

Biosimilars versus originators: similarities and differences from development to approval

Due to the expiry of patents for biological pharmaceuticals, in forthcoming years there will be an increase in the approval of biosimilars by the international health authorities. The aims are an understanding of the natural variability of biological substances and the clinical relevance of the diverse product attributes, proof of comparability (similarity) as a self-contained concept in the development and approval of biosimilars and importance of extrapolation to other indications when comparability is demonstrated by comprehensive analytical and functional studies. Strict requirements by the European Medicines Agency guarantee the highest quality standards, which have led to significant savings in the healthcare system and an expansion of access to biological pharmaceuticals in many countries and for many patients.

Keywords: bioequivalence • biosimilar pharmaceuticals • glycosylation • health economics • monoclonal antibody

Biological pharmaceuticals have become increasingly important in the treatment of rheumatic diseases. Adalimumab, etanercept and infliximab were among the top four best selling drugs in 2013 [1]. Due to cost containment measures, access to biological drugs is not possible in ten out of 46 (22%) European countries [2]. Biosimilars, approved biologics with comparable safety, quality and efficacy to the originator, have resulted in substantial savings [3,4]. The process of development for these substances is strictly regulated by the European Medicines Agency (EMA) and requires innovative analytical technologies to investigate the variability to the reference product and the comparability of the biosimilar.

Biologicals are usually proteins derived from a living organism in cell culture in contrast to conventional drugs, which are created by chemical synthesis. Their molecular weight is higher by a factor of up to 1000 compared with conventional drugs. Therapeutic use includes autoimmune diseases like rheumatoid arthritis, psoriasis, psoriatic

arthritis, spondyloarthritis, multiple sclerosis, chronic inflammatory bowel diseases and cancer.

Monoclonal antibodies are of particular importance. They bind with high specificity to their target and exert their action in a tailored way. This gave rise, for the first time, to the development of targeted drugs. Further immunological reactions like antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) consequently cause the destruction of undesirable cancer or inflammatory cells.

Compared with low-molecular-weight drugs, monoclonal antibodies can act in a more efficient and specific way due to their targeted effect. Today, approximately 30% of all drugs in development are biologicals [1].

Biologicals in rheumatology

Molecular targets in rheumatology include proinflammatory cytokines like TNF- α , IL-1, IL-6, CD20, CD80 and CD86. Biological drugs that target these structures include the monoclonal antibodies infliximab, adalim-

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umab, golimumab and certolizumab (directed against TNF- α , respectively), as well as belimumab, a B-lymphocyte stimulating agent. Approved substances also include tocilizumab, which binds to the IL-6-receptor, the anti-CD20 antibody rituximab and the recombinant IL-1-receptor antagonist anakinra. Fusion proteins consist of the F_c-fragment of an antibody bound either to the extracellular ligand-binding domain of the human TNF-receptor (etanercept) or the extracellular domain of CTLA4, a receptor binding both to CD20 and CD80 (abatacept).

Approved indications in rheumatology, depending on the substance, are rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, juvenile idiopathic arthritis and systemic lupus erythematosus.

A recently published systematic review from the European League Against Rheumatism (EULAR) task force for recommendations on the management of rheumatoid arthritis, confirmed the enormous progress that has been achieved with these substances in the treatment of rheumatoid arthritis [5].

Costs of biologicals

Due to a different and more complex production process, biologicals are associated with significantly higher healthcare costs. On a global scale, costs for therapeutic proteins have risen from \$94 billion in 2008 to \$137 billion in 2013, with a projected further increase to \$194 billion in 2018 [1]. In 2013, seven of the ten best-selling drugs globally were biologics [1].

In approximately 25% of all European countries, patients with rheumatoid arthritis have no access to biologicals due to cost reasons; in the USA, Japan, Germany, France, Italy and Spain, only about 50% of

patients had access to biologicals in 2010, even in serious cases [2,6].

By 2018, the so-called 'speciality drugs', in particular biologics, are predicted to account for 50% of total drug expenditure in the USA [7]. Therefore, it appears that ways to provide access to biologics and achieve sustainable financing of healthcare systems without quality constraints are urgently required.

Biosimilars: the affordable alternative

Biosimilars are developed to the highest scientific standards and by means of rigorous regulatory requirements, after loss of protection of the originator. Since their introduction in clinical practice in 2005, biosimilars are required to demonstrate the same clinical benefit as the respective reference product. Their development follows a systematic process, using the most modern technology. Because all biologicals are produced in living organisms and hence are subjected to undergo changes, regulatory agencies have defined scientific criteria that ensure that these changes do not have clinical consequences. These criteria apply in the same way for biosimilars. Although biologicals are complex drugs, even minor details of their structure can be understood by modern analytical techniques.

Biosimilars are equivalent to their originators in terms of quality, safety and efficacy. Because of their complexity, which includes natural variability, they are strictly separate from generics.

The saving potential of biosimilars is huge; for instance, access to G-CSF for cancer patients in the UK was increased by 13% from 2008 to 2009 and by a further 17% from 2009 to 2010 [4]. Estimated savings

Basic requirements for granting approval of a biosimilar by the European Medicines Agency.

High analytical similarity

- Same amino acid sequence and folding.
- Highly similar analytical profiles based on highly sensitive methods.
- Same set of glycans, comparable levels of functionally relevant glycans.
- Comparable or lower levels of nonglycan variants (N- and C-terminal variants, aggregates, deamidation, oxidation...), all minor differences clinically not relevant.
- Comparable stability profiles.
- Closely matching functionalities for all relevant mechanisms of action.
- High purity, in other words, extremely low levels of contaminants from cell line and process.

Confirmation of biosimilarity in a PK/PD study and/or clinical study

- Comparable human PK and PD profiles.
- Comparable efficacy, safety and immunogenicity in a sensitive indication (large effect size, adequately immunocompetent population).

Extrapolation of indications based on the totality of the evidence

- High similarity is key, especially regarding functionalities (potentially) relevant to the mechanisms of action in the difference indications.
- Must be scientifically evaluated and is granted or rejected by the regulators separately for each indication.

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from the use of biosimilars range from 11.8 to 33.4 billion Euros in the EU [8].

Regulatory requirements

As for patent-protected biologicals, the EMA is the responsible authority for the approval of biosimilars. The EMA defines: “A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product)...” [9]. Basic requirements for attaining approval are shown in Box 1.

Historic development in the EMA

The procedure and the definitions for biosimilar approvals originated from EU directive 2001/83/EC, which states: “Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate preclinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I (of this directive) and the related detailed guidelines [11].”

Based on these regulations, the EMA has established a detailed set of guidelines. The basic requirements are outlined in:

- Guideline on similar biological medicinal products, CHMP/437/04 Rev 1 23 October 2014: this so-called ‘overarching guideline’ defines the general concept of biosimilars. Successful development depends on the ability to characterize the respective product and hence the similarity to the reference product [12];
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues, CHMP/BMWP/42832/2005 Rev 1 18 December 2014;
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), CHMP/BWP/247713/2012 22 May 2014;
- Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues, CHMP/BMWP/403543/2010 30 May 2012.

Furthermore, the EMA established a whole set of

product-specific guidelines, like those for epoetin, filgrastim, follitropin and insulin.

The EMA took on the leading role in the development and approval for biosimilars. Biosimilars, as all biologicals, can only be approved at the EU-level, national approvals are not possible. Thereby, it is ensured that biosimilars adhere to the same high quality requirements that originators do and that there are no imports of products with lower quality from other EU countries. The essential organizational body of the EMA is the Committee for Medicinal Products for Human Use (CHMP), which is responsible for granting centralized approval and publishing the scientific rationale in the European Public Assessment Report (EPAR). For queries relating to the approval of new drugs and the design of clinical trial protocols, the Scientific Advice Working Party (SAWP) is responsible, a committee of 28 experts that responds to specific queries from applicants. The Biosimilar Medicinal Products Working Party (BMWP) provides advice to the CHMP on queries relating to the approval of biosimilars and for the performance of respective test procedures. It has been chaired for several years by German experts: Christian Schneider (for Denmark) as chair and Martina Weise (for Germany) as vice-chair. Both the Federal Institute for Drugs and Medical Devices and the Paul-Ehrlich-Institute have participated substantially to the regulatory framework.

Box 1 shows the principal requirements for approval of a biosimilar. It is important to realize that a biosimilar must always have the same amino acid sequence and folding as the originator. Regarding product variations, the biosimilar must comply with the critical clinically relevant attributes within the variability of the originator. New product variants are considered very critical and must be avoided. Only minor, clinically nonrelevant differences in the concentration ratios of the product variants are acceptable. It is of particular importance that the biosimilar corresponds to the originator in all functional aspects that play a role in the approved indications. Comparability must remain constant until the date of expiry. This is tested in comparative stability studies. Purity requirements correspond to those for originators. These analytical and functional investigations are highly sensitive. Only biosimilars that comply with these requirements in all relevant criteria are allowed to enter clinical studies. Analytical comparability is a *conditio sine qua non*, hence cannot be replaced by extensive clinical studies.

Analytical comparability must then be confirmed in comparative clinical studies. These include pharmacokinetic (PK) and pharmacodynamic (PD) studies in humans (‘Phase I’), as well as efficacy and safety studies (‘Phase III’). Studies are designed to detect any ulti-

Table 1. Differences between generics, biological originators and biosimilar.

	Conventional generics	Originators	Biosimilars
Development effort			
Investment in US\$	2–3 Mio	800 Mio	75–250 Mio
Time to market (years)	2–3	8–10	7–8
Number of patients	20–50	800–1000	Ca. 500
Regulatory requirements			
Quality	'Standalone' program, comparison with reference product	'Standalone' program	'Standalone' program, very comprehensive comparison with reference product
Preclinical	No data required	Full preclinical program	Abbreviated program, depending on complexity of molecule
Clinical	Bioequivalence study	Phase I: pharmacokinetic and pharmacodynamic Phase II: dose-finding studies Phase III: studies in all targeted indications- risk-management plan	Phase I: pharmacokinetic and pharmacodynamic Phase III: study in one representative indication Risk-management plan

Ca.: XXX; Mio: XXX.

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mate remaining differences with the utmost sensitivity.

Biosimilars are not clinically tested in all the approved indications of the originator, but are evaluated using extrapolation. This is based on the clinical findings of the reference product and the proof of equivalence of the biosimilar in all clinically relevant attributes, and clinical study in a sensitive patient population ('worst case' testing).

Differences originator/generic/biosimilar

Regulatory requirements for approval of a biosimilar are closer to a (biological) originator rather than to a low-molecular generic [13]. Essential differences, also with respect to the originator are shown in Tables 1 & 2.

The foundation: analytical & functional comparability ('highly similar') in all relevant aspects

Regulatory relevant development of a biosimilar follows a structured multistep pathway aimed at being equivalent to the originator in all clinically relevant attributes.

Step 1: definition of the target

The attributes of the originator are the target for the development of a biosimilar; these must be understood in detail in their nature, their variability and their clinical relevance. For this purpose, numerous batches of the originator have to be analyzed over years. An overview over the process is given in Figure 1.

The target for each product attribute is defined by

two factors: the variability of the attributes in the originator. In this case it has been demonstrated in clinical and postmarketing studies that the product is safe and effective within this variability. The clinical relevance of the attributes. This is of particular importance if there are smaller deviations of the variability of the originator. Then it must be ensured that these do not impact PK, safety, immunogenicity and efficacy in a negative way.

Regarding variability, the structure of proteins is determined by the three-dimensional folding of the polypeptide chain, which itself is determined by the primary structure, which is the sequence of amino acids and, hence, by the genes encoding for it. Furthermore, glycoproteins carry branched sugar residues at distinct amino acid side chains, which arise through post-translational modification in the endoplasmic reticulum (*N*-glycosylation) and in the Golgi-apparatus (*O*-glycosylation). Contrary to the primary sequence of the protein backbone, the manner and extent of glycosylation is not determined by the gene sequence, but depends on the host cell line, the magnitude of the expression and metabolic status, the latter two factors potentially being influenced by small changes in the production process.

Consequently, even strictly controlled production processes result in several hundred different glycoforms of the same amino acid sequence of the originator [14]. This can be caused by [14]:

- Inherent batch-to-batch variability in the manufacturing process.

- Planned changes in the production process.

Variability of the sugar components is most often unproblematic. It occurs in each living organism, including humans, and is dependent on the metabolic status. The basic blueprint is given by glycosylation enzymes in each cell line and, for this reason, in most cases the same cell line is used for biosimilars as for originators. Hence, variability affects the internal ratios of the sugars, but not new variants.

Changes in the production process need to be approved in advance and must comply with the stringent international guideline ICH Q5E [15], which stipulates that changes have no unfavorable impact on safety or efficacy of a drug [15]. Therefore, it is acceptable according to EMA quality guidelines [16] to define the complete variability of the originator as target: “The ranges identified before and after the observed shift in quality profile could normally be used to support the biosimilar comparability exercise at the quality level, as either range is representative of the reference medicinal product. Quality attribute values which are outside or between the range(s) determined for a quality attribute of the reference medicinal product should be appropriately justified with regard to their potential impact on safety and efficacy” [16].

The above citation also describes how to manage minor modifications in the variability of the originator. There is a need for systematic assessment of the clinical relevance of these minor deviating attributes. Long-term experience and systematic investigations can be exploited. Nowadays, knowledge on clinical relevance is comprehensive:

- PK: critical attributes for absorption, distribution and metabolism are amino acid sequence, structure, disulphide bridges, free thiols, oxidized methionine, sialylation.
- Safety/toxicity: biologics are highly specific. Adverse events are almost always caused by interac-

tion with the target. Same target and same mode of action cause same toxicities.

- Immunogenicity: amino acid sequence, structure, aggregates, disulphide bridges, free thiols, degradation products, glycosylation products, etc. are critical attributes, the equivalence of which needs to be confirmed by the most accurate analytical procedures.
- Efficacy: for monoclonal antibodies, both binding to the target and eventual effector functions (ADCC, CDC) need to be evaluated. Besides the already-mentioned attributes, deamidation, glycation and different types of glycosylation are of importance.

The variabilities of the originator and the clinical relevance of the product attributes for PK, PD, efficacy, safety, and immunogenicity are crucial factors for the definition of the developmental target. Also, the interaction of the various factors need to be considered.

Step 2: hitting the target

After successful definition of the target it must be met as close as possible. This will be ensured by highly targeted development of the cell lines and the manufacturing process. As variability is determined biologically, particular attention is paid to selection of the proper cell line. From up to 1000 clones, the one whose product profile is closest to the originator will be selected. Depending on the cultivating process in the bioreactor, certain attributes can still be adjusted. In the downstream (isolation and purification) process, highest purity is achieved by applying the same quality standards as for the originators. The development process is shown in [Figure 2](#).

Table 2. Main differences: originator versus biosimilar.

	Originator	Biosimilar
Target definition	Receptor, surface antigen, effector molecule	Analyses of the variabilities of the originator over years, cell line and product development
Proof of similarity	NA	Complex analytics, functional tests
Preclinical	Bioassay, toxicology	Reduced program
PK and PD studies	PK and PD studies	Often larger PK and PD studies
Dose finding	Phase II studies	No Phase II studies
Phase III studies	All indications	1–2 indications
NA: Not applicable; PD: Pharmacodynamic; PK: Pharmacokinetics. Reproduced with permission from [10] by courtesy of Springer-Verlag GmbH.		

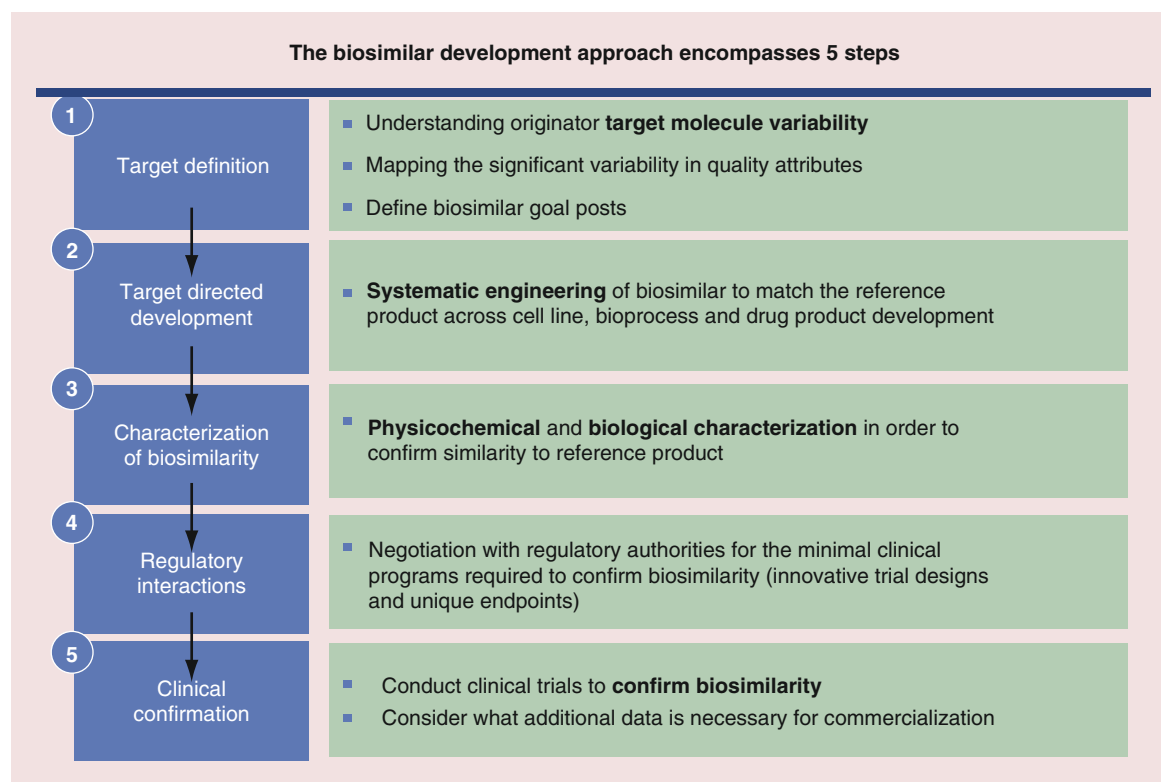


Figure 1. The five steps to approval of a biosimilar. Reproduced with permission from [10] by courtesy of Springer-Verlag GmbH.

After finishing product development, similarity has to be confirmed in an extensive comparison with the originator. The most modern physical and chemical-analytical methods are deployed. For monoclonal antibodies, more than 40 different procedures are used to detect the numerous quality attributes, such as primary structure, impurities, biological activity, higher-dimensional structures and post-translational modifications. Furthermore, approximately 15 functional and biological methods are used for antibodies, which test all functions of the molecule individually and combined. They range from binding to the target to highly complex and sensitive measurement of the ADCC in a biological system. These methods are more sensitive than those obtained for toxicological investigations in animals, for which reason EMA does not recommend animal testing in case of high similarity. An overview is shown in Figure 3.

The confirmation: clinical similarity

After proof of biosimilarity by means of the mentioned analytical methods, similarity is confirmed in pharmacological and clinical studies. This is called confirmation, because the sensitivity of the analytical methods is higher than the clinical endpoints and the residual uncertainty is hence very low. The aim of these studies is not at all to establish safety and efficacy again.

Instead the study designs aim at detecting potential differences, although most unlikely, with highest sensitivity.

PK and PD studies in humans are very sensitive and often very extensive. Numerous PK parameters allow detailed conclusions on the behavior of the molecule in the body and PD parameters can most often be selected in a way that they allow determination of the relevant mode of actions.

Phase III studies in general are required for one to two 'sensitive indications', in other words, in immunocompetent patients, and in which a strong effect can be expected. A strong effect is important as it allows detection of even small differences. With respect to immunocompetence, the patient population must allow detection of potential differences in immunogenicity with the same or higher certainty as in other approved patient populations. Hence, one can speak of 'worst case' studies.

Examples of the successful development of biosimilars that have used the mentioned methods are granulocyte colony-stimulating factor (G-CSF) [17], epoetin alfa [18] and rituximab [19]. For G-CSF, a total of four Phase I studies in volunteers and one Phase III study in breast cancer patients, who were treated with a combination of doxorubicin and docetaxel, were performed. The marker for the PD study was the absolute

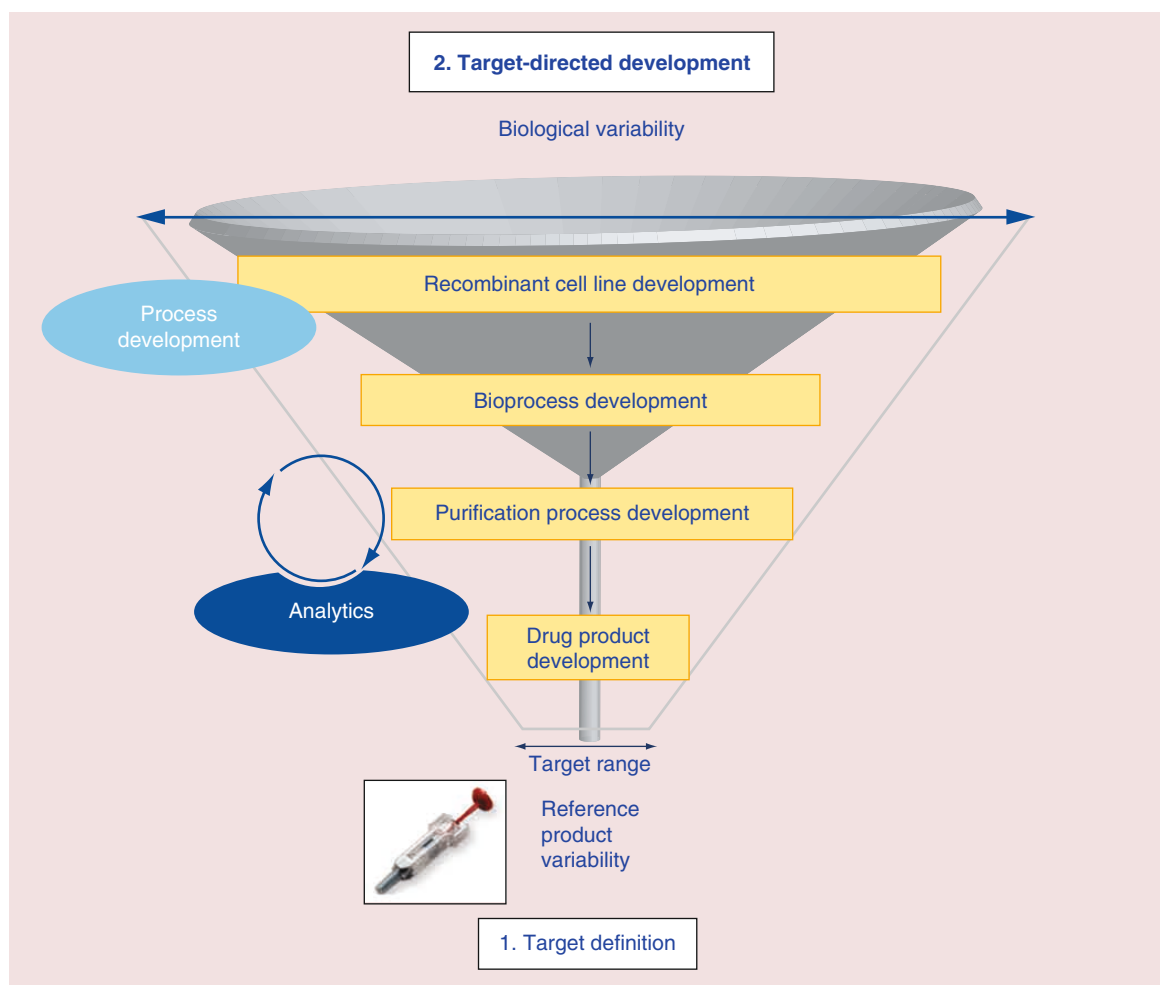


Figure 2. Overview of the process of target development. Reproduced with permission from [10] by courtesy of Springer-Verlag GmbH.

neutrophil count at different dosages [17]. For epoetin alfa, a Phase III study in anemic tumor patients, who received palliative chemotherapy, was performed. The marker in this study was the course of Hb-values [18]. In both the G-CSF and epoetin studies, potential antibody development was analyzed. Epoetin was given subcutaneously because this route of administration is more 'sensitive' regarding the observed effect, a potential immune response, in other words, this study was designed for a strong effect, to detect potential differences with the highest sensitivity.

Further good examples are potential study designs for TNF- α antagonists like adalimumab or etanercept. As described above, the range of indications includes rheumatoid arthritis, psoriasis and spondyloarthritis. The strongest effects have been demonstrated for rheumatoid arthritis [20] and psoriasis [21], hence these are the most sensitive indications with respect to efficacy. Regarding immunogenicity, psoriasis is favorable, as there is no need for immunosuppressive comedication. Psoriasis is the most sensitive model, which is of par-

ticular relevance for extrapolation of indications (see below).

Taken together, the decision for approval is in contrast to the originator based on the whole proven evidence, not only from clinical trials alone, that confirm the preclinical, pharmacokinetic and PD results.

The consequence of high similarity: extrapolation into other indications

Originators are usually approved for several indications (i.e., rheumatoid arthritis, spondyloarthritis, juvenile idiopathic arthritis, psoriatic arthritis). If similarity has been demonstrated for a biosimilar with all the required data, including clinical trials in one indication according to the described standards (analytical and functional, PD and efficacy/safety in a 'sensitive' indication), it is accepted to extrapolate into further indications.

There are many misunderstandings with respect to extrapolation, in particular that it is done arbitrarily from one clinically approved indication to the other,

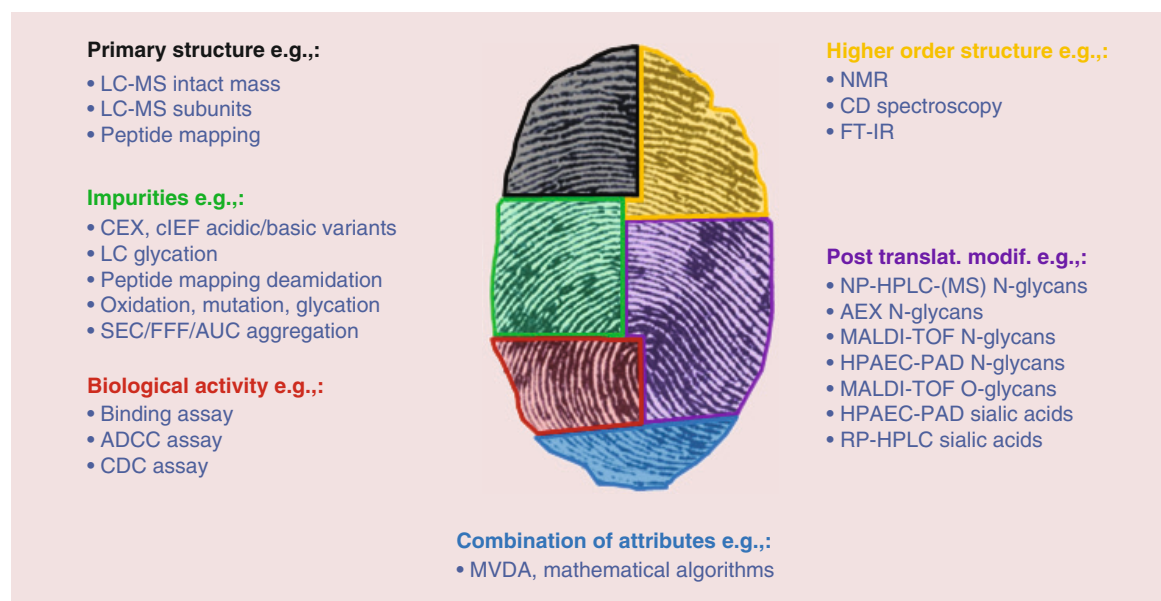


Figure 3. State-of-the-art technologies used to create biosimilars that match originator products across multiple quality attributes. AEX: Anion exchange chromatography; AUC: Analytical ultracentrifugation; CD: Circular dichroism; CEX: Cation exchange chromatography; cIEF: Capillary isoelectric focussing; FFF: Field-flow fractionation; FT-IR: Fourier transform infrared spectroscopy; HPAEC-PAD: Anion exchange chromatography at high pH values with amperometric detection; LC-MS: Liquid chromatography coupled to mass spectroscopy; MALDI-TOF: Matrix-assisted laser desorption/ionization mass spectroscopy with time-of-flight analyses; MVDA: Multivariate data analyses; NMR: Nuclear magnetic resonance; NP-HPLC-(MS): Normal phase high performance liquid chromatography; RP-HPLC: Reverse phase high performance liquid chromatography; SEC: Size-exclusion chromatography.

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which is not the case. Extrapolation, however, underlies three factors:

- The clinical trial and experience with the originator in all indications;
- Linking this experience to the biosimilar by means of high comparability on all levels;
- Clinical confirmation in a 'sensitive' indication with large effect size and appropriate immune competence ('worst case' testing).

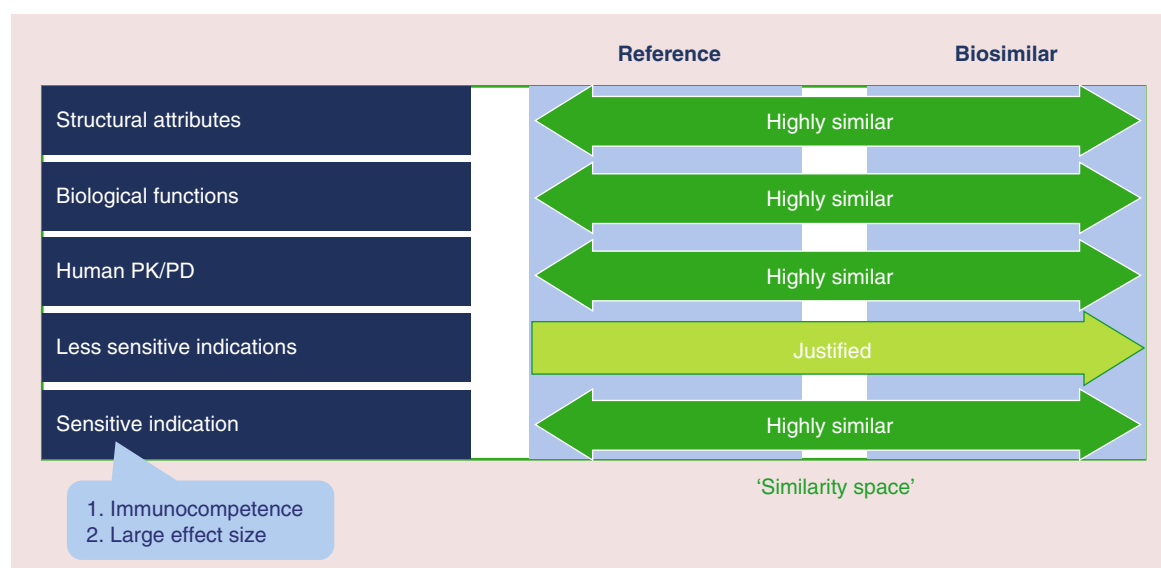


Figure 4. Extrapolation: overview of the procedure. Reproduced with permission from [10] by courtesy of Springer-Verlag GmbH.

Using this approach, a data space is created in which the safety and efficacy of the product is established – the ‘similarity space’. From a scientific point of view, it is more an interpolation rather than an extrapolation; however, the term extrapolation is used as it is defined by the EMA guidelines. This approach is summarized in **Figure 4**.

Nevertheless, a biosimilar is not automatically granted all indications of the originator. The applicant needs to submit a detailed scientific justification for each indication. This is subject to rigorous review by the authority and will be decided for each indication separately. Should analytical or functional differences occur for which it cannot be excluded that they might impact clinically untested indications, these indications will not be approved. Using this stringent and precautionary approach, it is ensured that biosimilars are safe and effective in all approved indications.

Conclusion

Biosimilars have been introduced to the market for 9 years. With more than 400 million days of treatment [22], their concept has proven extremely successful. Regarding safety profiles, no differences between biosimilars and their originators have been observed.

Future perspective

Development of a biosimilar focuses on matching the originator, a biosimilar must be equivalent in all relevant aspects and must not show clinically relevant differences. With the introduction of biosimilars, patient access to biological therapies has expanded and economic burden for healthcare systems has decreased. This is a requirement for future funding of innovative pharmaceuticals which target new structures and result in therapeutic improvements.

Disclosure

This paper has been published in German [10] and translated into English.

Financial & competing interests disclosure

J Windisch was an employee of Sandoz Biopharmaceuticals and is now an employee of Polpharma Biologics. He has shares in Novartis AG. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial assistance and translation by Content Ed Net GmbH was sponsored by Sandoz Biopharmaceuticals.

Executive summary

- Biological drugs play an important role in the treatment of rheumatic diseases; however, given their high costs, access is often not possible.
- Biosimilars are the cost-saving alternative.
- Stringent regulatory requirements set by the EMA guarantee high quality, matching that of the originator.
- Proof of similarity is demonstrated using state-of-the-art analytical and functional methods.
- Clinical studies confirm analytical results.
- Extrapolation into other indications is based on clinical experience with the originator, the high comparability of the biosimilar and clinical confirmation under ‘worst case’ conditions; each indication is assessed separately by the EMA.
- The overall concept has been established and proven successful for almost 10 years.

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