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Biosimilars: What do we need to consider?

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Foreword

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The introduction of biological agents (monoclonal antibodies and fusion proteins) in the early 1990s dramatically changed the clinical management and the course of immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, Crohn's disease (CD) and ulcerative colitis (UC). In particular, tumour necrosis factor (TNF) alpha-blockers, such as infliximab, etanercept and adalimumab, represent a tremendous advancement. Prolonged maintenance therapy with anti-TNF agents has been shown to avoid severe complications in inflammatory bowel disease as well as reduce the need for surgery and hospitalisation. In the case of PsA, RA and AS, treatment with TNF blockers achieves rapid disease control and prevents long-term radiographic progression and irreversible joint damage. Patients with psoriasis were astonished to see very fast clearance of skin lesions when starting anti-TNF antibodies. The rapid and sustained improvement in patients' quality of life offered by these treatments has never been so intense before. More recently, it has been shown that early treatments of CD, UC and RA can alter disease course with early remission and long-term benefits. Finally, the long-term experience with these drugs and the data from very large national registries worldwide is very reassuring as far as the long-term safety concerns.

The main restriction to the use of biologics is related to their cost. Biologics are very complex and large molecules produced by living cell cultures, thus requiring large technological investments. The use of biologics for patients with chronic disease might be very expensive over time, especially for national healthcare systems. Several studies across different specialties have indeed shown that the main limitation to biologics use is the cost, followed by safety concerns. Biosimilars represent an important and direct opportunity for reducing the cost of biologic therapy. Biosimilars are biologic products developed using a step-wise approach to result in a biologic that demonstrates no clinically meaningful differences in terms of quality attributes, efficacy, safety, and immunogenicity compared with an existing licensed, reference biologic. Anti-TNF biosimilars offer direct cost savings, which might support healthcare sustainability and would further increase patient access to biologic therapy. Lower drug cost might indeed translate into an earlier, optimal and equal access to these very effective and consolidated treatments.

US Food and Drug Administration and European Medicines Agency regulatory pathways for approving biosimilar are very stringent and allow only high quality manufactured biosimilars to enter the market. A major issue with biosimilars is extrapolation, that is, the use of the drug in a disease in which the biosimilar has not been directly tested but the reference is indicated. However, data from registries and studies are accumulating and provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine. Interchangeability and traceability are also very relevant to provide a reliable identification system, related to all production and distribution phases, both the reference and the biosimilar used in clinical practice, so that possible adverse events can be certainly identified for each product. The importance of an uninterrupted supply of biological drugs, including biosimilars, is also very important to avoid drug shortages and ensure optimum drug efficacy.

In conclusion, biosimilars offer a very important opportunity to effectively treat patients in need. Health care professionals (physicians and pharmacists) should share their experiences and concerns for an optimal usage in patients. Issues related to immunogenicity, interchangeability, automatic substitution and extrapolation of indications should continue to be studied and debated for the benefit of patients.

Manufacturing biosimilars

Manufacturing a biosimilar requires significant expertise to ensure that it is 'highly similar' to the reference (originator) biologic with no clinically meaningful differences in safety, efficacy, or immunogenicity

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Whereas generics are always exact copies of a respective reference drug, biosimilars are developed to closely resemble a well-established biopharmaceutical. This is a major difference because it is practically impossible to obtain biosimilars as exact copies of biopharmaceuticals. This is not only due to the much larger molecular weights of these molecules compared with generics but also to the fact that, unlike generic drugs, biopharmaceuticals are always produced from living cells as a result of biochemical processes. A biopharmaceutical is a mixture of molecule variants, which is complex but not arbitrary in its composition. Therefore, copying a biopharmaceutical ultimately requires copying this complex molecular mixture.

Basic principles

Microheterogeneity

An inherent feature of all biological products is that they comprise complex molecular mixtures, the individual components of which have subtle differences to the intact biomolecule.[1] This microheterogeneity results from variants (artefacts) that are present at specific concentrations in all biopharmaceuticals.

The principle of inherent microheterogeneity applies to biosimilars as well as to innovator drugs used as a copy template (reference drug); the consequence is that a biosimilar can be similar but never identical to the reference drug. However, the structural deviations of the biosimilar from its corresponding reference drug are by no means arbitrary. They must not be greater than the deviations within different batches of the reference drug. In fact, different batches of the reference products selected as reference drugs are always only similar, but never identical, to each other.

> The biosimilar must have the same amino acid sequence as the reference drug – no differences between the original and the copy are permissible

Amino acid sequence

The biosimilar must have the same amino acid sequence as the reference drug – no differences between the original and the copy are permissible.[2] However, it is possible that individual amino acids are modified by environmental influences including pH, temperature, pressure, etc (for example, oxidised variants of methionine, cysteine, tryptophan, tyrosine and histidine; deamidated variants of asparagine or glutamine; hydrolysed disulfide bridges). Furthermore, details of the glycosylation pattern may differ between the original and the copy as well as between different batches of the original and the copy, respectively. These variations are part of the general microheterogeneity of biopharmaceuticals and thereby also of biosimilars and of reference drugs.

'The product is the process'

This refers to the importance of a rigorously specified production process as a basis for batch-to-batch consistency, which applies to all biopharmaceuticals, including biosimilars. However, this process does not have to be identical to the process used to manufacture the batches of active substances used in the approval studies. Processes can be modified, or even redesigned, providing that the changes are first approved by the European Medicines Agency (EMA).

A study carried out in 2016,[3] determined the number of changes in the manufacturing processes of 29 monoclonal antibodies. A total of 404 process modifications were found in the European public assessment reports (EPARs) of the EMA – 50 of which were for the production of the reference drug Remicade® (infliximab). A total of 32 of these changes were serious interventions, such as a change of cell line for the production of active substances. On average, there were 1.8 changes in the production process per year and per biopharmaceutical.

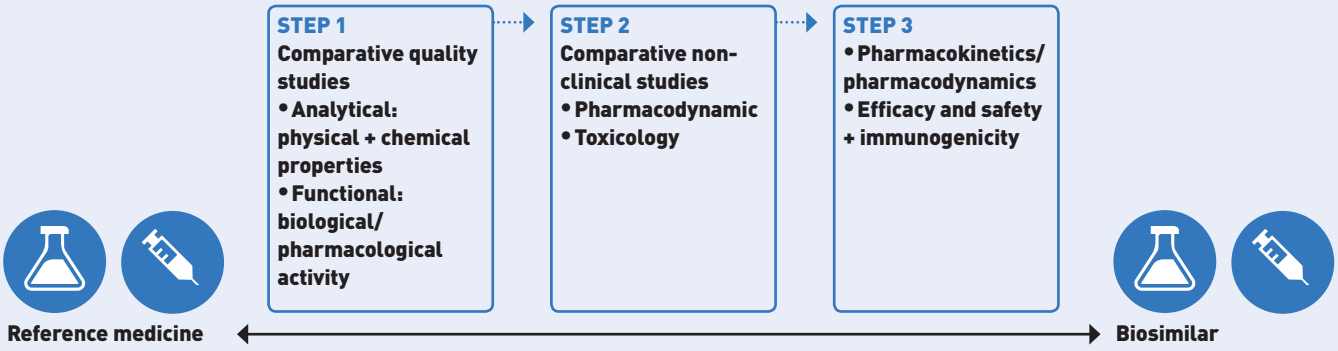
The approval of a process change for an originator biopharmaceutical is granted by the EMA on the basis of data that the pharmaceutical manufacturer must collect and submit to the authority.[4] These data are obtained from 'bridging studies'. Active substance batches from the original process are compared with active substance batches from the modified process (the comparability exercise). The most important methods used are bioanalytical techniques, because they have high sensitivities in detecting potential differences.[5] Therefore, these methods are of particular importance in the context of a comparability exercise. These analyses are supplemented by preclinical tests and, if necessary from a regulatory point of view, by clinical studies.

If a process change is approved, this affects all indications for which the active substance is approved. This also applies if a clinical study considered necessary within the framework of the comparability exercise was carried out in only one (sensitive) indication. This procedure is based on the principle of 'extrapolation of the indication', which has been used in biopharmaceuticals for years and has proven itself over time, even when major process changes had to be decided.[6] For example, the subcutaneous administration of the monoclonal HER2 antibody trastuzumab (Herceptin®) was also approved for neoadjuvant therapy on the basis of data from patients with metastatic disease.

Another important aspect in the evaluation of a biopharmaceutical is its immunogenic potential (for

FIGURE 2

Developing a biosimilar: a stepwise process



further details of the key concepts in development of biosimilars and regulatory approval processes, please see the dedicated article in this handbook).

The manufacturing process

Manufacturing a biologic consists of genetically modifying a cell, which becomes the basis for a cell line used for the production of the necessary protein for the drug. The protein is then separated from the cells and purified.[7]

Each step of the manufacturing process can modify the product, and the process requires controlling numerous input parameters, each of which can impact the safety and efficacy of the final product.[8]

The manufacturing process can be divided into four steps. The aim is not to develop a new molecule with unknown clinical properties, but to copy a molecule that has undergone full clinical evaluation (reference drug) in the best possible way so that all available data on the reference drug can also be used for the biosimilar.

Step 1

This involves full bioanalytical examination of the structural characteristics of the reference drug to determine exactly what needs to be copied. For this purpose, the biosimilar manufacturer purchases large quantities of the reference drug on the relevant markets, whereby as many different batches as possible should be represented. Structural characteristics include modifications such as oxidised or deamidated variants of different amino acids, modified N- and C-terminal ends of protein chains, glycosylation characteristics, the proportion of denatured protein, and protein aggregates, among others. This is necessary because these structural variants also have to be copied. Of course, the biosimilar must not be worse than the reference drug, but it must also not be better.

> Manufacturing a biosimilar requires significant expertise to ensure that it is 'highly similar' to the reference biologic, with no clinically meaningful differences in safety, efficacy and immunogenicity

Step 2

In the second step, the biosimilar manufacturer must define variation parameters for the reference drug on the basis of the analytical data collected that determines the limits of microheterogeneity. The upper and lower limits for the biosimilar must not exceed or fall below the corresponding limits of the reference drug. Expiration of a patent does not necessarily mean that the manufacturing process of the reference product becomes available to the biosimilar developer (for example, the cell line clone, growth medium used, etc) and full analyses of the reference drug is required for this important step.

By contrast, the regulatory authorities know all the details of the reference drug including the microheterogeneity limits. It is therefore not »

unusual that the scope for microheterogeneity in biosimilars is narrower than theoretically acceptable.

Step 3

The next step is the production of the biosimilar using the relevant set of complex biotechnology methods. First, different production clones are tested to determine to what extent they deliver products that are as similar as possible to the reference drug. Complex cycles of process variation and bioanalyses of the resulting products gradually lead to conditions that ensure the biosimilar resembles the reference drug in all aspects.

This process is then specified in every conceivable detail and forms the basis for the production of all batches of the biosimilar according to the 'the product is the process' principle.

Step 4

In the fourth step, the biosimilar is comprehensively checked – the 'comparability exercise'. A key feature of this step is that all tests are performed head-to-head between the biosimilar and the reference drug (which also applies to the required clinical study at the end of this comparison). This is also a sequential process.

Biosimilar development

Comparative quality

In the first step, quality, structural agreement, physicochemical and biological comparabilities are assessed. Possible deviations from the data of the reference drug must be explained adequately. Furthermore, the purity of the biosimilar is checked. The product is only released if previously defined specification criteria are fulfilled (see Figure 1).

Comparative non-clinical

In the second step, biosimilar and reference drug are compared in a preclinical setting (usually in vitro testing) and the required tests are specified in product-specific guidelines issued by the EMA. The pharmacokinetic and pharmacodynamic parameters and their predefined degree of similarity with the reference drug must be justified and determined.

Comparative clinical

In the third step, clinical comparability is demonstrated. These studies have more of the character of safety studies than efficacy studies. If the initial comparability exercise proves that the biosimilars and reference drugs are sufficiently similar, then it can also be expected that they will be clinically equivalent. However, these clinical studies are mandatory in order to prove the tolerability of the biosimilars. The manufacturing processes of biosimilars and reference drugs are inevitably different, so that it cannot be ruled out that components that are difficult or impossible to identify analytically might provoke clinical abnormalities. Phase I clinical studies initially focus on toxicology, pharmacokinetics and pharmacodynamics (purity, safety, uptake, distribution and excretion) and a safety profile is established.

This is followed by studies on efficacy and safety in terms of severity and frequency of various side effects. These are performed in one or more representative indications in order to demonstrate a comparable efficacy and safety, including a comparable immunogenicity profile for the biosimilar and reference drugs. The focus and requirements for these Phase III studies differ depending on the biosimilar class. However, in accordance with the diversity and complexity of biologic pharmaceuticals, the EMA defines the requirements individually and in accordance with the guidelines laid down for the manufacturers. Figure 2 summarises the processes for biosimilar and reference medicines.

Conclusions

Manufacturing a biosimilar requires significant expertise to ensure that it is 'highly similar' to the originator biologic with no clinically meaningful differences in safety, efficacy, or immunogenicity. This means extensively identifying and comparing the structural and functional properties of the biosimilar and selecting optimal cell lines for culture, scaling up, and purification of the protein. For a biosimilar, comparative structural and functional characterisation provide the greatest contribution to clinical predictability.

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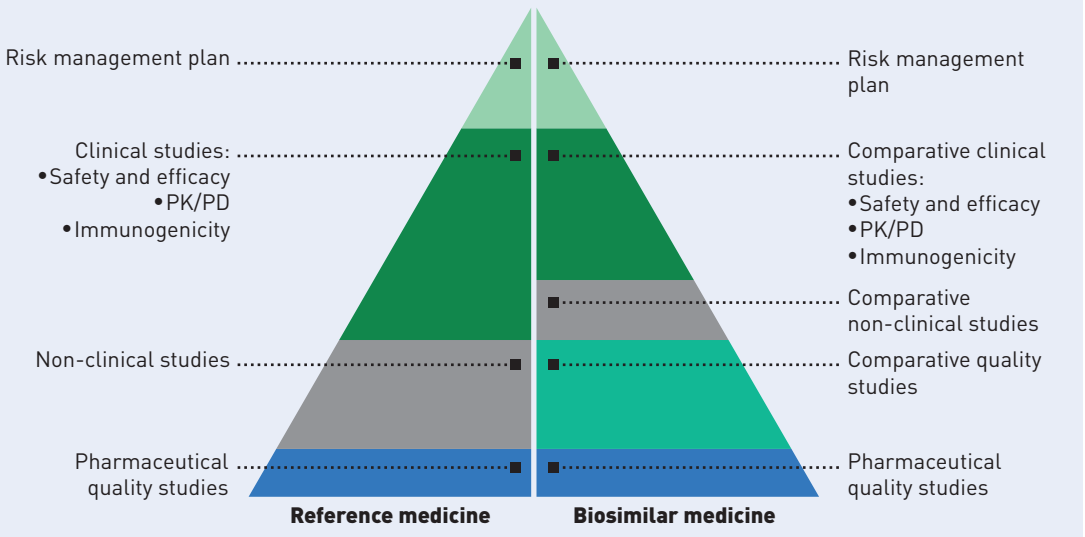
FIGURE 3

Summary of processes for biosimilar and reference medicines[9]



NOMENCLATURE

Naming conventions and nomenclature

Although there is a trend towards establishing differentiation between biologic originators and biosimilars through naming, there is still lack of global consensus

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A drug's name is required to prescribe any medicine and has a strong impact on product traceability for accounting and pharmacovigilance purposes, especially in the setting of switching or substitution of originator biologics and biosimilars (interchangeability in US Food and Drug Administration (FDA) terms) but there is no accepted worldwide naming convention for biosimilars and reference biologics.

How should biosimilars be named?

Naming should:

- Show that the reference biologic and biosimilar are highly similar, but not identical
- Differentiate the biosimilar from its reference product
- Differentiate biosimilar A from biosimilar B, C, D, etc.

Currently this is handled on a country-by-country basis.

Europe

The concept of a single non-proprietary name to be used worldwide for active pharmaceuticals was established by the World Health Organization (WHO) in 1950 and became operational in 1953. In the European Union, biosimilars and reference biologics are identified by the WHO international non-proprietary name (INN), followed by the brand name. Brand names are often the primary identifiers for reporting adverse events, and since 2010, the European Union legislation requires that member states take measures to ensure that trade names are used in health records and adverse event reports,[1] but their use is often inaccurate.[2] The European Medicines Agency's (EMA) solution of identifying products by a 'trade name' comprising the INN and the manufacturer's name[3] in the absence of a brand name would not work in the USA because this concatenation is not a recognised trade name, and the separate manufacturer name field is not routinely captured in health records or adverse events reporting systems.

WHO vs FDA guidelines

The WHO guidelines propose a system in which a randomly generated four-consonant suffix or biological qualifier (BQ), devoid of meaning, is assigned to all biological products.[4] The WHO proposal both acknowledges the biosimilarity concept and provides a mechanism for traceability, which bears some resemblance to the FDA's proposed biosimilar naming scheme first announced in August 2015 and published in 2017.[5] Figure 1 summarises the positions on naming of biosimilars.

The suffix

According to the FDA guidance, the proposed suffix should be:

- unique
- devoid of meaning
- composed of four lowercase letters, of which at least three are distinct
- non-proprietary
- attached to the core name with a hyphen
- free of legal barriers that would restrict its usage.

The first biosimilar approved in the United States, Zarxio (from Sandoz), was assigned an INN with a suffix related to the manufacturer's name: filgrastim-sndz. Non-proprietary naming of biosimilars approved after Zarxio followed the current FDA guidance, for example: Inflectra (infliximab-dyyb); Erelzi (etanercept-szzs); Amjevita (adalimumab-atto); Renflexis (infliximab-abda); Cyltezo (adalimumab-adbm); Mvasi (bevacizumab-awwb); Ogivri (trastuzumab-dkst); Ixifi (infliximab-qbtx); Retacrit (epoetin alfa-epbx). Remicade, marketed by Janssen in the US, would be named infliximab-hjmt according to this guidance and infliximab-jnsn if the suffix were manufacturer-derived.[8]

Many stakeholders (including pharmacists' associations and manufacturers of both references and biosimilars) have criticised random non-meaningful suffixes. While suffixes associated »

FIGURE 1

Summary of guidlines for naming conventions

WHO

- INN guideline with list of assigned INN names WHO/EMP/RHT/TSN/2016.1[6]
- WHO position on biologic qualifiers (INN Working Document 14.342)[4]

Current position: Random alphabetic suffix plus check sum for all biologics; independent element used in conjunction with the INN

FDA

- Non-proprietary naming of biological products (2017)[5]
- Labeling for biosimilar products. Guidance for industry[7]

Current position: Four-lower case letter, unique suffix added to the INN of biologics. Company can submit several suffixes with order of preference from which FDA will choose one. Current examples are with and without meaning (for example, -sndz vs -dyyb)

EMA

No position expressed or published

with the manufacturer's name would improve pharmacovigilance and reduce the risk of transcription and prescription errors, there are concerns that meaningful suffixes could become a proprietary item of the manufacturer associated with the product, and that through mergers and acquisitions the actual manufacturer might change while maintaining the original suffix. However, it is unlikely that prescribers, and to a lesser extent, patients, would remember the correct INN with a suffix including four random letters. Remembering the INN with the brand name or the manufacturer seems more likely.

Other areas

In Japan, biosimilars are referred to by the non-proprietary name of the reference biologic, followed by BS to denote biosimilar, the respective follow-on number and an abbreviation to reference the manufacturer.[9] Because the value of any distinguishable naming convention is dependent on its uptake by end-users, Health Canada intends to consult interested stakeholders to understand the compatibility of different schemes with the electronic systems used for the prescribing, dispensing and tracking of biologic drugs. In the meantime, biologics in Canada are identified by brand name, common or non-proprietary name, and drug identification number.[10] India, China, Colombia, and Mexico have marketed intended copies of etanercept, and some Latin American countries and India have approved and marketed an intended copy from rituximab. There is no homogenous naming convention, but the fact that these intended copies often share the INN of the original biologic and its biosimilars underscores the need for a naming convention that allows their differentiation.[11]

Conclusions

Although there is a trend toward establishing differentiation between biologic originators and biosimilars through naming, there is still lack of global consensus. This lack of harmonisation could have direct implications on pharmacovigilance data, monitoring interchangeability, automatic substitution, and even reimbursement processes.[12]

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Concepts and principles: Development in depth

In this article, key concepts and principles in the evaluation and approval of biosimilars are explained

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The European Medicines Agency (EMA) defines a biosimilar as a biologic medicine that is similar to an original medicine that has already been authorised for use in terms of quality characteristics, biological activity, safety, and efficacy.[1,2]

Core concepts in the development of biosimilars include:

- Extrapolation
- Comparability
- Immunogenicity
- Interchangeability/risk assessment
- Timelines.

Extrapolation

Extrapolation is a key issue of biosimilar development and relates to extending the findings from one set of conditions to another, such as extending and applying the safety and efficacy data from clinical studies regarding one indication (medical condition) to another indication, or extending data from clinical studies in one population (for example, adults) to another (for example, children). Extrapolation concerns four different aspects – efficacy, safety, immunogenicity and interchangeability – and might relate to the indication, population or both.

Much debate has centred on which data are required to grant an approval for the extrapolated indications of the reference product.[1,3] In clinical testing, regulators want to confirm the similarity of the molecules in disease indications; they do not want to reassess the clinical benefit of the drug per se. European guidance states that, if adequately justified, biosimilars can receive all authorised indications of the reference product, even though comparative clinical data are only provided for a subset of those authorised indications.[3–6]

Extrapolation is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. If pivotal evidence for comparability is based on pharmacodynamics, and different mechanisms of action are relevant (or uncertainty exists) for the claimed indications, then relevant data to support extrapolation for all the clinical indications claimed are required. Applications for extrapolations should also be supported by comprehensive discussion of the available literature, including the involved antigen receptor(s) and mechanism(s) of action.

The scientific justification of extrapolation should address:

- mechanism of action
- biodistribution
- immunogenicity
- expected toxicities in each patient population.

Additionally, any other factor that might affect the safety, efficacy, or immunogenicity of the product in each (approved or claimed) indication should be addressed. Supporting clinical data in a sensitive and representative population are therefore critical to justify extrapolation to other indications. This is a crucial consideration, because if clinical trials were to be conducted in each indication, the breadth of biosimilar development programmes would effectively negate the advantages of an abbreviated approval pathway based on developing a product that is highly similar to a reference product with an established risk–benefit profile.[7] Table 1 shows rationale for extrapolation as indicated by the European Medicines Agency (EMA).

TABLE 1

Rationale for indication extrapolation

- Extrapolation is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification
- If pivotal evidence for comparability is based on pharmacodynamics and different mechanisms of action (or uncertainty exists) for the claimed indications, then applicants should provide relevant data to support extrapolation to all claimed clinical indications
- Extrapolations should be supported with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action

Understanding the manufacturing process

To better understand the reasoning behind the approval process allowing for the extrapolation of indications, the biosimilar manufacturing process must be fully understood (for further details refer to to the article on manufacturing in this handbook). Biosimilars are systematically engineered to match the reference product in both structure and function. Process optimisation toward similarity and precise control during manufacturing to maintain similarity are important to ensure the quality of biosimilars, as is employing suitable test systems, especially those yielding the best results for »

establishing biosimilarity.[8–10]

Critical quality attributes of a biologic have the potential to affect its safety or efficacy through a variety of mechanisms; thus, the definition of these attributes is important for assuring the efficacy and safety of the product. In the case of monoclonal antibodies (mAbs), efficacy can be affected by changing the antibody's interaction with its target, for example, due to conformation alterations or chemical modifications of critical residues. These attributes might alter the safety profile of the therapeutic antibody, either by increasing potential immunogenicity or by causing an increase in off-target binding, for example.

A single quality attribute might affect multiple functions, and the degree of impact can be molecule-specific. Most therapeutic proteins undergo glycosylation, which can influence the biological activity of a protein. For example, glycosylation can affect half-life by influencing the clearance of a protein, and in the specific case of therapeutic antibodies, Fc glycosylation plays a role in functions such as antibody-dependent cellular cytotoxicity.[11–13]

Reverse engineering

The manufacturing process of biosimilars tries to 'replicate' that of the reference without full knowledge of its different steps – considering that it is proprietary – through detailed analyses of the reference product and using a 'reverse engineering' strategy. Given the structural complexity and variation of the molecules and the cell systems where they are produced, reverse engineering may result in significant differences in the production of the biosimilar (for example, different cell line, production and purification of the biosimilar from the cell line). This poses significant challenges to companies and their scientific teams in terms of expertise and capabilities as well as time and cost. However, because the focus of clinical trials involving biosimilars is on the need to show similar physicochemical and biological properties as well as efficacy and safety versus the original molecule, and not on elucidating the mechanism of action and proof of concept, the regulatory paths to approval are distinct and bypass some of these inherent difficulties.[14]

Comparability

Comparability studies need to be conducted to demonstrate the similarity in terms of quality, safety and efficacy, of the biosimilar and its approved reference drug.[2] In addition, the comparability and similarity of its biological activity is determined using assays relevant to the modes of action of the reference biologic in all potential indications (Table 2).[15] The mechanisms of action of the drug are assessed in all potential disease indications to confirm that it performs adequately and comparatively to the reference drug under clinical conditions. This thorough assessment is designed to show high similarity because all aspects of the drug are evaluated with the most sensitive and specific assays. Together these assays should broadly cover the functional aspects of the drug, even though some may not be considered essential for the therapeutic mode of action. Because in vitro assays can be more specific and sensitive than studies in animals, they are paramount in the non-clinical comparability exercise. This entirety of evidence ensures that all accumulated data (clinical and analytical) on the biosimilar candidate are considered. This includes comparison of the bioanalytical characteristics of batches of reference product and biosimilar, and the effects on the cellular and molecular mechanisms of action relevant to the disease indications of the reference drug.[16]

Immunogenicity

For a biologic that is administered to an individual more than once, alternating or switching between the biosimilar and reference products should not increase the risk of adverse events from using the reference product without such alternation or switching in terms of safety or diminished efficacy. Similarly, the risk associated with alternating or switching between biosimilars should not be greater than the the risk of uninterrupted use of the reference product.[17]

Therefore, immunogenicity (that is, the ability of the biosimilar to trigger an immune reaction) is a critical factor when assessing biosimilarity and should be evaluated in a risk-based manner. Most biologics can induce immune responses, which, in many cases, do not have clinically relevant consequences. Immune responses can include the development of antidrug antibodies or generation of neutralising antibodies that might potentially eliminate activity. The most severe scenario is the cross-reaction of antidrug antibodies with an endogenous protein, thereby eliminating its critical function and potentially causing harm. The extent of immunogenicity can vary due to changes in the manufacturing processes of the same biosimilar, or any biologic (including reference drugs), or among different manufacturers of biosimilars/reference products.[18–21]

Scientific and immunological reasons might

TABLE 2

Comparability testing for biosimilars

Quality attribute	Demonstration of similarity
Protein structure and manufacturing quality	Extensive laboratory analyses of molecular characteristics (in multiple batches)
Pharmacokinetics, pharmacodynamics and toxicity (in animals)	In vitro and in vivo assays (in vivo studies only if additional information is needed after in vitro evaluation)
Pharmacokinetics, pharmacodynamics and toxicity (in humans)	Early pharmacology studies
Clinical efficacy and safety	Pivotal clinical comparability trials, usually in the most sensitive indication

> Prescribers, pharmacists, payers and patients should feel confident in the sound, scientific approaches taken to evaluate and approve biosimilars

support a switch from originator to biosimilar, if certain conditions are fulfilled by the drug. Different immunogenic responses of the patient to the drug are dependent on the drug's quality characteristics, but not on the patient him/herself because the genetic background and nature of the disease is similar before and after switching. To further complicate this issue, immunogenicity is not only due to the drug, because other factors such as the status of disease and how the drug is administered can play a role, but also because clinicians are sometimes more concerned with the safety profile of the drug and how the different production process of a biosimilar affects the risk of the patient experiencing adverse events.[22]

Interchangeability and the issue of switching

Interchangeability implies that a biologic can be replaced by the biosimilar without intervention of the prescriber. However, there are discrepancies between countries about what constitutes an interchangeable product. Whereas the US Food and Drug Administration (FDA) might approve a product as such, the EMA does not to designate a product as interchangeable, with decisions regarding interchangeability occurring at the national level. FDA guidelines require that a biosimilar should produce the same outcome as the originator, without increased safety risks or reduced efficacy when switching from the reference product to the biosimilar. Once a product is approved as interchangeable, it becomes possible to substitute the reference product with the biosimilar.[23]

As explicitly defined by the guidelines pertaining to biosimilars, the data supporting biosimilarity are not only based on quality, but also on clinical confirmation. By contrast, the assessment of quality differences is not a relevant question in the clinical »

study programme of the original drugs, where the focus is the comparison of clinically relevant efficacy and safety profiles of two therapeutic regimens. In clinical studies, pre-existing pharmacovigilance data on the reference product help validate the safety data obtained from biosimilar studies, and are compared with historical data or in direct head-to-head comparability studies. Therefore, bridging studies correlating critical attributes of the antibody and pharmacovigilance data are required to support the use of biosimilars, irrespective of the source of the drug. Also, not only should patient data in the market be followed up over time (for example, safety data collection after approval), but data on the quality of the biosimilar should also be generated. Confidence in biosimilars will thus depend on how transparent this assessment is.

Risks associated with switching

Development programmes of several biosimilars have included studies in which the reference product has been switched to the biosimilar and, occasionally, back to the reference drug. Epoetin (EPO) is a highly glycosylated protein that depends on post-translational modification for its mechanism of action and is one of the few therapeutic proteins to induce severe immunogenicity reactions; however, no serious adverse events based on immunogenicity have been reported in regard to switching from EPO reference products to biosimilars.

Results regarding use of infliximab have not raised concerns either. Transition data from the PLANETAS and PLANETRA extension studies showed comparable rates of serious treatment-emergent adverse events between the maintenance and transition groups. The anti-drug antibody positivity and hypersensitivity reactions during the second year of both studies did not differ significantly between patients exposed to the reference product or biosimilar as compared with those who received only the biosimilar over two years.[24,25] This view is supported by the fact that switches between these reference products and biosimilars have been accepted in some EU Member States (Poland, Norway, Finland or Hungary). Data show that similar immunogenicity and safety exist between the biosimilar and the original infliximab, and these results have resulted in some regulatory bodies in the EU supporting interchangeability.[26,27]

Data from an independent study sponsored by the Norwegian government (NOR-SWITCH) designed to assess the efficacy, safety and immunogenicity of biosimilar Remsima have added to the real-world evidence that supports switching patients from reference infliximab to biosimilar infliximab. The biosimilar was non-inferior to its reference product in adult patients who had been switched to receive treatment with the biosimilar for 54 weeks; all participants had been on stable treatment with the reference product for at least six months prior to switching to the biosimilar.[28]

Development timelines

It is the general perception that biosimilars can progress from bench to shelves in a shorter period of time than conventional biologics and small-molecule drugs. The stages of comparative analysis, process development, scale-up and validation, clinical trials, and review and approval of the biosimilar by regulatory agencies might in fact take 5–9 years, and the main challenge is conducting long and expensive studies, in particular because in many cases the study designs are not sensitive enough to detect differences between the reference product.[29] Another challenge in terms of timelines for development concerns the degree of protection conferred by patents for the original biologics, which have a period of exclusivity that varies per country once the agent receives approval for commercialisation, during which a biosimilar cannot be marketed.

Conclusions

Taking all this into account, prescribers, pharmacists, payers and patients should feel confident in the sound, scientific approaches taken to evaluate and approve biosimilars, including switching and interchangeability and indications granted via extrapolation.

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PHARMACOVIGILANCE

Traceability and pharmacovigilance

An important requirement for the safety monitoring of all biologics (including biosimilars) is the need for awareness of adverse events, and product and batch traceability during clinical use and at all levels in the supply chain

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Pharmacovigilance is defined as the practice of monitoring the effects of licensed drugs, especially in order to identify and evaluate previously unreported adverse reactions.[1] To do this, it is crucial to ascertain if the adverse event is actually caused by a drug and, in the case of polytherapy, to identify which drug might be responsible. The batch must also be identified, because a specific impurity or degradation product present in a specific batch could be involved. Thus, for a proper pharmacovigilance, the traceability of the drug (knowing the batch reference, its history, storage conditions, identification of the patient who received it, etc) is mandatory.

Traceability and risk management

Traceability is a key element in monitoring the safety of biologics by enabling pharmacovigilance measures. Real life conditions, such as risks of drug–drug or drug–food interactions are not accurately evaluated by clinical trials. Thus, long-term follow-up is essential to establish a risk management plan (RMP). The aim of risk management is to address uncertainties in the safety profile at different points in the lifecycle, and to plan accordingly. This procedure was put in place in 2005 as part of European pharmacovigilance legislation and comprises part of the marketing authorisation application of a drug.[2]

RMPs include plans for pharmacovigilance activities designed to gain greater knowledge and explain how risks will be minimised in patients, and how those efforts will be measured (see Figure 1).

An RMP is required for all drugs containing a new active substance. The RMP might also be implemented after the product has been marketed if significant changes occur (for example, new indication, new dosage, new route of administration, new manufacturing process) or if a significant risk has been identified after the drug has reached the market. The RMP is also required for biosimilar products registered in the EU. The World Health Organization has published guidance on scientific principles for regulatory risk assessment of biotherapeutic products, including RMPs.[3]

For a biosimilar, as for any biologic, variability between products from different manufacturers with the same active substance and batches of the same product from the same manufacturer need to be considered.[4] Moreover, numerous changes in the production process during the life of the biologic might induce large modifications in its composition, as demonstrated, for example, for rituximab originator.[5] Thus for each physicochemical or biological parameter, a biosimilar must fall in the range of variability observed for the originator.[3,6] Through the extensive comparability exercise for the originator drug and its biosimilar candidate, including a Phase III clinical trial, the tolerance and the classical side effects can be demonstrated as identical for both originator and biosimilar. However, immunological side effects remain a key, even controversial, issue, and are frequently cited by opponents of the use of biosimilars, particularly with regards to switching, interchangeability and extrapolation procedures.[5,6] Thus, it is paramount to verify whether a biosimilar has more or fewer immunological side effects compared with the reference drug.

For biologics that are the subject of a suspected adverse event, it is of particular importance that the batch number, in addition to the brand names or name of the manufacturer, is reported.[7] Some immunological side effects, such as the presence of neutralising antibodies, are due to factors not directly related to the drug. For example, the production of neutralising antibodies for a biologic is not only related to the drug itself (that is, specific antigenic sequences, presence of foreign proteins and aggregates) but also to the patient's characteristics, co-medications and pathology.[8,9] »

FIGURE 1
Risk management plan

Thus, an objective comparison between reference and a biosimilar must determine not only the frequency of an undesirable event but also the relative occurrences of the drug-related and non-drug-related causes.

The RMP is the responsibility of the manufacturer and the use of the drug must adhere to conditions outlined in the Summary of Product Characteristics. However, drugs are used in many locations and under differing circumstances (for example, medicines dispensed through a hospital pharmacy in the inpatient setting are administered to the patient by a healthcare professional within the hospital, whereas medicinal products dispensed through an outpatient or community pharmacy in primary care are administered by the patient at home) and it is therefore extremely difficult to monitor all side effects that occur in all these situations.

As a consequence, only serious adverse events can be identified and recorded but monitoring is very dependent on the local organisation of pharmacovigilance. The recent introduction of serialisation following EU directives (falsified medicines directive; FMD) should theoretically facilitate traceability. The EU FMD (2011/62/EU) was adopted in 2011 and introduced new harmonised measures to ensure that the use of medicines in the EU is as safe as possible, and that trade in medicines is controlled properly.[10]

Safety features introduced for the packaging of medicines include: a unique identifier (a 2D data matrix code and human readable information) that must be scanned at fixed points along the supply chain; and an anti-tampering device, allowing verification of whether the packaging of a medicine has been compromised. However, this system has been developed to ascertain that medicines are genuine and not counterfeit, but not for pharmacovigilance purposes.

The RMP required by the European Medicines Agency for a biosimilar is expected to take into account any identified or potential risks also covered in the RMP of the reference product.[2,11] Therefore, implementing traceability at the level of hospital and community pharmacies, both for reference drugs and biosimilars, is complex. Indeed, at present, traceability by batch is not required for reference biologics.[12] The anticipated great increase in the number of authorised biosimilars would necessitate development of specific systems to trace all batches regardless of their origin (reference or biosimilar) but also across different brands of a specific biosimilar.

At the community pharmacy level, all brands of a biosimilar plus the reference drug should be available because substitution by the pharmacist (such as for generics) is not allowed in many countries (see key concepts chapter in this handbook). Implementation at community levels is therefore likely to be problematic and costly.[12,13]

Questions arise regarding the availability of the traceability data generated by hospital and community pharmacies.[14] Whose property are these data? Will these data be freely accessible even though they will comprise data specific to each biosimilar and reference?

Considering the decline in available health resources in many countries, mainly related to increasing costs of medicines and innovations, it is unlikely that public funds would be made available to help implement widespread traceability systems. The manufacturer of a specific biosimilar might perhaps be willing to pay to obtain traceability data of their own product but might be unlikely to support the expenditure required to follow all prescriptions or switching activities. At a community pharmacy level, the problem seems quite unsolvable.

Conclusions

These practical, but fundamental, considerations might impact on the implementation of biosimilars in several countries. In contrast to biosimilars, which are considered as new compounds, traceability data are not required for reference drugs more than 20 years old. Therefore in community pharmacies, there might be a temptation to prescribe and dispense the reference instead of the biosimilar to avoid complicated procedures. However, at the hospital level, financial incentives to prescribe bisosimilars, such as those being implemented in many countries, could help mitigate this risk.

Healthcare professionals can improve pharmacovigilance through a number of ways, including:

- Recording the trade name and batch number at all levels, including at dispensing and patient administration.
- Ensure that trade name and batch number are reported in case of suspected adverse events, according to local practice and national regulations
- In primary care and community pharmacies, the trade name and batch number of the biologic medicine should be provided to the patient
- In any cases of switching, it is important to record the trade name and batch number for each of the medicines.

Furthermore, what about risk analysis and related cost–benefit analyses? Indeed, as previously discussed, biosimilarity is ascertained by rigid, extensive physicochemical and biological tests, and clinical trials.[2-4] Some of these preclinical tests allow all the drug-related parameters implicated in immunological tolerance to be determined. The primary structure of the reference and biosimilar are the same, therefore, by definition, the antigenic properties of all particular sequences should be identical. The level of foreign protein, and also the level and the characteristics of aggregates that can induce antigenic behaviour, must also lie in the range observed for the reference, and biosimilars and reference products should have comparable levels of safety. Thus, to believe that the risk of a biosimilar, which conforms to the characteristics of the reference, inducing more or new side effects compared with the reference, has no real meaning from a scientific point of view.

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EU regulatory framework for biosimilars

The regulatory policy for biosimilars is outlined mainly in general and product class-specific guidelines issued by the European Medicines Agency, addressing quality, non-clinical and clinical issues

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When patent and data protection of a medicinal product have expired, new manufacturers might choose to market a copy of the product. Because the copy of a biologic medicinal product can only be demonstrated to be similar, but not identical, to the one previously authorised, it is defined as a biosimilar.[1]

Marketing authorisations and biosimilars

The requirements for the marketing authorisation (MA) of a biosimilar medicinal product include the demonstration of the similar nature to the reference product in terms of quality, efficacy and safety (biosimilarity). Biosimilarity is demonstrated through an in-depth comparison of physical, chemical and in vitro biological characteristics, and comparative non-clinical and clinical studies, which together comprise the comparability exercise.[2]

As for any complex drug, the physicochemical characteristics of a biologic are influenced greatly by the manufacturing process, and they cannot be exactly duplicated when producing a copy, or necessarily even maintained when a change in manufacturing occurs.[1] Even without changes in the manufacturing process, batch-to-batch variability is to be expected and should be monitored. Moreover, biologics cannot be completely characterised using available analytical methods, and bioequivalence is not enough to guarantee therapeutic equivalence because the pharmacodynamics can be different.[3] The conclusions of a comparability exercise are valid for a given time only; thus, it would be preferable to demonstrate the similarity over the whole product lifecycle with regard to the effects on the biosimilar's characteristics, such as therapeutic equivalence. For this reason, the assessment of therapeutic equivalence should not end with the MA, but should be managed for the entire lifecycle of the product.[4-6]

The assessment of therapeutic equivalence influences the way a medicinal product is managed, namely the policies on interchangeability and substitution, and the possibility of pharmacist and clinician intervention at the dispensing level. Moreover, a substitution programme can be introduced by the public administration on the basis of interchangeability.

Regulatory issues

Interchangeability is a scientific concept directly related to intrinsic drug characteristics, and it follows from therapeutic equivalence. Due to its complexity, the assessment of interchangeability requires the scientific knowledge that only regulatory agencies possess at an institutional level.

Unlike generics, which are interchangeable by definition, biosimilars are not interchangeable *per se*. The policy of the European Medicines Agency (EMA) comprises a mandatory comparability exercise to grant a MA for biosimilars, but the regulatory guidelines do not include recommendations on interchangeability because all decisions are regulated at the national level.

The term 'substitution' could be used to indicate the prescription of a biosimilar to naive patients, or the switch, made by the prescribing physician, between two medicinal products. Because in these cases the prescriber's choice is not limited to interchangeable products, this term is better avoided, and only used with the meaning of 'automatic substitution' at the dispensing level. The term 'substitution' should be avoided even when, due to the payer's policies, physicians might be forced to prescribe a biosimilar instead of the reference product; the term 'constrained prescription' could be used instead.[7]

In the EU, the policy of automatic substitution is left to local authorities, which can introduce it based on a demonstration of interchangeability, even though many countries do not allow automatic substitution at the dispensing level.[7] Even in countries where it might be allowed, automatic substitution at the dispensing level makes traceability more difficult to deal with, as it can imply the loss of essential information for this class of medicines and might compromise traceability during the product's lifecycle and its identification in the pharmacovigilance report. While this is accepted in the case of small molecule generics, it might raise concerns when extended to biologics.

The publication of the results from NOR-SWITCH, a randomised, non-inferiority, double-blinded, Phase IV trial addressing the issue of switching from the reference infliximab to a biosimilar in stable patients, has shed some light on a highly debated topic. The conclusions of the study can be seen as reassuring for prescribing physicians, at least in the case of infliximab.[8]

From a product liability perspective, 'failure to warn' or 'design defect' liabilities cannot be considered ascribable to the generic MA holder. Indeed, the generic must have the same labelling as the originator. Redesign or label modification, intended to improve the risk–benefit ratio, are not possible for generics, because the generic drug is required to have the same active ingredients, route of administration, dosage form, strength, and labelling as the reference (21 U.S.C. 355(j)). As a consequence, the extent to which a generic »

> EU regulatory policies, mainly established by guidelines issued by the EMA and revised periodically, can now draw upon more than a decade of experience

manufacturer could be held liable in failure to warn or design defect claims is limited.[9]

From a medical liability perspective, if a patient switched to a biosimilar experiences adverse events or loss of efficacy, the medical liability chain will be different from that in the case of generics. Moreover, the case of treatment-naïve patients will be different from that of non-naïve patients. In the case of naïve patients, physicians choose from a range of medicinal products with the same unknown/the same risk (it is not possible to know patients' responses to each therapeutic option until they have taken the drug). In contrast, in the case of non-naïve patients, when physicians switch to a biosimilar, they are switching from an option where the individual response is known to an option where it is unknown.[9]

The EU legislative framework

In the EU, biotechnological medicinal products fall under the provisions of Regulation EC No. 726/2004, while the legal basis for biosimilars lies in the Directive 2001/83/EC (as amended). The authorisation process for biosimilars of polypeptide-based products is the same as that of protein-based products. The regulatory policy for biosimilars is outlined mainly in general and product class-specific guidelines issued by the EMA, addressing quality, non-clinical and clinical issues.[10] Table 1 summarises some of the guidelines.

The MA application is supported by a dossier containing the required data in a standard format (known as the common technical document (CTD)). The CTD is composed of five modules:

- **Module 1**: specific administrative data;

- **Module 2**: summaries of quality, non-clinical and clinical data;
- **Module 3**: chemical, pharmaceutical and biological information (quality);
- **Module 4**: non-clinical reports (safety);
- **Module 5**: clinical study reports (efficacy).[12]

For biosimilars, the requirements for MA applications are based on the demonstration of the similar nature of the two biological products, based on the comparability exercise.[2] The number and extent of comparability studies that form the comparability exercise is outlined in guidelines issued by the EMA.[10] In the dossier of biosimilars, comparability studies are required in modules 3, 4 and 5; in the case of generics, non-clinical studies (module 4) are omitted and the demonstration of bioequivalence replaces module 5.[1] Indeed, generics, which are copies of medicinal products based on active ingredients obtained via a synthetic pathway, do not require pharmacodynamic investigations if the pharmacokinetic parameters can be used to demonstrate that the generic and reference are essentially the same. By contrast, because of the complexities of bioproduction, even minor modifications to manufacturing processes can yield substantial differences in pharmacodynamic parameters, so pharmacokinetic data alone are not sufficient for the demonstration of biosimilarity.

Conclusions

Biosimilars are a reality of the pharmaceutical market. EU regulatory policies, mainly established by guidelines issued by the EMA and revised periodically, can now draw upon more than a decade of experience.

Biologics are complex drugs. As such, their characteristics depend considerably on the manufacturing process, and their complete characterisation cannot be achieved by current analytical methods. The complexity of biologic medicinal products has clear repercussions on the assessment of therapeutic equivalence and, consequently, on interchangeability and substitution. For this reason, when copies of biological products are manufactured, they cannot be considered as small molecule generics. The EMA has led the way in the development of a regulatory framework of biosimilars. The EMA has the scientific competence and the broad view required to assess the interchangeability of biotechnological medicinal products. The EMA's assessment of interchangeability could then be used as a basis, by local regulatory agencies, to allow automatic substitution. The EMA, though, have chosen to leave decisions on interchangeability of biosimilars to national authorities. Therefore, it is of paramount importance to define the pharmacist's/clinician's role in the choice of switching between reference and biosimilars, especially in hospitals. It is highly recommended that both the pharmacist and the prescribing physician decide whether to always purchase the cheapest biosimilar or which patients have to be treated with the reference product, as a precautionary measure to assure continuity of care.

Where national authorities decide to allow automatic substitution without the prescriber's prior consent, the traceability of the administered medicinal product should be mandatory, in order to allow the prescribing physicians to monitor which medicinal product is actually dispensed to their patients as specified in good pharmacovigilance practice guidance.

TABLE 1

Key EMA scientific guidelines on biosimilars[2,10,11]

Overarching biosimilar guidelines

- Similar biological medicinal products
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues

Product-specific biosimilar guidelines

- Biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)
- Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins
- Non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
- Similar biological medicinal products containing interferon beta
- Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues
- Similar biological medicinal products containing recombinant erythropoietins
- Similar biological medicinal products containing recombinant follicle-stimulating hormone
- Similar medicinal products containing somatropin (Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues)
- Non-clinical and clinical development of similar biological medicinal products containing recombinant interferon alpha or pegylated recombinant interferon alpha

Other guidelines relevant for biosimilars

- Comparability of biotechnology-derived medicinal products after a change in the manufacturing process – non-clinical and clinical issues
- ICH Q5E Biotechnological/biological products subject to changes in their manufacturing process: comparability of biotechnological/biological products
- Immunogenicity assessment of biotechnology-derived therapeutic proteins
- Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use

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LANDSCAPE

Evolving landscape of biosimilars current and future

Since 2006, approximately 50 biosimilars have been authorised by the European Medicines Agency and continuing pressure on healthcare budgets is expected to force a change in attitude towards these drugs

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The European biosimilar market is the most mature in the world. The first guidance on biosimilars was issued by a European authority, the European Medicines Agency (EMA), and subsequently, many health authorities, including the World Health Organization, implemented specific regulations for the approval of biosimilars. Today most countries have specific regulations for the approval procedure of the follow-on products of recombinant biologics when the reference products come off patent.

Expiry of the patent protection and competition by biosimilars usually favours the reduction of prices for the reference product and biosimilars. The economic benefit of biosimilars depends on the specifics of the individual healthcare system, especially regarding the pricing and reimbursement structures. While the rates of discount generally amount to 90% for generics, they are expected to amount to less than 50% for biosimilars. The development process for biosimilars is expensive and takes a long time because of the mandatory clinical programme required by the regulatory authorities. In addition, the contribution of analytical studies to cost and time must not be underestimated. It takes up to eight years to bring a biosimilar to market, and development costs range from US$100–250 million (about 50-times that to launch a conventional generic).[1]

Since the very beginning of the biosimilar era, European hospital pharmacists engaged in the field of biosimilars. At first, we had to learn that biosimilars represent a new entity of medicinal products according to the licensing procedure of the EMA. Very soon, hospital pharmacists embraced the topic and set guidelines and conditions for the use of biosimilars in hospital patients. In 2005, a special interest group of pharmacists published a checklist to aid hospital pharmacists in the evaluation of biosimilars.[2] At that time, most of the biosimilars coming to the market were hormones and cytokines. While this so-called first generation of biosimilars was established, another, and much more complex, class of biologics – monoclonal antibodies (mAbs) and their derivatives (for example, fusion proteins, receptors, incomplete antibodies) – continued to revolutionise the treatment of patients with oncological diseases, autoimmune diseases, asthma, wet macular degeneration, and others.

Of note, hospital pharmacists gradually became more familiar with the subject and a panel of experts (authors) reviewed the 31 previously drawn evaluation criteria for biosmilars[2] and produced a shortlist of ten criteria relevant for clinicians, pharmacists and clinical practice.[3] These included: how long the drug had been on the market; number of registered indications; serious and mild adverse events and their frequency; differing contraindications; and precautions or warnings compared with the reference compound, among others. The publication also suggested a decision matrix system to enable physicians and pharmacists to give their own weight to these criteria. This decision matrix system was designed to support objective decision-making and rational selection of biosimilars by Pharmacy and Therapeutics committees in hospitals. While a general selection matrix can be regarded as an important step forward, additional, more refined selection matrices for specific groups of biosimilars are necessary and their implementation requires expert knowledge. Various parameters of biosimilars should be assessed specifically at product level and on a case-by-case basis. Moreover, additional efforts for registries/Phase IV studies and potential additional costs arising for stock keeping and administration should be considered. The varying consequences deriving from initiating treatment with a biosimilar for naïve patients or switching experienced patients from the reference to a biosimilar, as well as multiple switches between the reference and one or more biosimilars, are not described in the current decision matrix system.

Additional studies and more experience will make us more confident about the therapeutic equivalence in extrapolated indications, potential safety issues, multiple switching, naming and traceability, as well as the economic impact of biosimilars. Meanwhile formulary management of biosimilars and the good prescribing, distribution and administration practices will remain a challenge. In the hospital, local guidelines for prescribing, substitution, switching and pharmacovigilance have to be developed in an appropriate and pragmatic manner. Useful information can be found in the European Public Assessment Reports (EPARs) and various position statements of associations of healthcare professionals. Post-marketing pharmacovigilance is mandatory to determine the benefit–risk profile of biologics and biosimilars throughout their life cycle. Different post-marketing commitments for different biosimilars of the same reference product can be required. Especially in the case of switching, patients should be monitored closely for adverse drug reactions, and reporting by hospital pharmacists should be encouraged.

Approved biosimilars

Since 2006, about 50 biosimilar products across 15 different biological classes have been approved by the EMA (Table 1).[4] In 2017 and 2018, biosimilar products »

TABLE 1

Authorised biosimilars (to October 2018)

Product name	INN/active substance	Therapeutic area	Marketing authorisation holder	Marketing authorisation date
Omnitrope	Somatropin	Dwarfism, Prader-Willi syndrome, Turner syndrome	Sandoz	12/4/2006
Abseamed	Epoetin alfa	Chronic kidney failure	Medice	28/8/2007
Binocrit	Epoetin alfa	Chronic kidney failure, anaemia	Sandoz	28/8/2007
Epoetin alfa Hexal	Epoetin alfa	Chronic kidney failure, anaemia	Hexal	28/8/2007
Retacrit	Epoetin zeta	Anaemia, autologous blood transfusion, chronic kidney failure	Hospira	18/12/2007
Silapo	Epoetin zeta	Anaemia, autologous blood transfusion, chronic kidney failure	Stada	18/12/2007
Ratiograstim	Filgrastim	Cancer, haematopoietic stem cell transplantation, neutropenia	Ratiopharm	15/9/2008
Tevagrastim	Filgrastim	Cancer, haematopoietic stem cell transplantation, neutropenia	Teva Generics	15/9/2008
Zarzio	Filgrastim	Cancer, haematopoietic stem cell transplantation, neutropenia	Sandoz	6/2/2009
Filgrastim Hexal	Filgrastim	Cancer, haematopoietic stem cell transplantation, neutropenia	Hexal	6/2/2009
Nivestim	Filgrastim	Cancer, haematopoietic stem cell transplantation, neutropenia	Hospira UK	8/6/2010
Inflectra	Infliximab	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis	Hospira UK	10/9/2013
Remsima	Infliximab	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis	Celltrion Healthcare Hungary	10/9/2013
Ovaleap	Follitropin alfa	Anovulation	Teva Pharma	27/9/2013
Grastofil	Filgrastim	Neutropenia	Apotex Europe	18/10/2013
Bemfola	Follitropin alfa	Anovulation	Finox Biotech	27/3/2014
Accofil	Filgrastim	Neutropenia	Accord Healthcare	18/9/2014
Abasaglar	Insulin glargine	Diabetes	Eli Lilly Regional Operations	9/9/2014
Benepali	Etanercept	Rheumatoid arthritis, psoriatic arthritis, psoriasis	Samsung Bioepis UK	14/1/2016

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TABLE 1

Authorised biosimilars (to October 2018) (Continued)

Product name	INN/active substance	Therapeutic area	Marketing authorisation holder	Marketing authorisation date
Flixabi	Infliximab	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis	Samsung Bioepis UK Limited	26/5/2016
Inhixa	Enoxaparin sodium	Venous thromboembolism	Techdow Europe AB	15/9/2016
Thorinane	Enoxaparin sodium	Venous thromboembolism	Pharmathen SA	15/9/2016
Lusduna	Insulin glargine	Diabetes	MSD	04/01/2017
Terrosa	Teriparatide	Osteoporosis	Gedeon Richter	04/01/2017
Movymia	Teriparatide	Osteoporosis	Stada Arzneimittel	11/01/2017
Truxima	Rituximab	Chronic lymphocytic leukaemia, granulomatosis with polyangiitis, microscopic polyangiitis, non-Hodgkin's lymphoma, rheumatoid arthritis	Celltrion	17/02/2017
Amgevita	Adalimumab	Ankylosing spondylitis, Crohn's disease, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	Amgen	22/03/2017
Solymbic	Adalimumab	Ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	Amgen	22/03/2017
Flixabi	Infliximab	Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, ulcerative colitis	Samsung Bioepis	26/05/2017
Riximyo	Rituximab	Chronic B-cell lymphocytic leukaemia, microscopic polyangiitis, non-Hodgkin lymphoma, rheumatoid arthritis, Wegener granulomatosis	Sandoz	15/06/2017
Rixathon	Rituxumab	Chronic B-cell lymphocytic leukaemia, microscopic polyangiitis, non-Hodgkin lymphoma, rheumatoid arthritis, Wegener granulomatosis	Sandoz	19/06/2017
Erelzi	Etanercept	Ankylosing spondylitis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis	Sandoz	23/06/2017

Product name	INN/active substance	Therapeutic area	Marketing authorisation holder	Marketing authorisation date
Blitzima	Rituximab	Non-Hodgkin lymphoma, chronic B-cell lymphocytic leukaemia	Celltrion	13/07/2017
Ritemvia	Rituxumab	Wegener granulomatosis, microscopic polyangiitis, non-Hodgkin lymphoma	Celltrion	13/07/2017
Rituzena (previously Tuxella)	Rituxumab	Wegener granulomatosis, microscopic polyangiitism non-Hodgkin lymphoma, chronic B-cell lymphocytic leukaemia	Celltrion	13/07/2017
Insulin lispro Sanofi	Insulin lispro	Diabetes mellitus	Sanofi Aventis	19/07/2017
Imraldi	Adalimumab	Ankylosing spondylitis, arthritis, Crohn's disease, hidradenitis suppurativa, psoriatic arthritis, psoriasis, rheumatoid arthritis, ulcerative colitis, uveitis	Samsung Bioepis	24/08/2017
Cyltezo	Adalimumab	Crohn's disease, hidradenitis suppurativa, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, uveitis	Boehringer Ingelheim	10/11/2017
Ontruzant	Trastuzumab	Early breast cancer, metastatic breast cancer, metastatic gastric cancer	Samsung Bioepis	15/11/2017
Mvasi	Bevacizumab	Breast neoplasms, fallopian tube neoplasms, non-small-cell lung carcinoma, ovarian neoplasms, peritoneal neoplasms, renal cell carcinoma	Amgen	15/01/2018
Herzuma	Trastuzumab	Early breast cancer, metastatic breast cancer, metastatic gastric cancer	Celltrion Healthcare	09/02/2018
Semglee	Insulin glargine	Diabetes mellitus	Mylan	28/03/2018
Kanjinti	Trastuzumab	Early breast cancer, metastatic breast cancer, metastatic gastric cancer	Amgen	16/05/2018
Zessly	Infliximab	Ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, ulcerative colitis	Sandoz	18/05/2018
Halimatoz	Adalimumab	Ankylosing spondylitis, hidradenitis suppurativa, juvenile rheumatoid arthritis, psoriatic arthritis, psoriasis, rheumatoid arthritis, uveitis	Sandoz	26/07/2018

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TABLE 1

Authorised biosimilars (to October 2018) (Continued)

Product name	INN/active substance	Therapeutic area	Marketing authorisation holder	Marketing authorisation date
Hefiya	Adalimumab	Ankylosing spondylitis, hidradenitis suppurativa, juvenile rheumatoid arthritis, psoriasis, uveitis	Sandoz	26/07/2018
Hyrimoz	Adalimumab	Ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, juvenile rheumatoid arthritis, papulosquamous skin disease, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, uveitis	Sandoz	26/07/2018
Trazimera	Trastuzumab	Stomach neoplasms Breast neoplasms	Pfizer	26/07/2018
Hulio	Adalimumab	Ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, uveitis	Mylan/Fujifilm Kyowa Kirin Biologics	CHMP positive opinion 26/07/2018
Pelgraz	Pegfilgrastim	Neutropenia	Accord Healthcare	Committee for Medicinal Products for Human Use (CHMP) positive opinion 26/07/2018
Udenyca	Pegfilgrastrim	Neutropenia	ERA Consulting	CHMP positive opinion 26/07/2018
Ziextenzo	Pegfilgrastrim	Neutropenia	Sandoz	CHMP positive opinion 20/09/2018
Pelmeg	Pegfilgrastrim	Neutropenia	Cinfa Biotech	CHMP positive opinion 20/09/2018
Fulphila	Pegfilgrastrim	Neutropenia	Mylan	CHMP positive opinion 20/09/2018

referencing to the high-selling biologics trastuzumab, adalimumab, and pegfilgrastim were approved and entered the market. Up to ten adalimumab biosimilars are expected to launch over the next year.

The EMA publishes an EPAR for every medicine granted marketing authorisation via the centralised mechanism. Each EPAR represents a highly valuable and useful information resource for health care professionals who are interested in in-depth information on a particular medicine. In addition, the EMA and the European Commission have published an information guide for healthcare professionals to provide reference information on the science and regulation of biosimilar medicines.[5] However, the EMA's evaluation of biosimilars does not include recommendations on interchangeability. Automatic interchange of biosimilars at the pharmacy level is a national prerogative and regulations differ throughout the EU.

Bioidentical products

Some of the authorised products are based on the same regulatory dossier (same date of authorisation) and are manufactured in the same cell line using the same manufacturing process.

These so-called 'bioidenticals' are the same (not similar) products but carry different brand names and are marketed by different manufacturers. In fact, substitution of bioidenticals at the pharmacy level is allowed. The identification of bioidenticals is not easily possible for physicians and pharmacists and differing regulations for the substitution of biosimilars and bioidenticals make it even more complex. Additional labelling might be useful and considered by the health authorities.

Biosimilars in the future

There are hundreds of biologics on the market today and most of the innovative medicinal products contain proteinaceous active substances. Additional top sellers of the mAb class will lose patent protection relatively soon (for example, ranibizumab, aflibercept) and further in the future

(for example, checkpoint inhibitors). Manufacturers of the reference products develop next-generation products as a life cycle management, which sometimes will also run off patent. Therefore, it will be necessary to continuously evaluate new biosimilars, and each active substance will contain its own specifics and challenges. At the same time, healthcare professionals will become more experienced and the market's willingness to adopt biosimilars is likely to increase. Moreover, continuing pressure on healthcare budgets is expected to force a change in attitudes and will result in an increase in the use of lower cost biosimilars across Europe. Hospital pharmacists might join efforts in regard to identification and documentation of the particular medicinal product used in an individual patient. The various aspects of the use of biosimilars make it necessary for us, as hospital pharmacists, to thoroughly and continuously keep ourselves updated in order to be able to advise physicians and patients about biosimilars and the concept of biosimilarity.

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Benefits of biosimilars

Prescribers, as well as other health professionals, payers, and patients, should be aware of the potential advantages and disadvantages of biosimilars in order to allow for an optimal treatment plan, and one that is adapted to the patients' particular conditions, needs, and preferences

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Despite some uncertainty surrounding the bioavailability, onset of action, duration of action, and adverse events of biosimilars, their development and subsequent regulatory approval these past years have been received with great expectation, given the potential substantial gains their use brings to health systems in general and patients in particular. Although there has been a rapid increase in the number of biosimilars available worldwide recently, mainly in the fields of oncology and rheumatology, their uptake has been comparatively slow, which is in part due to lack of knowledge of their benefits by the different elements in the process of treatment decision making.[1,2]

Clinicians

Currently, the US Food and Drug Administration only requires proof of similarity to the reference product in terms of structure and function, with no significant differences in purity, safety and efficacy. In the EU, the functional and structural characteristics must be similar between the reference biologic product and follow-on biosimilar, and the pharmacokinetic, efficacy, safety and immunogenicity data must be consistent for both molecules.[2,3] Other countries might have less stringent requirements for approval of a biosimilar, and the subsequent post-marketing monitoring and surveillance needs might differ as well. However, given the unavailability of precise methodologies to determine the structure of large biological molecules, the standards applied to evaluate the original molecules may not be appropriate to evaluate the biosimilar copies.[1]

These limitations can have a significant influence

on the long-term efficiency and safety of biosimilars. Because different manufacturing and purification processes, and even distinct storage conditions and distribution chains, make it almost impossible to replicate the reference molecules, there are currently concerns regarding the structure, purity, and immunogenicity of the biosimilars. In addition, different biosimilars for the same reference product may present varying features and may not be interchangeable. Despite the much anticipated reduced healthcare costs associated with the use of these molecules, which partially result from the less extensive clinical development program required to support product registration with the regulatory authorities (evaluation of the similarity of physicochemical, preclinical, and clinical data only), biosimilar products may impact clinical practice and patients in other ways.[2,3]

Immunogenicity, thought to be a function of a molecule's physicochemical features, is a key safety item from the regulatory point of view and can be determined using in vitro (recognition and binding assays with an array of antibodies against the drug) and in vivo (cross-reactivity assay of anti-drug antibodies isolated from treated patients) methods. However, negative results in vitro may not necessarily exclude immunogenic responses in actual patients, and the immunogenicity might not be comparable across studies due to differences in methodologies, patient populations, prior exposure to the reference product, concomitant drug use, and the disease itself. For these reasons, immunogenicity testing is a requirement in safety evaluations as well as in post-marketing pharmacovigilance programmes.[2,4]

Clinicians must also be aware of how biosimilars can affect patient adherence to treatment so that potential issues can be addressed early on, before any switch from a branded drug to its copy (in particular how patients view these replacement drugs in terms of potency and efficacy).[1] Many factors are known to contribute to poor adherence, including difficulties administering a drug, and inconvenient, complex, and strict regimens. However, patients' attitudes towards medications can also negatively impact the way they feel about their new treatment regimens (for example, uncertainty about the quality of the replacement drug, fear of side effects, difficulties using a new delivery system).[5]

Educational initiatives focusing on the science behind the manufacturing process and on the available clinical experience with biosimilars are therefore needed and can ultimately lead to improved treatment plans, and subsequently clinical outcomes, for patients together with improved treatment adherence.[3]

> Increased awareness of these drugs, how they are developed, and the current regulatory framework, can play a significant role in increasing confidence regarding their use, not only for clinicians but also for patients

Pharmacists

As for clinicians, pharmacists need to be aware of the potential benefits and concerns of biosimilars because they are likely to see increasingly higher numbers of prescriptions for these drugs in the next years as the patents and exclusivity periods for several biologics expire, hence the need to be able to provide recommendations regarding optimal use for patients.[1]

This is of particular relevance in countries such as the USA, where pharmacists are allowed to fill a prescription with the brand drug or a replacement without consulting the physician or the patient. In some countries, insurance plans or governmental directives may even mandate a switch to a biosimilar whenever possible in order to reduce the burden to healthcare systems. However, switching from branded drugs to biosimilars has been reported to affect dosing accuracy and adherence in some cases, resulting in dosing errors or treatment lapses.[5]

Pharmacists should be aware that questions about interchangeability (the practice of substituting one drug for another with the same clinical effects under similar conditions by the prescriber or with his/her agreement), switching (the practice of substituting one drug for another with the same therapeutic intent), and automatic substitution (the practice of substituting one drug for another interchangeable drug at the pharmacy level without consulting the prescriber), as defined in the EU, still persist and that these practices are not consistent between countries.[4]

Switching and substitution can in fact constitute a cause of anxiety for patients who have doubts about the efficacy and safety of biosimilars and who may associate unrelated, undesirable events with the new regimen. In addition, nomenclature and traceability are particularly important for pharmacists to facilitate the identification of the active ingredient, and pharmacovigilance programmes should distinguish between the brand names of the biosimilar and reference drug, including batch manufacturing information.[4]

Patients

The main advantage of biosimilars is the potential to provide similar clinical benefits with cost savings, thereby allowing more patients to have access to treatments that might otherwise be a prohibitive expense in the long term, with limited availability and accessibility due to restrictions in insurance and public payer coverage, limited reimbursement, and high out-of-pocket costs. Inadequate insurance »

coverage can also exacerbate financial constraints that result in differences in equality in access to treatment and care.[2,3]

In addition, the commercialisation of biosimilars may extend the current indications of their reference products. This can occur when the reference product is approved for an additional indication, which results in registration of this new indication for the biosimilar without conducting further clinical trials. This significantly reduces the investment in time and resources in the development of the biosimilar. However, this process of 'extrapolation', which is usually done when changes in the manufacturing process of the reference products are introduced, is not widely accepted when it refers to new indications, and may not be applicable to all types of molecules.[2]

Nonetheless, not all patients may agree with a switch from branded drug to biosimilar, for several reasons, and they should be informed that a biosimilar may not be identical to the reference drug and that close monitoring may be needed during the transition process.[1] Moreover, with the increased availability of biosimilars, these agents might be the first choice in some cases, or even when a switch is needed due to formulary changes. There is currently a dearth of data in regard to the potential risks and benefits of multiple switches and of alternating between a reference biologic and its biosimilar. Likewise, comparative studies of different switching strategies with adequate power to evaluate non-inferiority or equivalence between reference and the corresponding biosimilar are lacking.[3]

Payers

Considering the increase in costs associated with drug development in recent years, which have translated into higher prices for payers and direct consumers, insurers have long been considering alternatives to costly drugs, the benefits of which outweigh costs, that do not jeopardise safety and clinical outcomes in the long term. As for generic small-molecule drugs, the introduction of biosimilars can contribute to substantial cost savings, although at a reduced scale given the complexity of the manufacturing process for biologics and their copies. It cannot be ignored that the availability of biosimilars at lower prices might have an impact on the price of their reference products. If they are widely used, biosimilars can potentially lead to lower prices through competition.[2,5]

Moreover, biosimilars can create opportunities for research on new agents and/or stimulate innovation with existing molecules (for example, new cell lines used to produce the biosimilar). The increasing availability of biosimilar versions for the same reference is an incentive for companies to promote the advantages of their own biosimilars versus the competitors, and may encourage the generation of efficacy and safety data for new indications not attributed to the reference molecule.[2]

Current obstacles to a broader use of biosimilars include insufficient funding and education and variable approaches to healthcare management across countries. Administrative barriers, prescribing restrictions, and absence of well-defined clinical criteria for the initiation, discontinuation, and maintenance of biosimilars may also play a role in limiting access to treatment. To circumvent some of these difficulties, governments can create incentives at the hospital and clinical level to promote use of biosimilars. Support for monitoring and pharmacovigilance programs are also valid strategies that foster a competitive market, resulting in price reductions, while increasing the willingness of both clinicians and budget holders to use lower-cost products whenever feasible. At the pharmacy level, clear regulations for substitution are needed, although automatic substitution is controversial.[3,4,6]

In order to determine the impact of biosimilars on healthcare systems, real-world studies are needed to examine the effect on budgets and resource utilisation as well as on pricing practices resulting from the use of biosimilars. High-quality outcomes data will ultimately support the introduction of substitution regulations and the update of prescribing guidelines.[6]

Conclusions

In summary, prescribers, as well as other health professionals, payers, and patients, should be aware of the potential advantages and disadvantages of biosimilars in order to allow for an optimal treatment plan, one that is adapted to the patients' particular conditions, needs, and preferences. Biologics used in the treatment of cancer and inflammatory diseases have been available for some time, but few studies have evaluated their effectiveness in the real-world. Moreover, some biologic agents may still have an overall high cost, which limits their widespread and rapid uptake. Therefore, increased awareness of these drugs and how they are developed, as well as of the concept of biosimilarity and the current regulatory framework, by prescribers and allied healthcare professionals can play a significant role in increasing confidence regarding the use of these drugs, not only for clinicians but also for patients.

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