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Biosimilars – What Clinicians Should Know

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Abstract

Biosimilar medicinal products ('biosimilars') have become a reality in the EU and will soon be available in the US. Despite an established legal pathway for biosimilars in the EU since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy, particularly in 'extrapolated' indications, and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biological Medicinal Products (BMWP) of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators.

Introduction

A similar biological medicinal product, commonly referred to as 'biosimilar', is a copy version of an approved original biological medicine whose data protection has expired. Since the implementation of a biosimilar approval pathway in 2005, several biosimilars which include somatropins, filgrastims and epoetins have been licensed and become available in the European Union (EU) and numerous other biosimilars, most importantly monoclonal antibodies, are being developed.¹ Recently, a biosimilar infliximab has been filed for regulatory review to the European Medicines Agency (EMA).² Product-class specific guidelines for these and other biologicals describing a targeted non-clinical and clinical development programme are in place or currently under development.³ In the US, after the recent enactment of a specific approval pathway for biosimilars⁴ and publication of the first draft guidelines on biosimilar product development by the US Food and Drug Administration (FDA)⁵, biosimilars are expected to be available soon. An "EMA-FDA Biosimilar Cluster" has been established for scientific discussion between the US-FDA and EMA and facilitation of global development of biosimilars. However, uptake of biosimilars in the European market has been slower than expected, which may, at least partly, be attributed to a lack of trust in the efficacy and safety of biosimilars as well as their interchangeability with the originator product by both patients and clinicians.⁶

This article addresses frequent concerns raised about biosimilars in the medical community and explains the scientific principles underlying the 'biosimilar concept' established in the EU and put forward in the US, allowing the licensing of biosimilars based on a 'reduced', or better 'scientifically tailored' data package which relies, as appropriate, on the extensive knowledge gained with the originator product.

What is special about biosimilars?

In principle, biosimilars are the biological medicines' equivalent of chemical 'generics'. However, biologicals are derived from living cells or organisms and consist of relatively large and often highly complex molecular entities that may be difficult to fully characterise. Due to inherent variability of the biological system and the manufacturing process, any resulting biological will display a certain degree of variability ('microheterogeneity'), even between different batches of the same product. Due to unavoidable differences in the manufacturing processes, a biosimilar and the respective originator product, the reference product, will not be entirely 'identical'. However, the amino acid sequence is expected to be the same and only small differences in the microheterogeneity pattern of the molecule may be acceptable. A very thorough comparison of the structural and functional characteristics, and the product and process-related impurities of the biosimilar and the reference product will be necessary. Any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar.^{5,7}

Data requirements for the development and licensing of biosimilars are considerably greater than for small chemically synthesised and easily characterisable generic products. For a generic, physicochemical identification and demonstration of a similar pharmacokinetic profile ('bioequivalence') to the originator product is usually sufficient to conclude on therapeutic equivalence. In contrast, a biosimilar needs to be developed based on a more extensive head to head comparison with the reference product, to ensure close resemblance in physicochemical and biological characteristics, safety and efficacy.^{3,5} It should be emphasized that the scientific principles underlying the comparability exercise for biosimilars are the same as those for changes in the manufacturing process of a given biological, for which guidance

and experience already exist.⁸ However, since the biosimilar will be produced by a different manufacturer, the data requirements for demonstration of biosimilarity will usually be more extensive than for demonstration of comparability of a given biological before and after manufacturing changes by the same manufacturer.

As with generics, biosimilars are intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as their reference products. Therefore, the focus of biosimilar development is not to establish patient benefit *per se* (this has already been done for the originator product) but to convincingly demonstrate high similarity to the reference product as basis for relying, in part, on its efficacy and safety experience. For these reasons, the study design, patient population and/or endpoints used in studies comparing the biosimilar with the reference product may be different from those previously used to establish therapeutic benefit of the reference product.

The type and extent of clinical data requirements for biosimilars vary and depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate endpoint to compare efficacy, on the type and seriousness of safety concerns that have been encountered with the reference product or the substance class, and the possibility to extrapolate efficacy and safety data to other indications of the reference product which have not been studied for the biosimilar. However, a repetition of the entire development programme of the reference product is scientifically not necessary and could even be considered unethical.

Frequent concerns about biosimilars

Frequent concerns about biosimilars voiced by clinicians, mainly through learned societies, relate to their pharmaceutical quality, safety and their interchangeability

with the reference product. They also include doubts about clinical efficacy and safety in 'extrapolated' indications for which no formal clinical studies have been performed with the biosimilar. Inconsistent terminology may also add to misperceptions about biosimilars.⁹ It is thus necessary to discuss these concerns in view of the scientific principles established for biosimilars in the EU and shared in other highly regulated regions of the world:

- The fear of “low quality” or “substandard” biosimilar products is not substantiated because the manufacturing process for a biosimilar must comply with EU-quality requirements just as for any ‘new’ biological, and thus must demonstrate that the production process is capable of consistently producing a high quality product. The manufacturing process needs to include state-of-the-art scientific knowledge and process understanding, which in some aspects may have evolved since the development of the originator product.^{5,7} The extensive comparison of physicochemical and functional characteristics of the biosimilar with the reference product is an additional requirement and the foundation of biosimilar development. A recently published analysis supports the high pharmaceutical quality of biosimilars licensed in the EU.^{8,10}
- In our experience, the ‘similar but not identical’ paradigm of biosimilars appears to fuel uncertainties about them. However, this principle is not new to biotechnology: Even consecutive batches of originator products are never “identical” to each other (this is normal and is why adequate controls on batch to batch consistency have to be imposed). In fact, biosimilars are usually specifically engineered and designed to closely resemble the originator molecule to the best extent possible using current technologies. Small differences, e.g. in epitope or binding characteristics of a biosimilar monoclonal antibody, may have

an impact on efficacy, but these would normally be picked up early on in product development from the extensive physicochemical and functional characterization required for biosimilars and biologicals in general. Sensitive state-of-the-art methods and methods orthogonally complementing these are very sensitive when used in combination. As mentioned above, structural differences between a biosimilar and its reference product are only acceptable within the heterogeneity pattern of the molecule and any differences found will need to be explained and justified with regard to the potential impact on the clinical performance of the biosimilar. One example of a difference, which has been accepted by EMA, is the increased level of phosphorylated high mannose type structures in a biosimilar epoetin alfa compared to the reference product since the applicant could prove that these are common glycoforms of recombinant erythropoietins and cytokines and a large variety of non-lysosomal proteins from human plasma.¹¹

- Concerns have been expressed that the safety database of biosimilars could be insufficient at the time of approval with immunogenicity being a particular concern.¹²⁻¹⁹

For a biosimilar, an extensive comparability exercise with the reference product is required including human efficacy and safety data. Based on similarity being demonstrated with the reference product, the biosimilar can also refer to the safety experience gained with the reference product. Particularly for adverse drug reactions (ADRs) that are related to exaggerated pharmacological effects, the demonstration of similar physicochemical characteristics, biological activity, pharmacokinetics and efficacy will already provide reasonable reassurance that such events can be expected at similar frequencies for the biosimilar and the reference product. The risk for detection of new (serious) adverse effects after

licensing is considered much lower for a biosimilar than for a biological containing a new or modified active substance.

Immunogenicity, on the other hand, is an ongoing concern, especially for biologicals for which immune responses have been linked to serious safety issues, the most quoted example being pure red cell aplasia (PRCA) caused by cross-reacting neutralizing antibodies against erythropoietin. Immunogenicity may be influenced by patient-, disease- or product-related factors. Patient- and disease-related factors are already known from the experience gained with the originator product and therefore do not need to be re-investigated for the biosimilar. The focus of the evaluation is thus on potential product-related factors such as structural alterations (e.g. aggregation, which has been implicated in the immunogenicity of epoetins²⁰) or impurities/contaminants, most of which are readily detected by state-of-the-art analytical methods. However, even seemingly small differences may have an impact on immunogenicity and analytical or animal data cannot predict immune responses in humans. Therefore, human immunogenicity data are generally necessary before licensing to exclude a marked increase in immunogenicity of the biosimilar compared to the reference product.^{3,5,21} If the incidence of the immune response is known to be rare and thus unlikely to be captured pre-licensing, an additional post-marketing study designed to detect more subtle differences in immunogenicity may be requested which, as in the case of biosimilar epoetins, can be of substantial size.

The current pre-licensing requirements are supported by the finding of excessive immunogenicity for a biosimilar somatropin due to the presence of increased amounts of host-cell-protein, which could be eliminated by introduction of an additional purification step²² and, more recently, the observation of two cases of

neutralising anti-epoetin antibodies associated with the subcutaneous use of a biosimilar epoetin alfa in a clinical trial in patients with renal anaemia, resulting in premature study termination.²³ A thorough root-cause analysis of the latter cases identified tungsten-mediated unfolding and aggregation of the epoetin alfa as a potential cause for the increased immunogenicity.²⁰ Since the soluble tungsten found in some of the syringes used for the product is not present in the drug product *per se* but stems from the manufacture of the syringes, this problem, if confirmed, could also be relevant to other epoetin-containing products. It should be emphasized that immunogenicity is a potential concern for all biologicals, not just for biosimilars.

- The need for strict post-marketing surveillance and potentially large, post-marketing studies for complete reassurance regarding the safety of biosimilars, particularly epoetins, has been highlighted.^{6,18} For a biosimilar, as for any new drug, a comprehensive risk management plan including a plan for post-authorisation safety surveillance has to be submitted to the authorities at the time of the marketing authorisation application.²⁴ This must address identified and potential safety concerns for the biosimilar, the reference product and/or the substance class. The post-marketing programme for a specific drug product is tailored taking into account these considerations and to best evaluate potential remaining risks. Thus, the safety of biosimilars is actively and comprehensively followed-up on an ongoing basis.
- The basis for considering the efficacy of a biosimilar to be comparable to that of the reference product has been questioned.⁶ Specifically, the acceptance range for therapeutic equivalence for biosimilar epoetins was considered wide.

As stated above, the intention of the biosimilar development is to show similarity with the reference product, not to independently demonstrate patient benefit. Therefore, the study population should be as homogeneous as possible, reasonably sensitive to the effects of the biological and the endpoints should ideally reflect its unconfounded pharmacological action in order to create a 'sensitive test model'. This should be able to detect potential drug-related differences in efficacy and safety and to minimize variability due to disease- or patient-related factors. Endpoints measuring activity of the drug are usually more sensitive for detecting product-related differences than 'hard' endpoints evaluating patient benefit and may be acceptable if they are clearly related to the desired clinical effects. Examples of pharmacodynamic parameters that have been accepted as surrogate endpoints for the evaluation of efficacy of biosimilars in the EU include 'glucose infusion rate' in clamp studies for insulins, 'absolute neutrophil count' for G-CSF and 'number of oocytes retrieved' (in the context of *in vitro* fertilization) for follicle-stimulating hormones.³ On the other hand, efficacy of a biosimilar somatropin still has to be assessed in a clinical trial of at least 6 months duration in growth hormone-deficient children since insulin-like growth factor 1, although a good marker of pharmacological activity of a somatropin, lacks clear relationship with growth response.

In a statistical and regulatory sense, therapeutic equivalence infers that the test drug does not have better or worse efficacy than the reference product, thus allowing the use of the same dosage for the same indication, as is intended for biosimilars. When defining comparability margins clinical considerations need to be taken into account, i.e. the selected margins should represent the largest difference in efficacy that would not matter in clinical practice. Treatment

differences within these margins would thus be acceptable because they have no clinical relevance. The principles of margin selection are not unique to biosimilar testing but are used in any clinical trial comparing treatment alternatives or pre- and post-change product in case when a biological has undergone a change in its manufacturing process and clinical data are required for assessment of comparability. Comparability margins proposed for licensing studies for a given medicinal product, including biosimilars, will always need sound scientific justification to be acceptable for regulators.

The acceptance range of ± 0.5 g/dL in blood haemoglobin concentrations for demonstration of similar efficacy of two epoetins as suggested in the respective EMA guideline is considered tight in the view of the rather high background variability in blood haemoglobin levels in patients with renal anaemia, especially those on dialysis.³ It should be noted that, not only the observed mean treatment difference (between biosimilar and reference product) but also the 95% confidence interval of this difference needs to be fully contained within the equivalence margins, thus providing sufficient statistical reassurance that efficacy is indeed similar. The assumption that patients switched from an originator product to the respective biosimilar may need to change dosage, dosage intervals or route of administration is unsubstantiated.²⁵

- Concerns have been expressed about using biosimilars in indications or in patient populations that are approved for the reference product but have not been formally investigated during the clinical development of the biosimilar, and therefore have been licensed on the basis of extrapolation of efficacy and safety data.^{6,12,17,19,25-28} In this respect, particular concerns have been raised regarding the use of biosimilar G-CSF for the mobilisation of stem cells in healthy donors

and the use of biosimilar epoetins in patients with cancer.^{25,29,30} In addition, there is growing concern in the rheumatology, gastroenterology and dermatology communities regarding the future use of biosimilar anti-inflammatory monoclonal antibodies based on extrapolation of data.³¹⁻³³

It must be clearly understood that a biosimilar, as opposed to a small chemical generic, cannot automatically claim all indications of the reference product and that any extrapolation of data requires sound scientific justification.³⁴ For extrapolation of data to be considered, several requirements need to be fulfilled.

Firstly, similarity with the reference product based on the totality-of-the-evidence for this from a thorough comparability exercise has to be convincingly demonstrated. Clinicians need to be aware that clinical data are not the only cornerstone of a biosimilar development to be relied upon. Extensive characterisation and comparison of the physicochemical properties and biological activity of the biosimilar and the originator product play a fundamental role in this and close similarity in these aspects is a prerequisite for any reduction in the amount of non-clinical and clinical data requirements. Clinical data provide complementary information, e.g. regarding the clinical relevance of any observed differences and on immunogenicity.

Secondly, if clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible, e.g. if the relevant mechanism of action and the receptor(s) involved in the extrapolated indications are the same.³ If the mechanism of action is different or unknown, additional convincing data (e.g. on pharmacodynamic parameters and/or specific and sensitive functional assays reflecting the respective pharmacological action(s)) are necessary to provide further reassurance that the

biosimilar will behave as the originator product in these indications. In this sense, comparative pharmacodynamic studies in healthy subjects are required for biosimilar G-CSF, evaluating – in addition to absolute neutrophil count – the CD34+ cell count to assess mobilisation of stem cells from the bone marrow.³ Such data should not be considered in isolation but as a further building block in the overall proof of biosimilarity. Based on such considerations, extrapolation of efficacy and safety data to other indications of the reference product has been approved for biosimilar somatropin, epoetin and filgrastim-containing medicinal products.¹

Another prerequisite for extrapolation is that the safety profile of the biosimilar must have been properly characterised and unacceptable immunogenicity excluded. Extrapolation of immunogenicity data is only possible from high risk to low risk patient populations and clinical settings. For example, pure red cell aplasia (PRCA) due to neutralising anti-epoetin antibodies is a potential concern for subcutaneous use of epoetins in patients with renal anaemia but less for intravenous administration or use in cancer patients receiving chemotherapy. Therefore, extrapolation of immunogenicity data is considered possible from subcutaneous use in renal anaemia patients to intravenous use in the same population or to subcutaneous use in immunocompromised cancer patients but not vice versa. In this respect, the concern expressed in a recent review³⁵ that immunogenicity data collected for intravenous use of epoetin could be extrapolated to subcutaneous use is not substantiated since the respective guideline³ clearly states that comparative immunogenicity data will always be required for subcutaneous use, if applied for.

In this context it should be emphasized that the scientific principles of extrapolation of data is not new for biosimilars but also apply to the comparison of pre- and postchange product upon a change in the manufacturing process of a biological, which is already licensed for use in several indications. To the knowledge of the authors, up to now there has not been a case – even with extensive changes to the manufacturing process - where new clinical data have been generated or requested in every indication, since the overall data from the comparability exercise already conclusively demonstrated that the manufacturing change has no adverse impact on efficacy and safety.

In conclusion, extrapolation of data to other indications of the reference product – and thus formal lack of a clinical trial in the respective clinical indication – does not imply less reassurance as regards efficacy and safety of the biosimilar if all the above considerations are taken into account, and represents a logical consequence of the scientific concept. Therefore, clinicians should have confidence in using biosimilars for all indications for which they have been licensed.

- The question has been raised whether biosimilars could be considered interchangeable (in the sense of a therapeutic alternative initiated by, and under surveillance of the treating physician) with the respective reference product and, consequently, the concern that automatic substitution at the pharmacy level (without the knowledge of the physician) might follow.^{6,18,28}

Undoubtedly biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products. Interestingly, it has been stated that the originator products epoetin alfa and epoetin beta are considered as interchangeable by healthcare professionals due

to the long medical experience with both products.³⁶ Although both epoetins can without doubt be considered efficacious and safe, similarity has never been demonstrated in a head-to-head comparison and dosage recommendations are not fully identical as would be required for a biosimilar.

The main argument against automatic substitution is the concern regarding traceability, which is necessary for a root cause analysis in case an ADR occurs.^{6,17,30,35} The importance of reliable traceability of biologicals has been acknowledged, particularly for epoetins, and a respective statement has been introduced into the prescribing information of all epoetins licensed in the EU.³⁷ In addition, the novel pharmaceutical pharmacovigilance legislation being implemented in 2012 will, amongst other things, ensure European wide traceability of medicinal products.³⁸ Another, more theoretical concern regarding automatic substitution is the possibility that repeated switches between the biosimilar and the reference product may increase immunogenicity with potentially negative effects on the safety and/or efficacy of the products.^{13,36} This would, however, also apply to switches between different originator biologicals of the same class. Automatic substitution may be difficult from a practical point of view, especially for patients self-administering the medicinal product, in case of differences in injection devices, preparation and handling of the biosimilar, which may increase the risk of medication errors or impair treatment compliance.

It has been suggested that a change from an 'established' epoetin to a biosimilar agent should require informed consent from the patient.³⁹ Although, the authors agree that patients should always be informed about the medicine they are prescribed or given, the necessity of an informed consent for the switch to a biosimilar is considered a disproportionate measure since biosimilars, as any

new drugs, are scrutinized by the competent authorities during the marketing authorisation procedure to ensure that only products with adequate quality, efficacy and safety are approved.

It should be noted that substitution policies are decisions outside the remit of the EMA since the regulation of substitution of medicinal products is the responsibility of the individual EU member states. To our knowledge, up to now automatic substitution has not been implemented for any biosimilar in the EU and, according to the European Generics Association, more than a dozen countries across Europe have introduced rules to prevent automatic substitution of biological medicines by biosimilars.⁴⁰

Implications for patients and treating physicians

The expected benefits of biosimilars are reductions in acquisition expenses and consequently better access to biotherapeutics while containing health expenditure.⁴¹ Due to the long development time and related high costs of biosimilars, partly due to considerable regulatory requirements to ensure their quality, safety and efficacy, the reduction in their acquisition price is unlikely to be as profound as for 'chemical' generics. Still, the absolute price difference between biosimilar and originator products can be substantial for expensive biopharmaceuticals, and can be expected to increase as biosimilars gain market share. For instance, it has been estimated that a 20% price reduction of five off-patent biopharmaceuticals would save the EU more than €1.6 billion per year and the U.S. federal government \$ 9 to 12 billion over the next 10 years.^{41,42}

Of course, physicians should only prescribe medicines for which quality, safety and efficacy have been demonstrated according to state-of-the-art science and technology with the exception of drugs used in clinical trials or for compassionate

purposes. Since biosimilars are licensed based on a 'reduced data package', physicians might misinterpret this as a non-reassuring basis to use biosimilar drugs for their patients. To alleviate unsubstantiated fears, physicians need to gain a clear understanding of the 'biosimilar philosophy' including the scientific principles as discussed in this article. The data package required for licensing of a biosimilar is not simply 'reduced'. It is scientifically 'tailored' and includes an extensive comparability exercise using sensitive analytical tools and sensitive test models to provide reassurance that the biosimilar and the respective reference product are indeed highly similar. Based on such extensive comparative data, there is no scientific reason to assume that the biosimilar would behave differently from the reference product when used in clinical practice.

The understanding of the biosimilar concept will become increasingly important when even more complex biologicals such as monoclonal antibodies are developed as biosimilars.⁴³ For example, the most sensitive clinical model for investigating potential product-related differences in efficacy of anti-cancer monoclonal antibodies might not necessarily use 'overall survival' as the primary endpoint, which is usually considered as the gold standard to establish patient benefit. However, overall survival is usually confounded by many factors unrelated to the performance of the drug itself, which might, despite randomization, not be sufficiently balanced between treatment groups unless the study is extremely large. For a biosimilar, other primary clinical endpoints that are more sensitive (e.g. 'objective response rate' or 'change in tumour mass'), focussing on the detection of potential differences in efficacy rather than the demonstration of efficacy *per se*, may be more appropriate.⁴⁴

With regard to safety, physicians should understand that the non-identical nature of a biosimilar and the more familiar reference product is inherent to all biologicals, and is

also true for differences that might arise from a change in the manufacturing process of an established biological product.⁴⁵ It is well known that the problem of epoetin antibody-induced PRCA was first recognized after a major change in the manufacturing process used for an originator epoetin, and not with a biosimilar.⁴⁶ Since immunogenicity may be altered by such major but also by seemingly minor changes, human immunogenicity data are always required for the licensing of any biological including biosimilars.

Regulatory oversight and scrutiny is important to ensure the safe use of any biological. In particular, active post-authorisation surveillance is a key factor. Therefore, physicians would be well advised to always document exactly which biological is used for an individual patient, as has been established for plasma-derived medicinal products. If an ADR occurs or is suspected, it is important to identify the specific product causing it. Thus, ADR reports should include, in addition to the International Nonproprietary Name (INN), other indicators such as brand name, manufacturer's name, lot number and country of origin of the batch used.⁴⁷ This highlights the central role of well-informed and vigilant prescribing physicians and pharmacists in the overall concept of regulatory control of patients' health.

Finally, clear information about existing guidelines, access to unbiased information on biosimilars and education of physicians regarding the clinical utility of biosimilars as well as improved communication between learned societies and regulators has been requested.^{18,19,48}

Guidelines on the requirements for the development and licensing of biosimilars and responses to comments received during the external consultation phase are posted on the EMA homepage.³ Information on the documentation submitted in support of a specific biosimilar application and the related scientific discussion and considerations

of the CHMP are also publicly available as European Public Assessment Reports (EPARs).¹ In addition, the prescribing information of a biosimilar product provides information about its biosimilar nature and directs the reader to the EMA homepage for further detailed information, which may assist physicians in making informed and appropriate treatment choices for their patients. The BMWP is open to discussions with all stakeholders and welcomes scientific input on their guidelines. Considering the previous absence of feedback from the European medical associations on the biosimilar guidelines, BMWP considers a more pro-active approach to better involve the organised medical community in the public process of creating and updating the guidelines. To reassure practicing physicians, quality, safety and efficacy of biosimilars are a key priority and of paramount importance for the BMWP in its concern for the best interest of patients and particularly to ensure patient safety.¹⁸

Summary of Key Points

- The principles guiding biosimilar development are scientifically sound and shared in the EU and U.S. and other highly regulated regions of the world.
- The scientific principles for establishing 'biosimilarity' are the same as those for demonstrating 'comparability' after a change in the manufacturing process of an already licensed biological.
- A biosimilar should be highly similar to the reference product in terms of physicochemical and functional characteristics, and clinical performance.
- The focus of biosimilar development is not to establish patient benefit *per se* but to convincingly demonstrate close similarity to the originator product as a basis for relying, in part, on efficacy and safety experience gained with this 'reference product'.

- The biosimilar development programme is scientifically tailored using up-to-date analytical tools and sensitive test models to best detect even small potential product-related differences between the biosimilar and the reference product. Clinical endpoints may thus be different from those used in the reference product's clinical trials if clinically meaningful and scientifically justified.
- Extensive structural and functional characterization and comparison of the biosimilar and the reference product is the foundation of biosimilar development.
- The primary amino acid sequence should be the same for the biosimilar and the reference product. Small differences in the micro-heterogeneity pattern of the molecule may be acceptable if appropriately justified with regard to its potential impact on safety and efficacy.
- The requirements for the pharmaceutical quality of biosimilars are the same as for any new biological.
- The type and magnitude of clinical data requirements depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate endpoint to assess efficacy, on the type and seriousness of safety concerns, and the possibility to extrapolate efficacy and safety data to other indications of the reference product.
- Human safety (including immunogenicity) data are always required for biosimilars before approval.
- Extrapolation of efficacy and safety data to other indications of the reference product that have not been investigated during the clinical development of the biosimilar always requires convincing scientific justification, which should address the mechanism of action, toxicities and immunogenicity in each indication of use.

- Decision making of the regulatory authority is based on the totality-of-the-evidence provided by the applicant in support of biosimilarity.
- A risk management plan for post-licensing surveillance is routinely required for all new drugs including biosimilars.
- Traceability is important for all biologicals including biosimilars.
- Biosimilars can be considered therapeutic alternatives to the reference product.
- Information on licensed biosimilars is available from the European Public Assessment Reports and may further assist clinicians in making informed and appropriate treatment choices for their patients.

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Conflict of Interest

The authors declare no competing financial interest.

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