

biosimilar medicines

handbook



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ABOUT THE BIOSIMILAR MEDICINES GROUP

The Biosimilar Medicines Group is a sector group of Medicines for Europe and represents the leading companies developing, manufacturing and marketing biosimilar medicines across Europe. Our members bring competition to the biologic medicines market, thereby increasing access to highly innovative medical treatments to patients in Europe and around the world, and supporting the sustainability of the European healthcare systems.

ABOUT MEDICINES FOR EUROPE

Medicines for Europe (formerly EGA) represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines in Europe, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 160,000 people at over 350 manufacturing and R&D sites in Europe, and invest up to 17% of their turnover in medical innovation.

Medicines for Europe member companies across Europe are both increasing access to medicines and driving improved health outcomes. They play a key role in creating sustainable European healthcare systems by continuing to provide high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bringing to market value added medicines, which deliver better health outcomes, greater efficiency and/or improved safety in the hospital setting for patients.

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introduction

| WHAT THIS HANDBOOK COVERS

This handbook aims to provide updated information on the current progress of biosimilar medicines in the European Union (EU). The first edition of this short guide to **biosimilar medicines** was published in 2007. At the time of the first publication, only 5 biosimilar medicines had been approved in Europe, and both the legislation and concepts for these products were very new. Now the situation has further developed and changed, as will be described herein, and the clinical and health economic benefits offered by biosimilar medicines to patients, clinicians and healthcare providers are considerably clearer.

The handbook focuses on the current situation in the EU where, further to the approval and launch of 20 biosimilar medicines since 2006, regulators have gained the experience which has supported the continuous evolution of the scientific guidelines. The science-based EU regulatory framework has

This handbook describes the science and technology behind biosimilar medicines, how they are produced and regulated, and many specific questions surrounding them, namely:

- the terminology used
- the meaning of 'quality, efficacy and safety' and '**comparability**'
- the purposes and methodologies of non-clinical and clinical tests and trials
- the concept of **extrapolation of indications**
- access to medicines
- the importance of the **identification** of medicines
- the **interchangeability** of medicines in medical practice

proven robust and has evolved into a science and knowledge-based framework. In addition, some commentary on a global approach to biosimilar medicines is included. There is a dedicated section dealing with biosimilar monoclonal antibodies (mAbs), since this is an area in which significant developments have occurred, including the approval of the first two biosimilar

monoclonal antibody products containing the active substance infliximab in September 2013 and etanercept in January 2016.

A glossary of terms, highlighted in bold where they are first used in the text, and a list of acronyms or abbreviations as well as references are also provided at the back of the handbook.

| WHO IS THIS HANDBOOK FOR?

This handbook is intended to be a convenient and brief reference source for all those who need to understand and gain more insight into biosimilar medicines as a subclass of biopharmaceutical medicines, explaining their importance and benefits, and to provide answers to the many questions raised by this vital therapeutic option. The first and second editions (2007 and 2011, respectively) have already been welcomed by many stakeholder groups as a source of background information on biosimilar medicines. These groups include:

- patients and patient advocacy groups
- clinicians and prescribers
- retail and hospital pharmacists
- those responsible for funding health and healthcare on a regional or national basis
- national Health Technology Assessment (HTA) boards
- national pricing and reimbursement authorities
- politicians, policy advisers and makers, and healthcare payers



Pharmaceutical science, regulation and policy are rapidly changing areas, particularly in relation to **biotechnology**, and perhaps most particularly to biosimilar medicines, a subclass of **biopharmaceuticals**. The landscape of approved biosimilar products and guidelines has changed since 2006.

Questions posed and issues raised by the emergence of these products have become more pertinent with their increasing medical and economic importance. Perhaps most important of all is the huge impact of biosimilar monoclonal antibodies.

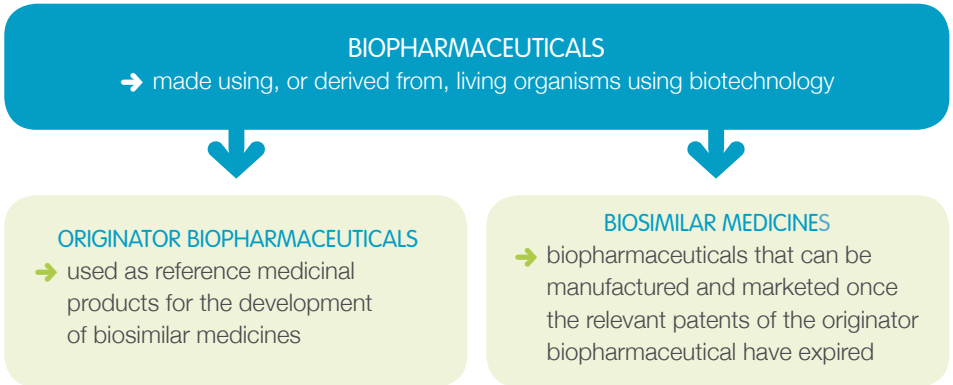
executive summary

Biosimilar medicines are an important sub-category of biopharmaceuticals, which may be defined for the purpose of this handbook as medicines made using, or derived from, living organisms using biotechnology. Biopharmaceuticals are one of the fastest growing segments of the pharmaceutical industry, outpacing the growth of small molecules and total pharma growth. In 2014, worldwide sales of biologicals was almost US\$200 billion. In Europe, 7 out of 10 of the most sold medicines in 2014 were biological medicines¹. The importance of these medicines to healthcare budgets, as well as to the pharmaceutical industry and its revenues, cannot be overstated. In 2014, some 245 biologic medicines had been authorised in the EU and US, representing 166 different active substances². Over 300 are being investigated in **clinical trials**³.

When relevant **patents** have expired, biopharmaceuticals can also be manufactured and marketed by companies other than the company that originally marketed the product. This novel subclass of biotechnological medicines is most commonly known as 'biosimilar medicines', which will be the term used throughout this handbook. In other texts they may be named 'similar biological medicinal products', 'biosimilars', 'follow-on biologics', 'subsequent entry biologics' or 'similar biotherapeutic products'.

Biosimilar medicines are versions of existing biopharmaceuticals, for which marketing exclusivity rights have expired, with proven comparable quality, efficacy, and safety to that of the **originator reference medicinal products**.

FIGURE 1 > OVERVIEW OF BIOPHARMACEUTICALS: BIOSIMILAR MEDICINES ARE A SUBCLASS OF BIOPHARMACEUTICAL MEDICINES



Biosimilar medicines offer a major opportunity to provide greater access to affordable healthcare. This opportunity is at least equally significant to the emergence of **generic medicines** over the past decades. Competition in the market resulting from the introduction of even a small number of cost-effective biosimilars will save the EU several billion euros annually. The longer-term potential for future savings from biosimilar medicines, including biosimilar monoclonal antibodies, will be much greater. This new field of biotechnological development has already made great progress since EU regulatory practice, standards and laws were first adopted in 2004⁴ to introduce this category of products into Europe. Since then, twenty biosimilar medicines have gained European approval to be marketed.

The vast majority biosimilar medicines are approved by the European Commission

(EC) through the European centralised procedure, which is overseen by the European Medicines Agency (EMA). The term 'biosimilar medicine' is derived from EU legislation governing this approval process, which refers to biosimilar medicinal products. As is the case for all medicines, European regulations and guidelines are in place to ensure the quality, efficacy, and safety of biosimilar medicines. Quality, in this context, means the controls and standards consistently applied for all manufacturing, preparation and processing of the product. Key quality aspects to be considered are the potency and purity of the product, which should be within the limits displayed by the reference product. The biosimilar development uses the latest state-of-the-art analytical and biotechnology methods, including some that may not have been available when the reference product was first approved.



In order to gain approval, biosimilar medicines have to demonstrate that they have the same quality, safety and efficacy profiles as those of the originator reference products.

Biosimilar medicines are thoroughly evaluated for their comparability with the reference product. The extent of this comparability exercise is defined for each product on a case-by-case basis in close collaboration with the EMA.

In line with all other medicinal products, biosimilar medicines, once approved, are permanently monitored to ensure continued

safety. Patient safety data is collected through robust pharmacovigilance activities. These include routine pharmacovigilance measures and specific monitoring as detailed in the **Risk Management Plan (RMP)**.

The terms 'biosimilar' or 'biosimilar medicines' should only be used to describe follow-on or new versions of biological medicines that have been approved following a rigorous comparability exercise as is required in the EU and other highly regulated markets.

Healthcare providers can now work with clinicians and pharmacists to improve access to important biosimilar medicines for more patients, confident in the knowledge that they have been thoroughly and scientifically assessed by the EMA and approved by the European Commission as safe and efficacious medicines.

the importance of biosimilar medicines for:

For more than 30 years⁵, patients in the EU have benefited from the availability of biopharmaceuticals. These medicines have revolutionised the management of some of the most difficult to treat diseases and have helped to prolong and improve the lives of many patients. However, these biopharmaceuticals are very costly and in many cases they are out of reach of some patients in the EU who could benefit from their use⁶.

Some manufacturers of medicines have the scientific capability to produce similar versions of biopharmaceuticals – known as biosimilar medicines. Once the relevant patents have expired, biosimilar manufacturers are able to bring these versions of biopharmaceutical medicines to European patients. Through a rigorous process of development and regulatory evaluation, these medicines are now being approved by the European Commission as being comparable in quality, efficacy, and safety to their predecessors.

PATIENTS

Patients in Europe deserve access to safe biological treatment options as they fight disabling and life-threatening diseases. Biosimilar medicines improve patient access to many of these biopharmaceuticals, sometimes significantly⁷. The potential savings which can be expected by the introduction of biosimilar medicines into EU healthcare are likely to result in more patients having access to the medicines that they require. Furthermore, patients can be confident that these products are assessed and approved for use in Europe by the same scientific authorities that approved their predecessors (i.e. the reference products). Information about specific biosimilar medicines is available from a number of sources, including the European Medicines Agency (EMA), and will help patients discuss the benefit of these medicines with healthcare providers.



CLINICIANS

Biosimilar medicines offer physicians a safe alternative therapeutic option to essential but expensive reference products.

The scientific principle of the development of a biosimilar medicine is a thorough comparability exercise at quality, efficacy, and safety levels, which aims to demonstrate the similarity of the biosimilar with the originator reference product. Once the comparability between a particular biosimilar product and the reference product has been successfully demonstrated, then, as a result, the safety and efficacy profiles established for the relevant reference product are also applicable for the biosimilar product.

The European Commission grants successful product applications a Marketing Authorisation within the European Union. This approval is based on the European Medicines Agency's positive scientific opinion following the thorough assessment of the data package. Therefore, all biosimilar medicines are approved only after extensive and rigorous regulatory evaluation of their registration data, which will always include a full comparability assessment.

Biosimilar medicines provide physicians with the opportunity to prescribe alternative high-quality safe and efficacious medicines to the benefit of their patient.

PHARMACISTS

Pharmacists have a leading role in ensuring that the most appropriate medicines are made available to the right patients at the right time. In doing so pharmacists are certainly aware of the burgeoning cost of biopharmaceuticals and are often tasked with helping to manage healthcare budgets as effectively as possible. Biosimilar medicines offer a safe alternative therapeutic option to established biopharmaceuticals and can help pharmacists to improve patient access to these important medicines whilst at the same time aiding them in the management of their pharmacy budgets.

Pharmacists have a major role to play in critically appraising biosimilar medicines and making recommendations for their use. Pharmacists are able to refer to the extensive data published on the EMA website to support their evaluations. They should also be reassured by the robust regulatory review systems that are in place in the EU which ensure that all approved medicinal products meet the required standards for quality, efficacy and safety.



HEALTH TECHNOLOGY ASSESSMENT BOARDS, HEALTHCARE PURCHASERS AND NATIONAL PRICING AND REIMBURSEMENT AUTHORITIES

Biosimilar medicines offer therapeutically equivalent and more cost-effective alternatives to existing, high-cost biopharmaceuticals. This means that more patients can be treated within the same budget and that, where appropriate, treatment can be initiated earlier in the treatment cycle.

Biosimilar medicines provide a unique opportunity to help manage the growing costs of biopharmaceutical medicines in Europe. In the same way that generic versions of chemical medicines are now very widely used throughout EU healthcare systems at levels far greater than during their original introduction in the 1980s, we can anticipate a similar process with biosimilar versions of biopharmaceuticals.

POLITICIANS, ADVISERS AND POLICY MAKERS AND HEALTHCARE PAYERS

Biosimilar medicines bring additional competition to the European biopharmaceutical product market, in the same way that generic pharmaceutical products bring competition to the non-biopharmaceutical product landscape. Through this competition, more patients can gain access to essential biopharmaceuticals and the treatment costs can be reduced. Competition stimulates further innovation in the European pharmaceutical industry. These benefits should encourage politicians, advisers and policy makers to continue their current support for the appropriate regulation and rapid introduction of biosimilar medicines into the European healthcare market.

Although the European Medicines Agency is the regulatory body that conducts the scientific assessment process, legally it is the European Commission that grants a marketing authorisation for successful product applications within the European Union.



health economic benefits of biosimilar medicines

Europeans are now able to lead active, healthy and participative lives well into old age. However, the combination of ageing and low birth rates also poses major economic and social challenges. Improving healthcare is one factor that has helped to increase life expectancy in the EU over the last century. In the EU, life expectancy at birth for males is expected to increase by 7.1 years, reaching 84.8 in 2060. For females, it is projected to increase by 6.0 years, reaching 89.1 in 2060⁸.

Ageing is accelerating. Our working age population in the EU will be reduced by about 7 million people by 2020 and even by about 39 million by 2060. By 2060, the EU will have about two working-age persons for every person aged over 65 years, coming from four working-age people for every person aged over 65 years in 2015⁸.

In supporting the growing elderly population, EU countries will be obliged to spend increasing proportions of their Gross Domestic Product (GDP) to provide the required level of healthcare coverage. New and innovative therapies, offering irrefutable advances, will continue to escalate costs and increase patient expectations. Healthcare expenditure is high on the agenda of every Member State in the EU, with all governments being tasked to deliver the best and most up-to-date patient care, whilst at the same time trying to limit the potentially huge increases in associated costs.

Pharmaceuticals make up a valuable and significant element of healthcare expenditure and healthcare providers across the EU are constantly looking for ways to reduce the cost burden of medicines.

Over the last 3 decades, the introduction of high quality generic medicines has made a significant impact in increasing access to medicines across the EU. These safe treatment alternatives to existing originator medicines have helped to significantly



increase access to important medicines for a greater number of patients while at the same time manage healthcare budgets. In a similar way, biosimilar medicines are now able to offer alternative treatment options to many expensive biopharmaceuticals, thereby allowing access for patients who need them.

High quality biosimilar medicines, approved in Europe by the process of extensive regulatory assessment, provide a major opportunity to help governments control the cost and availability of biopharmaceutical medicines. A 2012 IGES Institute study calculated expected savings of €11.8 to €33.4 billion for 8 EU countries over the period 2007-2020⁹.

These substantial benefits associated with biosimilar medicines could, however, only be achieved if mechanisms are available to support their entry into the market. Slower introduction of biosimilar products into clinical practice will result in a failure to realise the expected savings to healthcare budgets and may increasingly restrict access to medicines.

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The cumulative savings over the next five years in the EU5 and the U.S. combined could range from €49 billion to as much as €98 billion¹⁰.

”

nomenclature of biopharmaceuticals, including biosimilar medicines

Biopharmaceuticals have been available for more than 30 years. These include:

- hormone products, e.g. growth hormone for growth hormone disorders, erythropoietin (EPO) for **anaemia** in the kidney and other diseases, insulin for diabetes, and GCSF for chemotherapy induced neutropenia
- immunomodulators such as beta-interferon for multiple sclerosis
- monoclonal antibodies (mAbs) used primarily for treating cancer and autoimmune diseases
- blood coagulation factors, e.g. factor VIII and IX for blood disorders such as haemophilia
- enzymes for the treatment of a variety of conditions, including metabolic disorders such as **Gaucher's disease**
- vaccines for the prevention of many diseases, such as those caused by human papillomavirus infections

Manufacturers other than the originator companies have the scientific capability to produce biopharmaceuticals similar to the originator products. In the European Union, this new category of medicines is called biosimilar medicines, or 'biosimilars'. Sometimes the longer official term 'similar biological medicinal products' is used. They can be marketed following loss of patent and exclusivity protection of the originator product. Biosimilar medicines approved in the EU have been successfully compared to, and have demonstrated that they match, their reference products in terms of quality (methods and controls of manufacturing), efficacy (desired effect), and safety (risk/benefit assessment).

Details on approved biosimilar medicines are available through European Public Assessment Reports (EPARs), which are published on the European Medicines Agency websites¹¹.

Since the advent of the biosimilar legislative pathway in the EU, many such products

The terms 'biosimilar' or 'biosimilar medicines' should only be used to describe follow-on or new versions of biological medicines that have been approved following the assessment of a rigorous comparability exercise as is required in the EU and other highly regulated markets.

safe and efficacious biosimilar medicines have been used in the EU market for 10 years

containing a variety of biological **active substances** have been approved via the biosimilar pathway.

A full listing of all the individual biosimilar product approvals granted by the European Commission is shown in the following table.

TABLE 1 > LIST OF EU APPROVED BIOSIMILAR MEDICINES (MARCH 2016)

Active substance	Name of biosimilar medicine	Date of European Commission authorisation	Marketing authorisation holder	Reference product
SOMATROPIN	Omnitrope®	12-04-06	Sandoz	Genotropin®
EPOETIN	Abseamed®	28-08-07	Medice	Erypo®/Eprex®
	Binocrit®	28-08-07	Sandoz	
	Epoetin alfa HEXAL®	28-08-07	Hexal	
	Retacrit®	18-12-07	Hospira	
	Silapo®	18-12-07	Stada	
FILGRASTIM	Biograstim®	15-09-08	AbZ-Pharma	Neupogen®
	Ratiograstim®	15-09-08	Ratiopharm	
	TevaGrastim®	15-09-08	Teva	
	Filgrastim HEXAL®	06-02-09	Hexal	
	Zarzio®	06-02-09	Sandoz	
	Nivestim®	08-06-10	Hospira	
	Grastofil®	18-10-13	Apotex	
	Accofil®	18-09-14	Accord Healthcare	
INFLIXIMAB	Inflectra®	10-09-13	Hospira	Remicade®
	Remsuma®	10-09-13	Celltrion	
FOLLITROPIN ALFA	Ovaleap®	27-09-13	Teva	Gonal f®
	Bermola®	27-03-14	Finox Biotech	
INSULIN GLARGINE	Abasaglar®	09-09-14	Eli Lilly	Lantus®
ETANERCEPT	Benepali®	18-01-16	Samsung Bioepis	Enbrel®



Based on the numbers of EMA scientific advice opinions given over recent years, it is reasonable to expect further new applications

and approvals for biosimilar medicines in the years ahead, especially for biosimilar versions of monoclonal antibodies.

the science and technology of biosimilar medicines

Biopharmaceuticals contain much larger molecules than pharmaceuticals made of chemical active substances, and each has a set of characteristics naturally subject to some variability. They are usually proteins or polypeptides. This variability includes the 'shape' of the molecule (folding) and the type and length of any sugar or carbohydrate groups that may be attached to it (glycosylation).

All biopharmaceuticals, including biosimilar medicines, are produced using living organisms. The end product has to be purified from the thousands of other molecules present in a living cell or living organism and therefore the production process requires sophisticated and validated technologies.

FIGURE 2 > STANDARD PRODUCTION SEQUENCE IN THE MANUFACTURE OF A BIOPHARMACEUTICAL PRODUCT

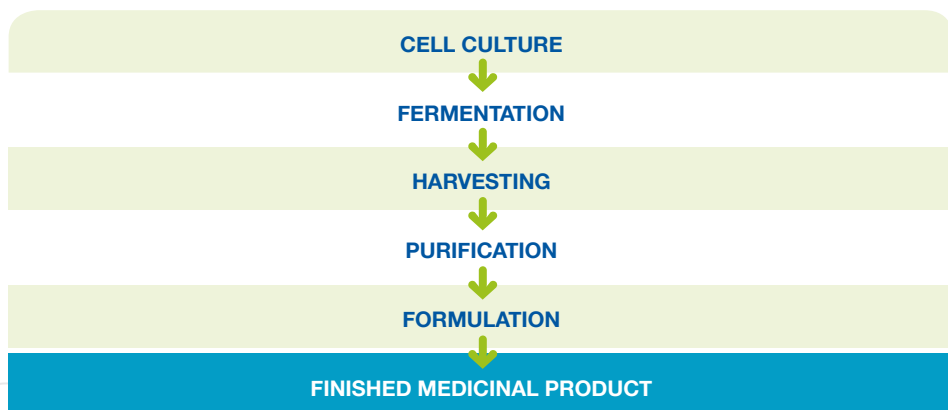
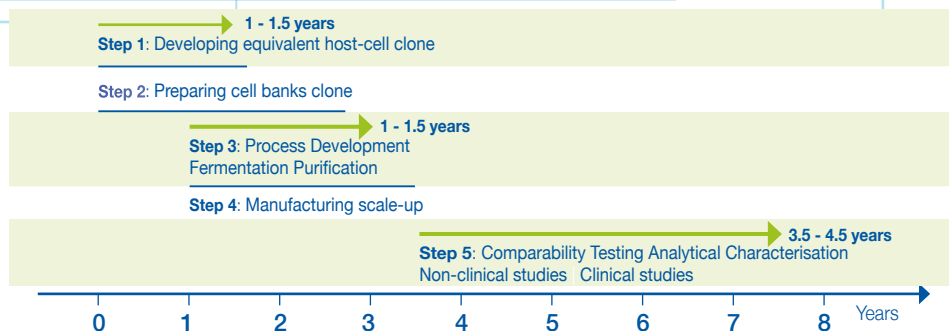


FIGURE 3 > TIMELINE FOR DEVELOPMENT OF A BIOSIMILAR MEDICINE



THE DEVELOPMENT OF BIOSIMILAR PRODUCTS

Introduction to the Concept of 'Biosimilarity': The Scientific Concept of Comparability

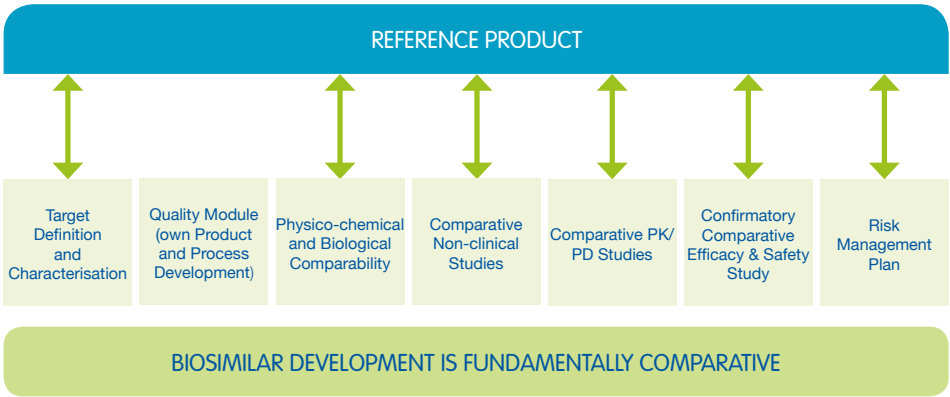
The basic principle underlying the development of a biosimilar product is the comparability with the reference product. This is not a new scientific concept that applies only to biosimilar medicines. Comparability, as assessed through a process known as a 'comparability exercise', is a critical concept that has been evolved in order to perform comparisons between different versions of any biological products in development. Data provided by such comparisons is needed to show that there are no significant differences in quality, efficacy and safety between the different versions of the product under development.

After any product has been approved by the regulatory authorities, it is not unusual for further changes to be made in the manufacturing process. Such changes are introduced during the life-cycle of the product after the initial approval. When changes are made, demonstration is needed that the safety and efficacy of the

products remain comparable to those of the product prior to the implementation of the manufacturing change. As a general scientific principle, comparability does not necessarily mean that the products manufactured before and after the change are identical; instead, comparability needs to be demonstrated. The comparability demonstrated through the comparability exercise, together with the existing knowledge, needs to be sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon the efficacy or safety of the product.

The same scientific principle of comparability applies to the development of a biosimilar product, which must be similar to the reference product in terms of quality, efficacy, and safety in order to be allowed on the EU market. The 'comparability exercise' required for the candidate biosimilar and the reference product is regarded as a complicated and difficult task. However, highly sophisticated analytical and validation tools are available today to allow for a detailed **characterisation** of these products and, whenever needed, scientifically sound, non-clinical and clinical studies can be conducted to confirm comparative clinical safety and efficacy.

FIGURE 4 > THE PILLARS OF A BIOSIMILAR PRODUCT DEVELOPMENT AND MARKETING APPROVAL



The Stepwise Comparability Exercise

The development of a biosimilar medicine requires a comprehensive product and process development plus comparative testing at all levels, namely at quality, non-clinical and clinical stages. The aim is to ensure that the biosimilar product matches its reference product in terms of quality, efficacy and safety. Therefore, the same reference product is used for the comparability exercise throughout the entire drug development programme of the biosimilar product.

- **First Step – Quality Comparability (Physicochemical and biological comparability)**

The quality development programme may include:

- A thorough characterisation programme

that needs to be carried out to compare the physicochemical and biological quality attributes including the purity of the potential biosimilar medicine as compared with the reference product. This is done using a large series and variety of different state-of-the-art analytical methods, as no single one can characterise all aspects of a product.

- A modified development process, if there are significant differences found in analyses, until the product generated has a profile that matches the profile of the reference product.
- Continuing modification at every stage of the development process so that the final biosimilar medicine matches the quality of the reference product by every criterion that is required by the European Medicines Agency when

the documentation is submitted for assessment and marketing authorisation.

• Second Step – Non-Clinical Comparability (Comparative non-clinical studies)

Non-clinical (sometimes also called pre-clinical) studies need to be carried out for biosimilar medicines as is the case for any other biopharmaceuticals before the initiation of any clinical trial involving human subjects. The non-clinical data for a biosimilar product is usually generated through a tailored programme of a variety of **in vitro** tests or, in exceptional cases, studies in animals, as required by EU guidelines. The non-clinical studies should be conducted in a stepwise approach: analytical studies and *in vitro* pharmacotoxicological studies should be conducted first and a decision then made as to the extent of what, if any, *in vivo* work in animal studies will be required. If an *in vivo* evaluation is deemed necessary, the design of PK and/or PD and/or safety studies should follow the principles of the 3Rs (replacement, refinement, reduction)¹². The aim of these studies is to further support comparability or to detect potential differences between the biosimilar and reference product.

• Third Step – Clinical Comparability (Comparative clinical studies)

The clinical trials are also comparative in nature in the case of a biosimilar development. However, clinical testing is not required to the same extent as would be needed for a new active substance due

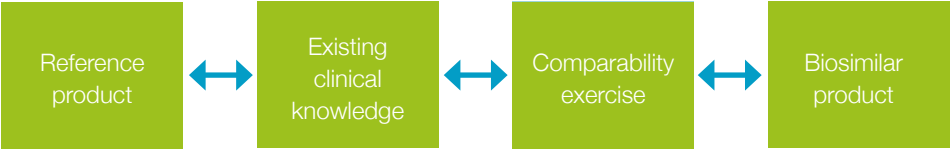
to the clinical experience acquired from the use of the reference product, accumulated over many years. Moreover, clinical trials of biosimilar medicinal products do not aim to demonstrate efficacy and safety *per se*, since this has already been established for the reference product. The purpose of the clinical trials is to confirm comparable clinical performance of the biosimilar and the reference product. Therefore, the design of the clinical development programme takes into account the nature and the characteristics of the medicine and its intended use, and also how comparable the profile of the biosimilar medicine is to that of the reference product. The closer the profiles of the biosimilar and reference products and the higher the similarity (that has been demonstrated through appropriate studies, e.g. comparative quality, biological and receptor-binding assays, and *in vitro* studies), the more a tailored clinical trial programme can be accepted by the regulators. This means that if in-depth comparability between the biosimilar and the reference product has been demonstrated, the clinical experience gained with the reference product and its established efficacy, and safety profile can be taken into account because the safety and efficacy profiles of the reference product are equally relevant for the biosimilar medicine – based on a successfully demonstrated comparability between reference and biosimilar products. Tailored clinical trials help to confirm that efficacy and safety profiles of the biosimilar and the reference product are comparable while unnecessary

human testing is prevented. Consequently, the very high development costs associated with clinical trials can be reduced.

The clinical comparability exercise is conducted in a step-wise approach and usually begins with pharmacokinetic and/or pharmacodynamic studies. As a further step, these studies can be followed by a comparative and confirmatory clinical

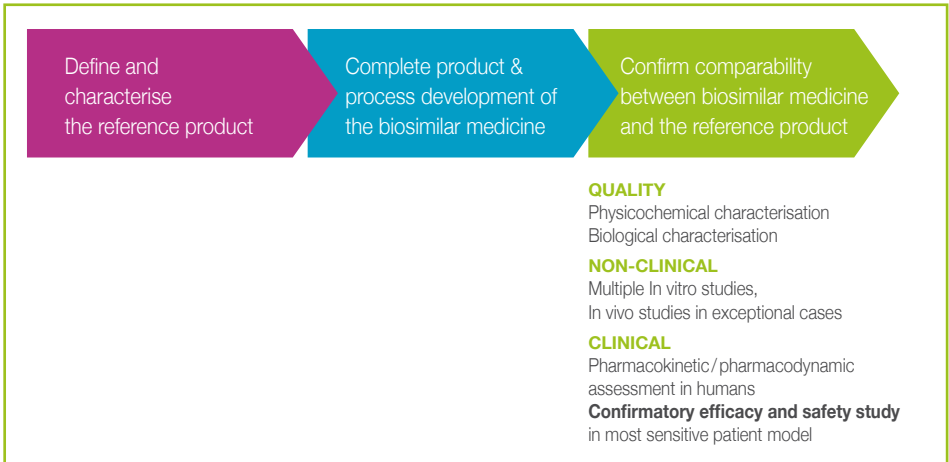
efficacy and safety study in a representative indication using the most sensitive patient population / model. Besides comparative efficacy, a comparable safety profile in terms of seriousness and frequency of different side-effects must also be shown. The assessment of comparable immunogenicity profiles for the biosimilar and the reference products is also part of the clinical safety data.

FIGURE 5 > THE PURPOSE OF THE COMPARABILITY EXERCISE



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The primary purpose of the assessment of a biosimilar product is not the characterisation of the benefit/ risk profile of the product as such, but the qualitative and quantitative evaluation of the comparability (similarity) of the biosimilar product to the reference product.
”

FIGURE 6 > STAGES OF DEVELOPMENT OF A BIOSIMILAR MEDICINE



EXTRAPOLATION OF INDICATIONS

Biopharmaceutical (originator) products are often used in more than one indication. The mechanism of action for these various indications is very often the same. It may be possible that the demonstration of clinical similarity proven for one indication can be extrapolated to other indications.

The current version of the CHMP biosimilar guideline on non-/clinical issues indicates: “When biosimilar comparability has been demonstrated in one indication, extrapolation of clinical data to other indications of the reference product could be acceptable, but needs to be scientifically justified.”

The scientific basis for this extrapolation of indications is the proven, in-depth comparability between the biosimilar

candidate and its reference product at all levels of the biosimilar medicines development. Therefore, the current guideline states:

“Extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data. It is expected that the safety and efficacy can be extrapolated when biosimilar comparability has been demonstrated by thorough physico-chemical and structural analyses as well as by in vitro functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication.”¹³

Biosimilar medicines are developed to match their reference product in terms of quality, safety and efficacy.

Consequently it is scientifically justified that the clinical experience gained with the biosimilar product in the tested indication(s) and in relevant PK/PD studies can be extrapolated to other indications for which the reference product is approved, provided that the mechanism of action for all these indications is the same.

Not all biopharmaceuticals will necessarily become available as a biosimilar medicine. The science and technology, the very high cost of development and production, and also the size of the market (number of

patients) have to be taken into account by a potential manufacturer.

QUALITY ASSURANCE FOR THE MANUFACTURE OF BIOPHARMACEUTICALS

Both originator reference products and biosimilar medicines are made under carefully controlled conditions to ensure that the products are consistently produced, and manufactured to the required quality. These controlled conditions are known as Good Manufacturing Practice (GMP).



In the European Union, to determine whether the required manufacturing conditions are in place, GMP inspections for all biopharmaceuticals (both originator and biosimilar medicines) are coordinated by the EMA and performed by National Regulatory Agencies.

Since the development and manufacture of biosimilar medicines is a complex field, it requires a high degree of specialised expertise and the establishment of an expensive technological background, thus it also carries a considerable degree of commercial risk.



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Biosimilar medicines are manufactured according to the latest state-of-the-art technology, ensuring the highest quality standards available.

Biosimilar medicines are usually better characterised than their reference products were characterised at the time of their initial approval 10 to 20 years earlier.

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regulation of biosimilar medicines

| SCIENTIFIC GUIDELINES

The EU was the first region in the world to have defined a policy and legal framework for the approval of biosimilar products. The concept of a 'similar biological medicinal product' was introduced into EU legislation in 2003, and further developed with the adoption of the revised EU pharmaceutical legislation in 2004¹⁴.

With the legal framework for biosimilar medicines established, the EMA, together with the Committee for Medicinal Products for Human Use (CHMP), the Biotechnology Working Party (BWP) and the Working Party on Similar Biological Medicinal Products (BMWP), released specific guidelines to deal with all aspects of the development, production, testing and regulation of biosimilar medicines. This was done after consultation with all the relevant stakeholders, which include national regulatory bodies, scientific advisory groups, industry, clinicians, and patient groups.

The initial guidelines, published in 2005 and 2006, comprised an overarching guideline as well as other more general guidelines concerning the product quality, clinical

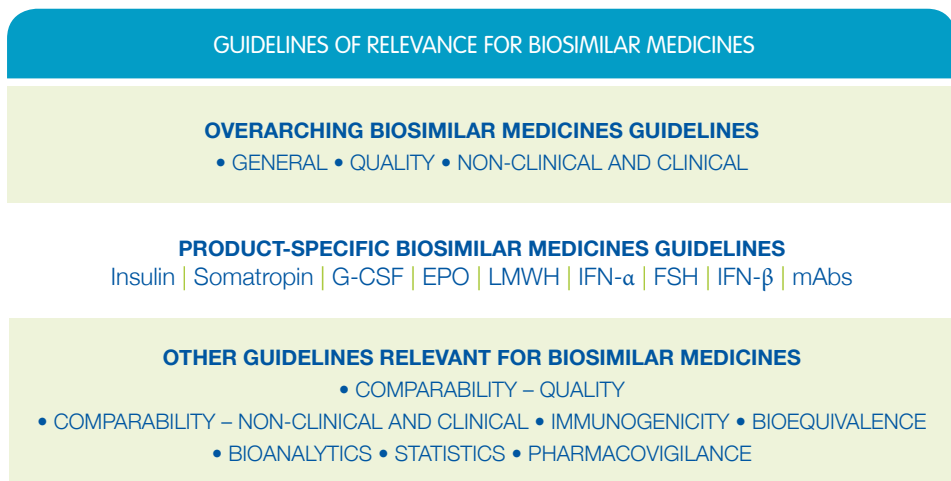
and non-clinical issues. These guidelines have been revised according to the latest views of the regulators which have evolved based on the scientific and technological developments as well as on experience gained in the past ten years since the first biosimilar products became available for EU patients.

In addition, product- specific guidelines listing the non-clinical and clinical requirements are also available, and the EMA is in the process of developing additional guidelines as well as revising existing ones (for more information, please see appendix 1).

| EMA building in London



FIGURE 7 > SCHEMATIC OVERVIEW OF CURRENT BIOSIMILAR MEDICINES GUIDELINES



| ASSESSMENT OF IMMUNOGENICITY

All biopharmaceuticals, in contrast to conventional pharmaceuticals, demonstrate a greater capacity to elicit an **immune reaction**, because they are polypeptides or proteins and might therefore be recognised by the immune system as foreign.

Immunogenicity is the capability of a specific substance to induce an unwanted **immune response** that is triggered by more than one single factor. The immunological response is complex and, in addition to antibody formation, other events such as T-cell activation or innate immune response activation could contribute to

any potential adverse response. In many patients, an immune response does not lead to any clinical consequences. However, the potential exists for general immune reactions that might cause symptoms of allergy or **anaphylaxis**. In addition, immune responses may cause reactions that lead to a loss of effect of the medicine or, on very rare occasions, reactions that cause an enhancement of activity of the immune system. Immunogenicity may be influenced by factors relating to the medicine itself, including the manufacturing process and **formulation**, and also by factors related to the individual susceptibility of a patient, the disease and the treatment method, including the immune status of cancer patients and route of administration¹⁵.

These factors are carefully evaluated during the development of all biopharmaceuticals, including biosimilar medicines. The immunogenicity of biopharmaceuticals often cannot be fully predicted using pre-clinical in vitro and ex-vivo studies and clinical immunogenicity studies are usually required before approval and sometimes also after approval.

Substantial guidance on the assessment of immunogenicity is given by a guideline compiled specifically for biotechnology-derived therapeutic proteins including biosimilar medicinal products. Product-specific requirements on the assessment of immunogenicity are detailed in the respective product-specific guidelines for biosimilar medicinal products. The increased size and complexity, and the nature of action of monoclonal antibodies compared to smaller biopharmaceuticals (e.g. epoetin), has led to the preparation of a guideline addressing immunogenicity associated with this type of medicinal product (please refer to table in Appendix).

As patient-specific immunogenicity may sometimes only emerge after extensive exposure and usage, further systematic immunogenicity testing may also be required after gaining marketing authorisation. Assessment of immunogenicity may be part of post-approval Risk Management Plans (RMPs) and pharmacovigilance activities.

The European Union continues to lead worldwide in developing scientific guidelines for biosimilar medicines.

| GAINING MARKETING AUTHORISATION

The application for a marketing authorisation for any biotechnology-derived product must be submitted to the European Medicines Agency and be assessed via the Centralised Procedure. This procedure involves two independent assessment teams from two Member States plus scientific experts from all other Member States evaluating the data in the registration dossier. Each individual national CHMP expert is supported by additional national experts who can also provide input. The EU regulatory authorities are known for their expertise in the assessment of biopharmaceuticals and are consequently very experienced in assessing data from comparability exercises.

The registration dossier for a biosimilar medicine that is to be submitted to these experts contains a data package based on the requirements laid down in the appropriate scientific guidelines. If this data is assessed as satisfactory in all respects, the biosimilar product will receive a marketing authorisation from the European Commission. Only then will the company be allowed to market the medicinal product in the European Union (and also the EEA–EFTA states of Iceland, Lichtenstein and Norway).

TABLE 2 > DATA PACKAGE REQUIRED FOR A MARKETING AUTHORISATION APPLICATION TO BE PRESENTED TO THE EUROPEAN MEDICINES AGENCY

QUALITY DATA	<p>The quality of the biosimilar medicinal products must meet the same requirements and standards as that of the reference product. The registration dossier includes all the necessary data to establish the quality of the product, including:</p> <ul style="list-style-type: none"> • Definitions and descriptions of the manufacturing process, and associated control tests and standards • Data on the consistency of manufacturing (quality control of the process) • Data on analytical tests (molecular structure, potency and purity/impurity profile) • Data on stability of the product <p>In addition, the results of the comprehensive comparability exercise with the reference product will be presented</p>
NON-CLINICAL DATA	<p>The registration dossier for a biosimilar medicinal product will usually include comparative non-clinical data.</p> <p>The amount of non-clinical data required is specific to the product, and will be determined on a case-by-case basis.</p> <p>Usually the following non-clinical tests are included:</p> <ul style="list-style-type: none"> • A variety of <i>in vitro</i> studies • In exceptional cases, pharmacokinetic/pharmacodynamic studies including local tolerance testing in appropriate models
CLINICAL DATA	<p>The registration dossier for a biosimilar medicinal product will usually include clinical data, summarising the results of comparative clinical trials conducted in healthy volunteers and in patients with the biosimilar product. For most biosimilar medicines, extensive comparative trials have been conducted, often including several hundreds of patients.</p> <p>Companies applying for a marketing authorisation must submit all the results from their trials, both positive and negative. Immunogenicity data are required.</p>
PHARMACO-VIGILANCE	<p>A Risk Management Plan (RMP), which is a detailed description of the company's risk management system, must be submitted with the registration dossier. The RMP describes what is known about the safety of the medicine and outlines how the manufacturer will further monitor and fill any potential or known gaps in knowledge as well as any measures needed to prevent or minimise any potential risk of the medicinal product.</p> <p>The Risk Management Plan also includes the description of the routine pharmacovigilance system, which requires the submission of Periodic Safety Update Reports (PSURs).</p>

Biosimilar medicines, as with all biopharmaceuticals in Europe, undergo rigorous regulatory and scientific assessment by the same scientific expert committees at the European Medicines Agency.

A summary of the data and the assessment regarding the medicinal product, known as the European public assessment report (EPAR) is made available to the public. The EPAR is compiled by the European Medicines Agency and is published on its website after issuance of the marketing authorisation by the European Commission.

| PHARMACOVIGILANCE

All European pharmaceutical companies are legally required to monitor the use and effects of all their medicines continuously. They must have systems in place to collect, detect, assess, understand and communicate any **adverse reactions** or any other medicine-related problem. The science and activities of these processes are known as 'Pharmacovigilance'.

As is the case with every new medicine, the company is required to submit a Risk Management Plan (RMP) which is a detailed description of the company's risk management system. This RMP must be agreed by the European Medicines Agency and is an integral part of the marketing authorisation. The RMP describes what is

known about the safety of the medicine and outlines how the manufacturer will further monitor and fill any potential or known gaps in knowledge as well as any measures needed to prevent or minimise any potential risk of the medicinal product. For a biosimilar medicine, the RMP essentially relies on the safety profile of the reference product and any studies required or known to be conducted for the reference product. The RMP is published in the European Public Assessment Report (EPAR) after authorisation of the medicine and needs to be updated throughout the lifetime.

Once the medicines are marketed, the companies must prepare regular reports to review all available safety data. These are known as Periodic Safety Update Reports (PSUR). The purpose of these reports is to detect any change of the risk-benefit balance of a medicine. Sometimes additional **Post-Authorisation Safety Studies (PASS)** are also required.

For adverse reaction (ADR) reports relating to all biopharmaceuticals, the definite identification of the medicine with regard to its manufacturing is of particular importance.

Therefore, for every adverse reaction report of a biological medicine, EU legislation requires the name of the medicine and the batch number to be included in the ADR report. In this way a suspected adverse reaction can be linked to the correct medicine.

The new EU pharmacovigilance legislation has also foreseen that for all medicines with a new active substance and all new biological medicinal products, including new biosimilar medicines, a black symbol and a sentence inviting all adverse reactions to be reported are to be added to the summary of product characteristics and the patient information leaflet.

The European Medicines Agency is also responsible for the development and maintenance of **EudraVigilance**, which is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development stage, and following the marketing authorisation of medicinal products in the European Economic Area (EEA). Within EudraVigilance, adverse reactions that are reported to the EMA or the National Competent Authorities (NCA) either by pharmaceutical companies, healthcare practitioners such as physicians, pharmacists or nurses, or patients, or that are retrieved from worldwide scientific literature through active continuous screening, are collated.



All biopharmaceuticals, including biosimilar medicines, follow the same pharmacovigilance rules. Additionally, adverse reaction reports of a biological medicine must contain the name of the medicinal product and the batch number.



introducing of biosimilar medicines into clinical practice

IDENTIFICATION

As required by law for all medicines in the EU, every biosimilar medicine will either have an invented (brand) name, or the name of the active substance together with the company name. Every biosimilar medicine is consequently clearly identifiable by its unique name, which has to be formally agreed by the EMA as part of the approval process.

The first two biosimilar medicines approved in Europe bear invented (brand) names (i.e. Omnitrope® and Valtropin®) and both contain the same active substance, somatropin. Somatropin is the scientific name for this active substance. The scientific name is usually called the INN (International Non-proprietary Name), which may sometimes be known as the generic name. The INN is also approved by the EMA during the scientific evaluation of the biosimilar medicine.

The name of a medicine is very important for clear identification, safe prescription and dispensing, as well as for monitoring the safe use of the medicine during the whole life cycle.

The new EU pharmacovigilance legislation also includes a provision regarding the identification of any biological product. This stipulates that the Member States shall, through the methods of collecting information and, where necessary, through the follow-up of adverse reaction reports, ensure that any biological medicinal product prescribed, dispensed, or sold in their territory, which is the subject of an adverse reaction report, is identifiable.

All pharmaceutical and biopharmaceutical manufacturers use a variety of techniques to be able to trace their medicine at all times. This includes unique labelling, batch numbering and packaging.

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All biosimilar products are clearly identifiable by their unique name.

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| INTERCHANGEABILITY

Interchangeability refers to the medical practice of changing one medicine for another that is equivalent, in a given clinical setting on the initiative or with the agreement of the prescriber. A medicinal product is considered to be interchangeable if it can be administered or dispensed instead of another clinically equivalent product. The regulatory scientific data, published via the EPAR (European Public Assessment Report), should guide prescribers' decisions on interchangeability.

In the context of interchangeability it should be noted that if an **originator company** changes the manufacturing process of an existing product, interchangeability between the pre- and post-change products is accepted as long

as the change is supported by a package of comparability data that reviews the pre- and post-change product. The same approach needs to be taken for biosimilar medicines, based on the comparability data with a reference product.

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Interchangeability refers to the medical practice of changing one medicine for another that is equivalent, in a given clinical setting on the initiative, or with the agreement of the prescriber.

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Biosimilars are interchangeable with their reference products under the supervision of a health care person.

The complete Finnish Medicines Agency's position towards interchangeability of biosimilars is accessible via the Fimea's website¹⁶.

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It is important to reiterate that biosimilar medicines match their reference product in terms of quality, efficacy and safety. A demonstration of therapeutic equivalence is usually required in order to adopt the posology (dose recommendations) of the reference product¹⁷.

The extensive comparability data, and also post-marketing data, will therefore demonstrate that it is safe and efficacious to switch dose for dose from the reference product to the biosimilar medicine.

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The patient file of a patient that is treated with a biological medicinal product should contain information regarding the biological medicinal product, including the batch number of such product in order to ensure that the product can be traced if problems should occur.

The 2015 revised Dutch Medicines Evaluation Board's position on biosimilars and interchangeability is accessible via the MEB's website¹⁸.

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the future and evolving landscape of biosimilar medicines

| BIOSIMILAR MONOCLONAL ANTIBODIES

Therapeutic monoclonal antibodies (mAbs) were first developed in the 1970s and 1980s, and have now become a very important class of biopharmaceuticals. They have the potential to target and cure many conditions such as cancer, rheumatoid arthritis, multiple sclerosis and other serious diseases, where immune disorders are thought to cause the disease process. Monoclonal antibodies are highly specific antibody proteins that are produced from a single clone of immune cells. This allows very specific target binding so that the resulting products have a precisely defined target.

The first biosimilar monoclonal antibody (infliximab) was approved in the EU in 2013.


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As biotechnology evolves at a rapid pace and experience with biosimilar medicines' applications increases, the EU regulatory framework is evolving continually.

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TABLE 3 > EXAMPLES OF CURRENTLY LICENSED MONOCLONAL ANTIBODIES

INN of active substance	Trade name	Function or target	Clinical use (examples)
Adalimumab	Humira®	Anti-TNF α	Rheumatoid arthritis, Crohn's disease
Alemtuzumab	Campath®	Anti-CD52	B-cell chronic lymphocytic leukaemia (B-CLL)
Basiliximab	Simulect®	Anti-IL2 receptor	Transplant rejection
Bevacizumab	Avastin®	Anti-vascular endothelial growth factor (VEGF)	Colorectal cancer, lung cancer
Cetuximab	Erbix®	Anti-epidermal growth factor receptor (EGFR)	Colorectal cancer, head and neck cancer
Daclizumab	Zenapax®	Anti-IL2 receptor	Transplant rejection
Infliximab	Remicade®	Anti-TNF α	Rheumatoid arthritis, Crohn's disease, psoriasis
Natalizumab	Tysabri®	Anti- α 4-integrin	Multiple sclerosis
Omalizumab	Xolair®	Anti-IgE	Asthma
Palivizumab	Synagis®	Anti-respiratory syncytial virus	Respiratory syncytial virus infection
Panitumumab	Vectibix®	Anti-epidermal growth factor receptor (EGFR)	Colorectal cancer
Ranibizumab	Lucentis®	Anti-vascular endothelial growth factor (VEGF)	Macular degeneration
Rituximab	Mabthera/ Rituxan®	Anti-CD20	B-cell non-Hodgkin's lymphoma, rheumatoid arthritis
Trastuzumab	Herceptin®	Anti-HER2	Breast cancer



In order to develop a biosimilar version of an existing therapeutic mAb, all structural features of the reference product, including the peptide chain, the structural folding, purity profiles and the glycosylation profile, need to be designed, checked, validated and reproduced. To achieve these goals, a comprehensive toolbox of analytical, biological and process engineering techniques is already available to allow for the optimisation of the manufacturing process and subsequently the determination of comparability between the final biosimilar mAb and the reference product.

Current expertise at the EU regulatory agencies and the European Medicines Agency for a sound scientific assessment is based on their experience gained from reviews of many originator mAb products, including the assessments made of the many manufacturing changes of these products, which have taken place over many years, as well as on the assessment of numerous biosimilar applications. Existing, overarching EU guidelines for biosimilar medicines are applicable for the development of biosimilar mAbs. In addition, specific guidelines on biosimilar monoclonal antibodies are being developed.

BIOSIMILAR REGULATORY FRAMEWORKS OUTSIDE THE EU

Due to its high quality, efficacy and safety standards, the EU regulatory framework provides an excellent model for countries around the world. The EU legal framework offers the key advantage of separating any

patent litigation from the regulatory approval processes. By doing so, it allows timely access to competitively-priced biosimilar medicines.

This EU regulatory framework has already inspired many countries around the world and is continuing to do so. In Australia the EU regulatory framework for biosimilar medicines was effectively adopted in 2006 and any revisions have been adopted since. In March 2009, Japan issued a similar set of biosimilar guidelines giving clear instruction on the requirements for development and registration of this group of medicinal products. In March 2010, guidance for SEBs (Subsequent Entry Biologics) was finalised and issued in Canada, with the first biosimilar medicine having been approved there in 2009 using the earlier draft guidelines. A revised version was released for consultation in 2015. In the USA the Biologics Price Competition and Innovation Act (BPCI Act) was signed into law in March 2010. This Act establishes an abbreviated approval pathway for biological products that are demonstrated to be 'highly similar' (biosimilar) to, or 'interchangeable' with, an FDA-licensed biological product. This approval pathway of biosimilar medicines was embedded in the March 2010 US healthcare law, i.e. the Patient Protection and Affordable Care Act (PPACA). The FDA has issued a set of biosimilar guidelines since 2012, 4 of them were finalised in 2015.

Finally, the FDA released in March 2016 its draft guidance "Labeling for Biosimilar Products" and announced that a guideline on interchangeability will be released within 2016.

"The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed product and the reference product, not to independently establish the safety and effectiveness of the proposed product. Consequently, a biosimilar product that is shown to be highly similar to an FDA-approved reference product may rely on our previous determination of the reference product's safety and effectiveness, rather than generate a full profile of product-

*specific nonclinical and clinical data. With this in mind, we are recommending an approach to biosimilar prescribing information, or "labeling," that also relies largely on the safety and effectiveness information from labeling for the corresponding reference product."*¹⁹

Leah Christl, PhD, Associate Director for Therapeutic Biologics - Therapeutic Biologics and Biosimilars Team, Office of New Drugs, CDER, US Food and Drug Administration (FDA)

There is a need to reach agreement on criteria and guidelines for biosimilar medicines all over the world in the interest of public health and better availability of high quality medicines.

TABLE 4 > LISTING OF FDA BIOSIMILARITY GUIDANCES

Source: FDA website¹⁹

CATEGORY	TITLE	TYPE	DATE
Biosimilarity; Procedural	Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants	Final Guidance	11/17/15
Biosimilarity	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	Final Guidance	04/28/15
Biosimilarity	Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product	Final Guidance	04/28/15
Biosimilarity	Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	Draft Guidance	05/13/14
Procedural; Biosimilarity	Reference Product Exclusivity for Biological Products	Draft Guidance	08/04/14
Biosimilarity	Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	Draft Guidance	05/12/15
Biosimilars	Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 Guidance for Industry	Final Guidance	04/28/15
Biologicals	Nonproprietary Naming of Biological Products	Draft Guidance	08/27/15
Biosimilarity	Labeling for Biosimilar Products	Draft Guidance	03/29/16

WHO GUIDELINES

The World Health Organization (WHO) published the final guidelines on evaluation of similar biotherapeutic products (SBPs) in April 2010²⁰. The basic scientific principles underlying the WHO guideline are the same as those in the EU guidelines. The intention of this document is to provide a globally acceptable set of principles for abbreviated licensing pathways for biosimilar medicines with assured quality, efficacy and safety. This guideline is available for adoption, either as a whole or partially, by national medicines regulators around the world or used as the basis for establishing national regulatory frameworks. Establishing a worldwide framework for biosimilar medicines is

expected to contribute enormously to public health and patients' access to medicines. In addition, the WHO released in 2016 a new draft guideline for the evaluation of mAbs as SBP candidates, which will be annexed, once final, to the existing 2009 SBPs guideline.

The basic scientific principles underlying the WHO guideline are the same as those in the EU guidelines.

further information

More and detailed information on the issues summarised in this short guide can be found via the following links:

TABLE 5 > USEFUL WEBSITE LINKS

European Medicines Agency (EMA)	http://www.ema.europa.eu/
U.S. Food and Drug Administration (FDA)	http://www.fda.gov/default.htm
World Health Organization (WHO)	http://www.who.int/en
European Commission, Directorate General Internal Market, Industry, Entrepreneurship and SMEs (GROWTH)	http://ec.europa.eu/growth/
European Commission, Directorate General Health and Food Safety (SANTE)	http://ec.europa.eu/dgs/health_food-safety/index_en.htm
Medicines for Europe	http://www.medicinesforeurope.com

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| DISCLAIMER

The information in this handbook contains the views of the Biosimilar Medicines Group member companies listed above, and is not to be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or any other regulatory agency, or any of their committees or working parties.

glossary

Active substance

→ Active ingredient or molecule that goes into a specific medicine and that provides this medicine with properties for treating or preventing one or several specific disease(s)

Adverse reaction

→ A response to a medicinal product which is noxious and unintended

Anaemia

→ Low red blood cell count

Anaphylaxis

→ An acute and severe allergic reaction in humans

Biopharmaceuticals

→ Medicines made, or derived, from living organisms using biotechnology

Biosimilar medicine

→ Medicine that is approved by the regulatory authorities as being similar in terms of quality, efficacy and safety to a reference biological medicine with which it has been compared

Biosimilarity

→ Property of a medicine to show similarity and lack of significant differences in terms of quality, efficacy and safety to a reference biological medicine to which it has been compared

Biotechnology

→ Technology that manipulates living organisms so that they produce a certain specific protein including hormones or monoclonal antibodies

Cell culture

→ The process by which cells may be grown outside the body under controlled conditions

Characterisation

→ Tests to determine the properties of a molecule or active substance, e.g. molecular size/weight, chemical structure, purity. These tests are also called physicochemical characterisation

Clinical study or trial

→ Study with the objective of determining how a medicine is handled by, and affects, humans. Clinical studies or trials are conducted in healthy volunteers or in patients. Pivotal clinical studies involving a larger group of patients provide evidence on whether the medicine can be considered both safe and effective in a real clinical setting

• Phase I clinical study or trial

→ Study with the objectives of determining how a medicine is handled by, and affects, humans, and of helping to predict the initial dosage range for the medicine. Although such studies are often conducted in healthy volunteers, phase I studies

in patients are also possible in some situations

- **Phase II clinical study or trial**

→ Study with the objectives of proving the efficacy concept of a medicine and of collecting data to establish the correct dose of that medicine. Phase II studies are not formally required for the development of biosimilar medicines as efficacy and the dose are already established for the reference product

- **Phase III clinical study or trial**

→ Study involving a larger group of patients, which aims to provide definitive evidence on whether the medicine can be considered both safe and effective in a real clinical setting

- **Confirmatory safety and efficacy study**

→ Clinical study in patients designed to confirm that there are no clinically meaningful differences between the biosimilar and the reference product

Comparability

→ The scientific evaluation of a comparison of two medicinal products to determine equivalence and any detectable differences at the level of quality, efficacy and safety

EudraVigilance

→ Data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA)

Fermentation

→ Chemical reactions induced by living organisms (or enzymes derived from living organisms) to produce raw material for pharmaceutical products

Formulation

→ The recipe and presentation of a medicine

Gaucher's disease

→ A rare inherited disorder of metabolism; people with this disease do not have enough of a specific enzyme called glucocerebrosidase, and may be treated with enzyme replacement therapy

Generic medicine

→ Medicine that has the same composition in active substance(s) and the same pharmaceutical form as the originator reference medicine, and whose bioequivalence with the originator reference medicine (i.e. the same behaviour in the body) has been demonstrated by appropriate bioequivalence studies

Glycosylation

→ The type and length of any sugar or carbohydrate groups attached to a given molecule

Harvesting

→ Separation of raw biological material from cell culture

Identification

→ The action of designating or identifying something

Immune response/reaction

→ Production of antibodies by the human body in reaction to, for example, viruses and substances recognised as foreign and possibly harmful

Immunogenicity

→ Capability of a specific substance to induce the production of antibodies in the human body. The biological response to such a substance is termed an immune response or reaction

INN

(International Non-proprietary Name)

→ Scientific or generic name of an active substance. INNs for new active substances are allocated by the World Health Organisation (WHO) in Geneva. The INN is a unique and universally accessible name. For generic and biosimilar medicines cross-referring to originator products, it is the regulatory authority that decides whether the INN of the active substance as submitted for the generic or the biosimilar medicine is scientifically acceptable

Interchangeability

→ Refers to the medical/pharmaceutical practice of switching one medicine for another that is equivalent, in a given clinical setting. A product is considered to be interchangeable if it can be administered or dispensed instead of another clinically equivalent product

In vitro

→ Biological or chemical work done in a test tube (in vitro is Latin for "in glass") rather than in living systems

Molecule

→ Compound made by atoms in a fixed and specific arrangement held together by strong chemical bonds

Monoclonal antibodies

→ Monospecific antibodies that are produced by a single clone of immune cells. They have become an important tool in molecular biology and medicine, and the basis of many biopharmaceuticals

Originator company

→ Company that was first to develop and produce a specific medicine (biopharmaceutical or pharmaceutical)

Originator reference medicinal product

→ Medicine that has been developed and produced by an originator company and that has been approved by the national regulatory authorities or the European Commission on the basis of a full registration dossier

Patent

→ Set of exclusive rights granted to a company for a given period of time in exchange for the disclosure of its invention

Pharmaceuticals

→ Conventional or traditional chemical medicines

Pharmacodynamic tests or studies

→ Study of the actions and effects of a medicine on living systems over a period of time

Pharmacokinetic tests or studies

→ Studies to determine how medicines are absorbed, distributed, metabolised and eliminated by the body

Pharmacovigilance

→ Science and activities relating to the detection, assessment, understanding and prevention of any adverse effects of medicinal products placed on the market

Physicochemical characterisation

→ Tests to determine the properties of a molecule or active substance, e.g. molecular size/weight, chemical structure, purity

Polypeptides

→ Molecules made up of chains of amino acids, which may be pharmacologically active in the human body. They contain fewer amino acids and hence have lower molecular weights than proteins

Post-Authorisation Safety Study

→ Any study with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures

Proteins

→ Large molecules made of amino acids arranged in chains, e.g. erythropoietin

Purification

→ Processes used to remove impurities (foreign or undesired materials) from a medicinal product

Risk Management Plan

→ Detailed description of the risk management system which is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks to a medicinal product, including the assessment of the effectiveness of those interventions



acronyms and abbreviations

BMWP	Biosimilar Medicines Working Party (EMA)
BPCI Act	Biologics Price Competition and Innovation Act
BWP	Biologics Working Party (EMA)
CHMP	Committee for Medicinal Products for Human use (EMA)
EC	European Commission
EEA	European Economic Area
EGA	European Generic medicines Association, now Medicines for Europe
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
EU	European Union
FSH	Follicle Stimulating Hormone
G-CSF	Granulocyte-Colony Stimulating Factor
GDP	Gross Domestic Product
GMP	Good Manufacturing Practice
INN	International Non-proprietary Name
LMWH	Low Molecular Weight Heparin
mAb	Monoclonal Antibody
NCA	National Competent Authority
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PASS	Post-Authorisation Safety Studies
PPACA	Patient Protection and Affordable Care Act
PSUR	Periodic Safety Update Reports
RMP	Risk Management Plan
WHO	World Health Organization

references

- 1 *The challenge of aligning healthcare costs with significant clinical advances*
Alan Sheppard, IMS, Presentation at NAPM biosimilars conference, Johannesburg 17/03/16 (p.8)
- 2 *Biopharmaceutical benchmarks 2014*, G. Walsh, Volume 32, Number 10, October 2014, Nature Biotechnology (p.8)
- 3 *Scrip-World Pharmaceutical News*–17 September 2007 (Ref. S00970766) (p.8)
- 4 *Directive 2004/27/EC* (p.9)
- 5 *EC 50 years of pharmaceutical legislation brochure*
Sept 2015 - http://ec.europa.eu/health/human-use/50years/docs/50years_pharma_timeline_v3.pdf (p.11)
- 6 Putrik et al. *Ann Rheum Dis* 2014;73:198-206 (p.11)
- 7 *IMS Health* (2015). *The impact of biosimilar competition* Nov 2015 (p.11)
- 8 *European Commission - The 2015 Ageing Report - Economic and budgetary projections for the 28 EU Member States (2013-2060)* (p.14)
- 9 *IGES study 2012* (p.15)
- 10 *Delivering on the Potential of Biosimilar Medicines – The Role of Functioning Competitive Markets – March 2016* <http://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf> (p.15)
- 11 *EMA link to European public assessment reports*
http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&id=WC0b01ac058001d124&searchTab=searchByAuthorType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter+keywords&searchType=name&taxonomyPath=treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit (p.16)
- 12 *Guideline on regulatory acceptance of 3R (replacement, 6 reduction, refinement) testing approaches* (Oct 2014)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500174977.pdf (p.21)
- 13 *EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*, EMEA/CHMP/BMWP/42832/2005 Rev1, 2014 (p.23)
- 14 *European Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC* (p.26)
- 15 *Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins* (Doc. Ref: EMEA/CHMP/BMWP/14327/06, publication date: Jan. 2008; effective date: Apr. 2008) (p.27)
- 16 *Finnish Medicines Agency's position towards interchangeability* <https://www.fimea.fi/web/en/-/are-biosimilars-interchangeable> (p.34)
- 17 *Report of WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products (19–20 April, 2007).*
The report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization (p.34)
- 18 *Netherlands MEB revises position on biosimilars and interchangeability* <http://www.biosimilarslawblog.com/2015/04/13/netherlands-meb-revises-position-on-biosimilars-and-interchangeability-2/> (p.34)
- 19 *FDA website* - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm> (p.38)
- 20 *The WHO SBP Guideline was adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization, 19–23 October 2009* (p.39)

appendix

| EUROPEAN GUIDELINES RELEVANT FOR BIOSIMILAR MEDICINES

The European Medicines Agency (EMA) has a dedicated webpage on biosimilar medicines which can be accessed here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp

An overview of all relevant scientific guidelines for biosimilar medicines can also be found on the EMA website and are directly accessible here:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

Scientific guidelines relevant for biosimilar medicines include:

- The overarching biosimilar guidelines
- Product-specific biosimilar guidelines
- Other guidelines relevant for biosimilar medicines

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The **Biosimilar Medicines Group** is a sector group of Medicines for Europe and represents the leading companies developing, manufacturing and marketing biosimilar medicines across Europe. Our members bring competition to the biologic medicines market, thereby increasing access to highly innovative medical treatments to patients in Europe and around the world, and supporting the sustainability of the European healthcare systems.