically not be entirely “identical”. However, the variability of the biosimilar is not expected to be greater than that of the reference product and all critical quality attributes, i.e. those which are important for the function of the molecule, must be comparable. (23)

Any given biological medicinal product is likely to be modified several times throughout its life cycle. (24) It is fair to say that the current, widely used biologicals are not, after several changes to their original manufacturing process, anymore identical to the original version at the time of marketing authorisation. Nevertheless, thorough comparisons between the pre- and post-change product, the so-called comparability exercise, is required by the regulatory authorities to ensure that quality, efficacy and safety are not adversely affected. (25) Over the past decades of biotechnology developments, regulators have accumulated extensive experience in the assessment and judgement of such changes. Once approved, the new version is expected to have the same efficacy and safety in all therapeutic indications.
From a scientific and regulatory point of view, the active substance of the biosimilar is just another version of the active substance of the originator product. This is important to state since the same scientific principles that underlie the comparability exercise for the purpose of demonstrating similarity of a product before and after a change in manufacturing process also apply to the comparability exercise for the purpose of demonstrating biosimilarity.\(^{(26)}\) The cornerstone of any such comparability exercise is the extensive comparison of the physicochemical and functional characteristics of the molecules (e.g. molecular structure including glycosylation, receptor binding, biological activity) using up-to-date analytical tools.

**When can extrapolation of data be considered?**

Extrapolation of data is already an established scientific and regulatory principle that has been exercised for many years, for example, in the case of major changes in the manufacturing process of originator biologicals. In such cases, clinical data are typically generated in one indication and, taking into account the overall information gained from the comparability exercise, may then be extrapolated to the other indications. In fact, the authors are not aware of any case where additional clinical studies with the changed product in other or even all approved indications have been provided by the marketing authorisation holders, or have been considered necessary by regulators.

Another example where extrapolation has already been accepted is the introduction of a new subcutaneous (SC) formulation of a hitherto intravenously (IV) applied product. Although the formulation and bioavailability of the SC product will be different, one clinical study is usually sufficient to grant all clinical indications approved for the IV product. This is illustrated by the recent approval of a SC formulation of an anti-Her2 monoclonal antibody (mAb) based on clinical data in the
neoadjuvant setting, which were extrapolated to the metastatic setting based on the “totality-of-the-evidence” from all data provided. It is notable that the SC formulation of that antibody contains recombinant human hyaluronidase (rHuPH20) as a permeation enhancer and is thus considerably different from the IV formulation. A formulation difference of this magnitude would not be acceptable for a biosimilar compared to the reference product.

In the context of biosimilars, extrapolation of efficacy and safety data from one indication to another may be considered if biosimilarity to the reference product has been shown by a comprehensive comparability programme as described above and elsewhere, including safety, efficacy and immunogenicity in a key indication that is suitable to detect potentially clinically relevant differences. If the relevant mechanism of action of the active substance and the target receptor(s) involved in the tested and in the extrapolated indication(s) are the same, extrapolation is usually unproblematic. It is more difficult when the mode of action is complex and involves multiple receptors or binding sites, the contribution of which may differ between indications or may not be well known. In such cases, additional data (e.g. in vitro functional tests or in vivo pharmacodynamic studies reflecting the respective pharmacological action(s)) are necessary in order to provide further reassurance that the biosimilar and the reference product will behave alike, also in the extrapolated indications. Importantly, provided that structure and function(s), pharmacokinetic profiles and pharmacodynamic effect(s) and/or efficacy can be shown to be comparable for the biosimilar and the reference product, those adverse drug reactions which are related to exaggerated pharmacological effects can also be expected at similar frequencies. Immunogenicity, on the other hand, is related to multiple factors including the route of administration (e.g. SC vs. IV), treatment regimen (e.g. continuous vs. intermittent),
and patient-, disease- and treatment-related factors (e.g. immune status). Therefore, extrapolation of immunogenicity data is not self-evident and always requires convincing justification.

**Examples of extrapolation of data from biosimilars licensed in the EU**

Concerns have been expressed about using biosimilars in indications of the reference product that have not been formally investigated during the clinical development of the biosimilar and have been licensed on the basis of extrapolation of efficacy and safety data. (2-21) The following sections will therefore explain the scientific basis for extrapolation granted for some recently licensed biosimilars.

**Biosimilar filgrastim**

Filgrastim is approved for treatment of neutropenia of various aetiologies and for the mobilisation of peripheral blood progenitor cells in patients and healthy donors. Several biosimilar filgrastims have been licensed in the EU and, in all cases, all indications of the originator product were approved. (1)

Learned societies have specifically criticized the extrapolation of data to stem cell mobilisation and collection in healthy donors, and warned against the use of biosimilar filgrastim in this indication before the availability of data specifically confirming efficacy and safety in this population. (13-15) However, the following scientific arguments support the extrapolation granted by the Committee for Medicinal products for Human Use (CHMP).

- All licensed biosimilar filgrastims demonstrated a high level of similarity in molecular structure and biological activity with their reference products.
- Pharmacokinetic profiles were comparable ensuring equivalent exposure.
• All pharmacological actions of filgrastim are mediated via a single affinity class cell receptor. Therefore, comparable receptor binding as demonstrated for the biosimilar and the reference filgrastims is expected to result in comparable downstream effects, regardless of potential differences in target cell-specific intracellular signalling pathways, e.g. in hematopoietic progenitor cells vs. mature neutrophils.

• Comparable pharmacodynamic activities, which reflect clinical performance and include the effect on peripheral neutrophil cell count and CD34+ cells, were confirmed in healthy subjects and/or patients.

• The safety and immunogenicity profiles were found to be comparable to those of the reference product, in patients and in pharmacology studies in healthy subjects. It should be noted that immunogenicity is not a specific concern for filgrastim as anti-filgrastim antibodies are infrequent and have not been associated with relevant clinical effects. In addition, filgrastim is a very well characterisable, non-glycosylated molecule, and close similarity of the molecular structure together with absence of impurities or excipients of concern already provide substantial reassurance that the resulting product will not be associated with undue immunogenicity.

Unsurprisingly, postmarketing studies confirmed efficacy and safety of biosimilar filgrastim products in the approved indications including the mobilisation of stem cells in healthy donors. (29-34)

Biosimilar epoetin

Recombinant erythropoietin (epoetin) is approved, amongst others, for the treatment of renal anaemia and chemotherapy-induced anaemia. The major concern with
epoetins is immunogenicity, i.e. the rare development of neutralising, cross-reacting anti-epoetin antibodies which can cause pure red cell aplasia (PRCA). Product-related factors like aggregation and contaminants such as leachables from the rubber stopper or tungsten from the needle of syringes have been implicated in the development of anti-epoetin antibodies.\textsuperscript{(35,36)} Whether the glycosylation pattern itself may influence immunogenicity is unknown.

Although epoetins are heavily glycosylated and rather complex molecules, thorough characterisation is possible with state-of-the-art methods. To ensure the absence of clinically relevant differences, the EMA guideline for the development of biosimilar epoetins requires a large battery of functional and clinical studies, including at least one clinical trial in patients with renal anaemia who do not have major complications that may impair the response to epoetin.\textsuperscript{(37)} Potential differences in the efficacy of the biosimilar and reference epoetin are expected to be more readily revealed in these patients with deficiency in endogenous erythropoietin and a responsive bone marrow than in cancer patients on chemotherapy with reduced and more variable responsiveness to epoetin. Patients with renal anaemia are also more suitable to assess immunogenicity of epoetins since they present the population at risk of developing PRCA whereas, up to now, no PRCA cases have been observed in cancer patients.

Despite these considerations and the approval of the cancer indication for all biosimilar epoetins in the EU, the use of biosimilar epoetins in cancer patients has been questioned (personal communication MW), the main argument being the absence of safety data for the high doses required in cancer patients.

Again, there are sound scientific arguments supporting the extrapolation from the renal anaemia to the cancer indication.
• All licensed biosimilar epoetins exhibit the same amino acid sequence as their reference product and structural differences are confined to the microheterogeneous pattern of the molecule.

• Pharmacodynamic studies indicated comparable stimulation of reticulocytes.

• Clinical trials in patients with renal anaemia confirmed equivalent effects on haemoglobin (Hb) concentrations.

• The desired pharmacological effect of epoetin is mediated by a single cell receptor and the mechanism of action is the same in all approved indications.

• The observation of equivalent effects of the biosimilar and the reference epoetin on reticulocyte count and Hb values already provides considerable reassurance that adverse events that are related to exaggerated pharmacological effects can be expected at similar frequencies, also at the high doses used in oncology patients.

• No differences in the safety profile and anti-epoetin antibody response were detected between the biosimilar and their reference products. As indicated above, extrapolation of immunogenicity data is possible from the population at increased risk, here patients with renal anaemia, to the population at low risk, here cancer patients on chemotherapy.

Taking above considerations together, there should be no doubt that the licensed biosimilar epoetins will behave as the reference product in all indications granted and that specific attention is paid to proper immunogenicity assessment, which includes both pre-licensing immunogenicity studies and extensive post-marketing surveillance programmes. In fact, no specific efficacy or safety issues have been identified in clinical practice for biosimilar epoetins licensed in Europe.\(^{(38-40)}\) For some biosimilar
epoetins, additional studies in cancer patients have been performed. These studies were not requested by the authorities, and may have been performed by the sponsors to increase acceptance of their biosimilars by physicians and patients.

**Biosimilar infliximab**

Recently, the first biosimilar mAb, i.e. infliximab, was approved in the EU. \(^{(41)}\)

Indications of the originator product Remicade® include autoimmune arthritis of various aetiologies, psoriasis as well as inflammatory bowel diseases (IBD: Crohn’s disease and ulcerative colitis). While in the EU, like in Korea \(^{(42)}\) and Japan \(^{(43)}\), all indications of the reference product were licensed, extrapolation from autoimmune arthritis to IBD was not granted in Canada \(^{(44)}\).

The scientific literature suggests that the mechanism of action of infliximab is similar in the rheumatological indications and in psoriasis, namely binding to soluble and membrane-bound TNF\(\alpha\). However, the Fc-region of infliximab may be involved in other potential mechanisms (antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity) that have been suggested in the literature to play a role in IBD. Therefore, extrapolation between these indications is not self-evident, especially since a difference in an ADCC activity test was observed between the biosimilar and the reference infliximab. Nevertheless, the following arguments supported the extrapolation granted by the CHMP:

- Extensive analytical tests showed physicochemical and structural comparability except for a small difference in the proportion of afucosylated forms. This glycoform is associated with the binding affinity of the molecule to the Fc\(\gamma\)RIIIa receptor expressed on various immune cells. The biosimilar and the reference infliximab demonstrated comparable binding to complement
receptor and all types of Fc-receptors except for FcγRIIIa/b, translating into lower ADCC activity. However, this difference disappeared under more physiological conditions, e.g. when serum was added, questioning the clinical relevance of the observed difference in FcγRIIIa-binding. Of note, similar differences in ADCC and glycosylation have been observed as a result of changes in the manufacturing process of the original rituximab. No clinical studies were performed and no evidence of an altered efficacy or safety has emerged. (45)

- The main mode of action in all therapeutic indications is binding to the soluble and/or the membrane-bound TNFα. The binding of the test and reference products were comparable as were the functions mediated by transmembrane binding, including reverse signalling and apoptosis.

- The company applying for marketing authorisation performed supplementary tests showing similar inhibition of direct effects of TNFα on epithelial cells that play an important role in Crohn’s disease.

- Induction of regulatory macrophages is implicated as a mode of action of infliximab in IBD. The biosimilar and the reference medicine displayed a similar induction of regulatory macrophages;

- A large (250 patients) multiple-dose pharmacokinetic study in patients with ankylosing spondylitis demonstrated bioequivalence of the biosimilar and the reference product and also provided supportive evidence for comparable safety, efficacy and immunogenicity. Since pharmacokinetics of infliximab is known to be similar in the therapeutic indications, exposure to infliximab can
be expected to be the same from the biosimilar and the reference products also in patients with IBD. Both recommended doses of infliximab were tested;

- Finally, equivalent efficacy as well as comparable safety and immunogenicity was demonstrated in a sizeable (606 patients) randomised controlled clinical trial in rheumatoid arthritis.

Thus, the totality of evidence indicated similar efficacy and safety of the biosimilar and the reference product in all therapeutic indications of infliximab.

The extrapolation of indications for the infliximab biosimilars has recently been challenged by learned societies.\(^{16-20}\) They require specific evidence obtained in patients with IBD to establish efficacy and safety for this indication. Regulators have responded to this criticism.\(^{46}\) An additional comment from ECCO stated that the equivalence margin chosen for the efficacy trial in rheumatoid arthritis would be considered too large for a trial in IBD as several drugs have been approved with this difference relative to placebo.\(^{16}\) However, it is obvious that a 2% difference between biosimilar and reference products as shown in the clinical trials for the ACR20 response (outcome used in rheumatoid arthritis) and ASAS20 response (outcome used in ankylosing spondylitis) is not expected to be numerically the same across all indications based on their specific scores (e.g. PASI for psoriasis, CDAI for Crohn’s disease). The choice of comparability margins is specific to each indication and depends on the chosen outcome, the difference for this outcome between the reference product and placebo in historic trials, and clinical judgement.

**Outlook**

The marketing authorisation of the first biosimilar infliximab was very likely only the starting point for more biosimilar mAbs to come. Indeed, a recent analysis showed
that regulatory scientific advice for biosimilars is now most frequently requested for mAbs.\(^{(47)}\) Also haematologists and oncologists will face biosimilar mAbs like rituximab, trastuzumab, and others. Regulators are well aware that these specialists deal with serious and life-threatening diseases. Therefore, comparative clinical data are required to confirm the similarity established by physicochemical, structural and \textit{in vitro} functional analyses. For this purpose, the study population must be sensitive enough to detect and the chosen comparability margins tight enough to exclude clinically relevant differences. Fortunately, there is abundant scientific literature that allows for careful selection of appropriate comparability margins for virtually any endpoint and patient population. In addition, internationally recognized guidelines provide general guidance on how to design comparative trials and select appropriate comparability margins.\(^{(48,49)}\) Discussions are ongoing as regards the preferred “model” indications to best compare the clinical performance a biosimilar mAb and its reference product. For example, in scientific conferences and in recent literature it is discussed if, for biosimilar mAbs for breast cancer, neoadjuvant treatment should be favoured over the metastatic setting or if, for a biosimilar rituximab, extrapolation from a non-oncological indication (rheumatoid arthritis) to an oncological indication (lymphoma) should be allowed at all.\(^{(50,51)}\) While the latter appears challenging, extrapolation may indeed be possible, provided that all active moieties of the antibody molecule are rigorously tested and compared, and all mechanisms of action (which are, for example, different in the various lymphoma indications of rituximab) are established to be the same. Notably, virtually all biosimilar developments – irrespectively of whether or not they employ the model systems that are emerging in clinical literature – have been critically discussed with regulators within scientific advice procedures.
Regulators may have to assume an increasingly prominent role in explaining their evaluation of biosimilarity and decision making, e.g. with regard to extrapolation of safety and efficacy from one therapeutic indication to another. We are aware that, in some cases, regulators in different regions of the world may draw different conclusions when assessing benefits and risks of medicines, including biosimilars. \(^{(41,44)}\) So far, no biosimilars have been approved in the US and, therefore, any assumptions whether the FDA may grant extrapolation in this or other cases remain speculative. Both the FDA and the EMA guidelines highlight the totality-of-the-evidence approach for the demonstration of biosimilarity and the possibility of extrapolation of indications based on scientific justification. \(^{(26,28,52)}\)

As pointed out, extrapolation of indications is not a new concept; it is based on scientific principles that have evolved over decades and have just recently become the focus of heightened interest since the introduction of biosimilar products on the EU market. Much emphasis has been put on the mechanism of action in different indications. While it is acknowledged that binding of the biological to the same receptor may have different effects in different target cells depending on differences in intracellular signalling pathways, this situation is not considered an argument to request additional clinical studies. On the other hand, if different active sites of the biotherapeutic or different receptors of the target cells are involved in different therapeutic indications, or if the historical safety profile of the reference product differs qualitatively between the different therapeutic indications, additional data may have to be generated to justify the extrapolation of safety and efficacy data. The EMA guideline does not specifically mention “clinical data”.\(^{(28)}\) The underlying scientific consideration is that the mechanism of action is mediated by the functional moieties
of the molecule in a disease-specific manner, which can usually be characterized much more sensitively by suitable assays, if available, than in clinical studies.

A summary of the key principles and considerations important for extrapolation of data is provided in Table 1. The knowledge and understanding of these principles will be increasingly important for the expected introduction of biosimilar mAbs for cancer treatment since haematologists and oncologists may feel adamant to use a biosimilar version that has not demonstrated a survival benefit in a clinical trial \(^{(51)}\) not to mention a biosimilar that has not been investigated in cancer patients at all. Extrapolation between different stages (e.g. metastasized vs. localized) of the same cancer type or between different cancer indications may be perceived as challenging and even more so extrapolation between autoimmune and cancer indications. If such extrapolation is granted by regulators, the European Public Assessment Report (EPAR), which is available on the EMA website for every centrally licensed medicinal product in Europe, is expected to provide a comprehensive explanation of the scientific rationale for accepting the extrapolation.

**Conclusion**

Approval of indications based on extrapolation of data is neither a “bonus” granted by regulators to biosimilar developers, nor is it driven by economic considerations to decrease the cost of biosimilars; rather, extrapolation is a logical consequence of the biosimilar concept that has been successfully implemented in the EU. Extrapolation has already been exercised for many years with changes in the manufacturing process for originator biologicals, where often more than minor changes were observed \(^{(45)}\), and virtually all mAbs have been subject to several changes after authorisation \(^{(24)}\) – a fact that is not well known by clinicians and that is rarely explicitly communicated. Many of the recommendations and position papers
published by learned societies require absolute certainty which is impossible to reach in any drug development. The weighing of benefits and risks of a medicinal product at the time of approval will always include some uncertainty which, however, is much less for biosimilars than for new innovative products. Biosimilars have been on the European market for several years and have performed as expected in all licensed indications, including extrapolated indications. In our view, generation of redundant or merely “comforting” data should not be requested. Instead, extrapolation should be based on sound and objective scientific criteria.

Table 1 Summary of key principles for extrapolation of indications

| In case the reference product has more than one indication, the efficacy and safety of the biosimilar has to be scientifically justified or, if necessary, demonstrated separately for each of the claimed indications. |
| Factors to be considered for such justification: |
| • Clinical experience with the reference product; |
| • Mechanism(s) of action/active site(s) of the active substance in each indication (including its degree of certainty); |
| • Target receptors involved; |
| • Differences in the safety/immunogenicity profile between the therapeutic indications, including considerations on patient-related factors, such as co-morbidities, co-medication and immunological status, and disease-related factors, such as reactions related to the target cells, e.g. lysis of tumour cells; |
| • The degree to which the functional moieties of the molecule can be analytically characterized and compared; |
The extent of data required, and the regulatory decision on acceptance of extrapolation will, amongst other things, involve the following considerations:

- Totality of the evidence of biosimilarity derived from the comparability exercise (i.e., how close is the resemblance of physicochemical and functional characteristics of the biosimilar to the reference medicinal product);
- Potential remaining uncertainties, e.g. based on overly insensitive (or overly sensitive) analytical or functional assays;
- Acceptable clinical safety profile must have been established for the biosimilar;
- Increased immunogenicity of the biosimilar must have been reasonably excluded;
- Extrapolation of immunogenicity is only possible from high to low risk patient populations and clinical settings (e.g., from SC to IV route of administration or from immunocompetent to immunocompromised patients, but normally not vice versa);
- Additional tests or studies may be needed to further support extrapolation, which should, if available, preferably include relevant pharmacodynamic parameters and/or specific functional assays reflecting the pharmacological action(s) of the molecule; clinical studies using outcome endpoints are usually less sensitive to detect potential differences between the biosimilar and the reference product.

Glossary

**Biosimilar**: A biosimilar is a biological medicinal product that contains a (copy) version of the active substance of an already authorised original biological medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the
reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

**Extrapolation**: The regulatory and scientific process of granting a clinical indication to a medicine without own/new clinical efficacy and safety data to support that indication. Extrapolation has been widely exercised, for example, for originator biologicals after changes in their manufacturing process.

**Originator/original product**: A medicine which has been licensed on the basis of a full registration dossier consisting of quality, non-clinical and clinical data; each approved indication for use was granted on the basis of own efficacy and safety data.

**Reference product**: A reference product is used as the comparator in head-to-head comparability studies with the biosimilar product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a reference product.

**Comparability exercise**: Head-to-head comparison of two versions of a biological medicine with the goal to establish similar quality, safety, and efficacy. It is used to compare, for example, a post-change product with the pre-change version when the manufacturing process is changed, or a biosimilar with its reference medicine.

**Totality of (the) evidence**: A scientific principle that, in the context of biosimilars, establishes biosimilarity by employing an extensive set of decisive methods, sensitive enough to detect relevant differences, if present. These methods involve a large battery of state-of-the-art physicochemical, analytical and functional methods as well as clinical studies.
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MW and CKS initiated and designed the manuscript. MW was the lead writer. All authors substantially contributed to the discussion, interpretation and revisions of the manuscript until its final form.

Conflict of Interest

The authors declare no competing financial interests.
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