



Making Medicines Affordable

biosimilars

handbook



contents

- Introduction**..... 6
 - What this Handbook Covers
 - Whom this Handbook is for
- Executive Summary**..... 8
- The Importance of Biosimilar Medicines** 11
 - For Patients
 - For Clinicians
 - For Pharmacists
 - For Health Technology Assessment Boards, Healthcare Purchasers and National Pricing and Reimbursement Authorities
 - For Politicians, Policy Advisers and Makers and Healthcare Payers
- Health Economic Benefits from Biosimilar Medicines** 14
- Nomenclature of Biopharmaceuticals, Including Biosimilar Medicines** 16
- List of European Commission-Approved Biosimilar Medicines** 17
- The Science and Technology of Biosimilar Medicines** 18
 - The Development of Biosimilar Products
 - Introduction to the Concept of ‘Biosimilarity’: The Scientific Concept of Comparability
 - The Stepwise Comparability Exercise
 - First Step – Quality Comparability (Physicochemical and biological comparability)
 - Second Step – Non-Clinical Comparability (Comparative non-clinical studies)
 - Third Step – Clinical Comparability (Comparative clinical studies)

Extrapolation of Indications	
Quality Assurance for the Manufacture of Biopharmaceuticals	
Regulation of Biosimilar Medicines	26
Scientific Guidelines	
Assessment of Immunogenicity	
Gaining Marketing Authorisation	
Pharmacovigilance	
Introduction of Biosimilar Medicines into Clinical Practice	32
Identification	
Interchangeability	
Substitution	
The Future and Evolving Landscape of Biosimilar Medicines	35
The EU Biosimilar Regulatory Framework Continues to Expand	
Biosimilar Monoclonal Antibodies: the Next Frontier	
Biosimilar Regulatory Frameworks Outside the EU	
WHO Guideline	
Further Information	39
Contributors	40
Disclaimer	
Glossary	41
Acronyms and Abbreviations	46
References	47
Appendix	48



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 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 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.

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 role of **pharmacovigilance** and risk management
- the significance of **immunogenicity**
- access to medicines, including the pharmaceutical practice of **substitution**
- the importance of the **identification** of medicines
- the **interchangeability** of medicines in medical practice

The handbook focuses on the current situation in the EU, although some commentary on global approaches to biosimilar medicines is included. There is a new section dealing with the question of biosimilar **monoclonal antibodies** (mAbs), since this is an area where there have been some important discussions and where there is likely to be significant development in the near future.

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.

WHOM THIS HANDBOOK IS FOR

This handbook is intended to be a convenient and brief reference source for all those who need to understand this relatively new subclass of biopharmaceutical medicines, explaining their importance and benefits, and to provide answers to the many questions raised by this vital new category of medicine. The first edition from 2007, has already received a favourable reception from all those groups who need to understand the background of biosimilar medicines, namely:

- 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 this special and new category of biosimilar medicines, a subclass of **biopharmaceuticals**. The landscape of approved biosimilar products and guidelines has changed since 2007. 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 potential impact of biosimilar monoclonal antibodies. For all these reasons the need for a revised and updated version of the handbook is clearly apparent. The authors hope that this new edition will fulfil current needs.

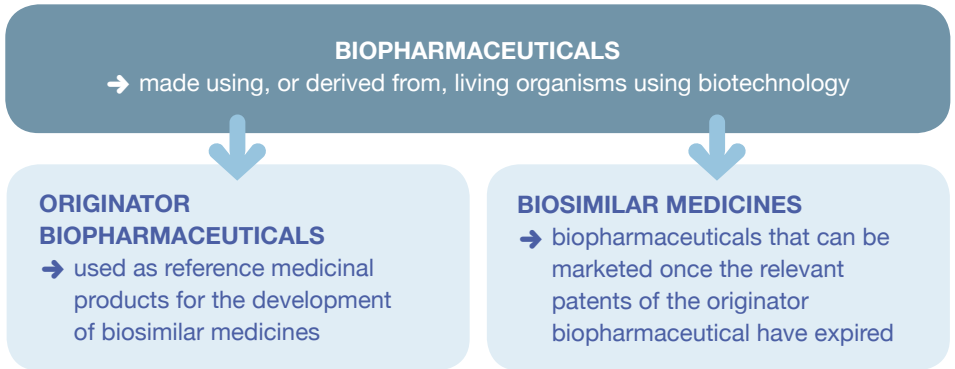
executive summary

Biosimilar medicines are an important and relatively new 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 already one of the fastest-growing segments of the pharmaceutical industry market, with a compound annual growth rate that has been estimated at being up to 20%¹. The importance of these products to healthcare budgets, as well as to the pharmaceutical industry and its revenues, cannot be overstated. There are more than 200 such products on the market today. Some 300 more are being investigated in **clinical trials**². When relevant **patents** have expired,

biopharmaceuticals can also be 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 therefore a subclass of biopharmaceuticals, with comparable quality, efficacy, and safety to that of **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 changed to introduce this category of products into Europe at the end of 2005. Since then, about a dozen biosimilar medicines have gained European approval to be marketed.

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 for all manufacturing, preparation and processing of the product. One key quality aspect to be considered is the potency and purity of the product, which should be within the limits displayed by the reference product. The biosimilar development process uses the latest state-of-the-art analytical and biotechnology methods, including some that may not have been available at the time the reference product was first approved.



In order to gain approval, biosimilar medicines have to demonstrate that they are as safe and as effective as the originator reference product, and have the same quality.

Biosimilar medicines are thoroughly evaluated for their comparability with the reference product. This evaluation is customised on a case-by-case basis for each biosimilar product.

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

continued safety. Patient safety data are 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 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 the availability and affordability of important biosimilar medicines to more patients, confident in the knowledge that they have been thoroughly scientifically assessed by the EMA and approved by the European Commission as safe and efficacious medicines.

the importance of biosimilar medicines

For more than 20 years 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 their use remains out of reach for some patients in the EU who could benefit from their use.

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 more affordable 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.

FOR PATIENTS

Patients in Europe deserve access to effective and affordable biopharmaceuticals as they fight disabling and life-threatening diseases. Biosimilar medicines can help to improve patient access to many of these biopharmaceuticals. 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 this should aid patients in discussing the benefit of these medicines with healthcare providers.



FOR CLINICIANS

Biosimilar medicines offer physicians an affordable and therapeutically equivalent alternative 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 level, which aims to demonstrate the similarity of the biosimilar with the originator reference product. Once a successful and complete comparability exercise has been demonstrated for a particular biosimilar product, then, as a result, the safety and efficacy profile established for the relevant reference product is 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 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 and cost-effective medicines to the benefit of their patients.

FOR 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 acutely aware of the burgeoning cost of biopharmaceuticals and are often tasked with helping to manage healthcare budgets as effectively as possible. Biosimilar medicines offer an affordable alternative to more established biopharmaceuticals and can help pharmacists to improve patient access to these important medicines whilst at the same time aiding them to manage 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, and should be assured by the robust regulatory systems that are in place in the EU to ensure that all medicinal products meet the required standards for quality, efficacy and safety.



FOR 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, or that savings can be made in order to fund other treatments.

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 conventional 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.

FOR POLITICIANS, POLICY ADVISERS AND MAKERS AND HEALTHCARE PAYERS

Biosimilar medicines bring additional competition to the European biopharmaceutical product market, in the same way that conventional generic pharmaceutical products bring competition to the non-biopharmaceutical product landscape. Through this competition, the cost of healthcare can be reduced, and more patients can gain access to essential biopharmaceuticals. 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 successful product applications a Marketing Authorisation within the European Union.



health economic benefits from 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. By 2060, EU life expectancy is projected to have increased by 8.5 years for men and by 6.9 years for women, resulting in around 20 to 25 years of life following retirement³.

Ageing is accelerating. Our working age population will be reduced by about 2 million by 2020 and the number of 60+ is increasing twice as fast as before 2007.

Presentation of European Commission President J.M. Barroso to the Informal European Council |11 February 2010

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 past 25 years, the introduction of high quality generic medicines has made a significant impact in reducing healthcare expenditure across the EU. These lower cost alternatives to traditional medicines have helped to manage healthcare



budgets and have allowed better access to important medicines for a greater number of patients. In a similar way, biosimilar medicines are now able to offer alternative treatment options to many expensive biopharmaceuticals, and so allow the potential for considerable cost saving.

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. Were biosimilar medicines to be used as an alternative to only the top 7 conventional biopharmaceuticals within the EU, then given, for example, a 20% price reduction for biosimilar medicines, the use of these products could result in savings of more than 2 billion Euros each year⁴. 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.



High quality biosimilar medicines provide a major opportunity to help governments control the cost and availability of biopharmaceutical medicines. If biosimilar medicines were to be used as alternatives to only 7 conventional biopharmaceuticals within the EU, savings of more than €2 billion could be achieved. Wider use of biosimilar medicines contributes to the sustainability of EU healthcare systems.



nomenclature of biopharmaceuticals, including biosimilar medicines

Biopharmaceuticals have been available for more than 20 years. These include:

- hormone products, e.g. growth hormone for growth hormone disorders, erythropoietin (EPO) for **anaemia** in the kidney and other diseases, and insulin for diabetes
- 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, these new categories of medicines are called biosimilar medicines, or 'biosimilars'. Sometimes the longer official term 'similar biological medicinal products' is used. They can be marketed following loss of patent protection of the originator product. Biosimilar medicines approved in the EU have been 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 and the European Commission websites.

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

list of european commission-approved biosimilar medicines

Since the advent of the biosimilar legislative pathway in the EU, many such products containing a variety of biological **active substances** have been approved via the biosimilar pathway. These include growth hormone (active substance: somatropin), erythropoietin

(active substance: epoetin alfa, epoetin zeta) and granulocyte colony stimulating factor (G-CSF) (active substance: filgrastim). A full listing of all the individual biosimilar product approvals granted by the European Commission is shown in the following table.

TABLE 1 > EU BIOSIMILAR LANDSCAPE OF APPROVALS (MARKETING AUTHORISATIONS)

INTERNATIONAL NON-PROPRIETARY NAME (INN) OF ACTIVE SUBSTANCE	MARKETING AUTHORISATION HOLDER	DATE OF EC APPROVAL	BRAND NAME	REFERENCE PRODUCT
SOMATROPIN	Sandoz GmbH	12 April '06	Omnitrope®	Genotropin®
	BioPartners GmbH	24 April '06	Valtropin®	Humatrope®
EPOETIN ALFA	Sandoz GmbH	28 August '07	Binocrit®	Erypo®/Eprex®
	Hexal GmbH	28 August '07	Epoetin alfa HEXAL®	Erypo®/Eprex®
	Medice Arzneimittel Pütter GmbH & Co. KG	28 August '07	Abseamed®	Erypo®/Eprex®
EPOETIN ZETA	STADA Arzneimittel GmbH	18 December '07	Silapo®	Erypo®/Eprex®
	Hospira UK Ltd.	18 December '07	Retacrit®	Erypo®/Eprex®
FILGRASTIM	Ratiopharm GmbH	15 September '08	Ratiograstim®	Neupogen®
	Teva Generics GmbH	15 September '08	TevaGrastim®	Neupogen®
	CT Arzneimittel GmbH	15 September '08	Biograstim®	Neupogen®
	Sandoz GmbH	6 February '09	Zarzio®	Neupogen®
	Hexal GmbH	6 February '09	Filgrastim HEXAL®	Neupogen®
	Hospira UK Ltd.	8 June '10	Nivestim®	Neupogen®



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

applications and approvals for biosimilar medicines in the coming years.

the science and technology of biosimilar medicines

Biopharmaceuticals contain much larger molecules than conventional pharmaceuticals, 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

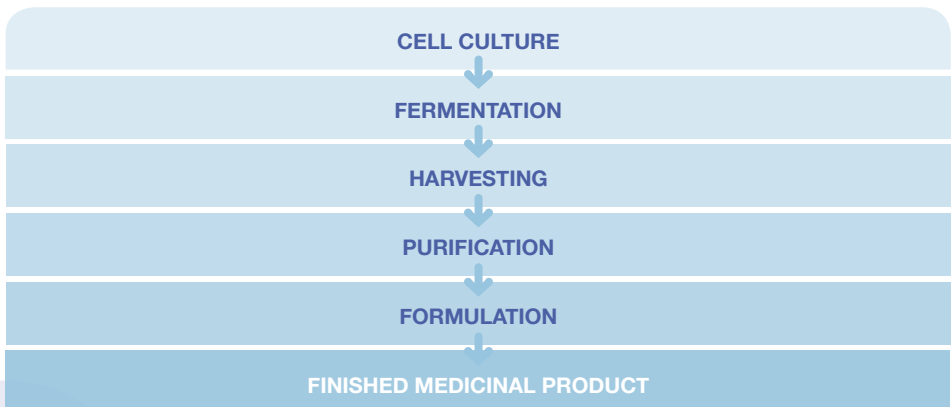
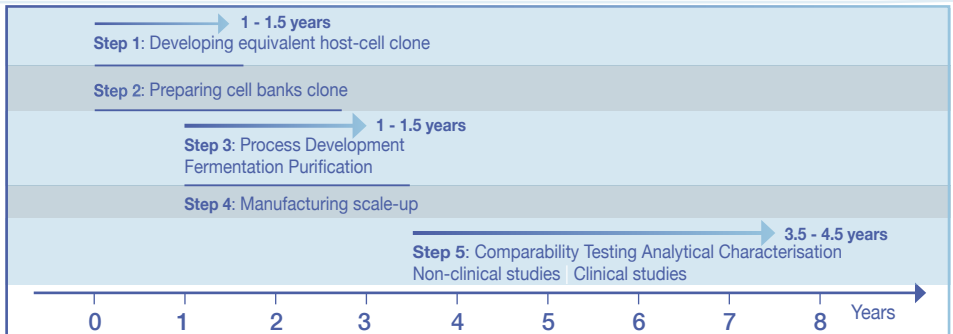


FIGURE 3 > TIMELINE FOR DEVELOPMENT OF A BIOSIMILAR MEDICINE



THE DEVELOPMENT OF BIOSIMILAR PRODUCTS

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

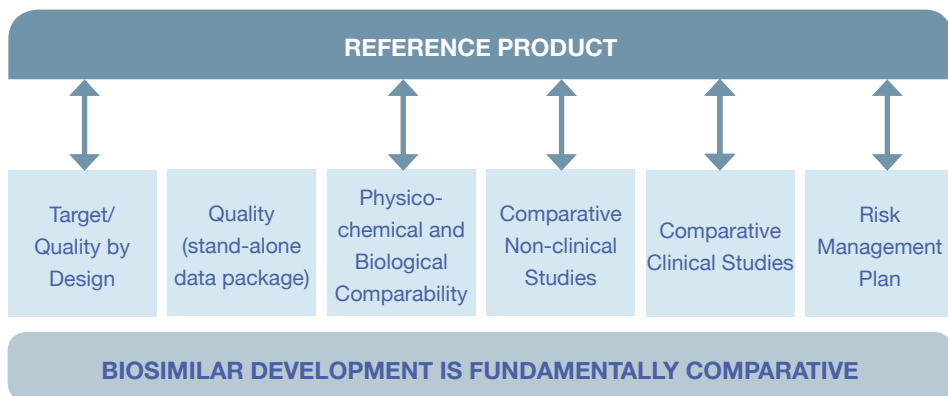
The basic principle underlying the development of a biosimilar product is comparability with the reference product. This is not a new scientific concept that applies only to biosimilar medicines. Comparability, as assessed through a process known as a 'comparability exercise', is a critical concept that has been evolved in order to perform comparisons between different versions of any new biological products in development. Data provided by such comparisons are 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, the manufacturers of the product are required to demonstrate 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, similarity needs to be demonstrated. The similarity 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 potential 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 programmes 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 of different state-of-the-art analytical tests, as no single method can characterise all aspects of a product.

- The development process to be modified, 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 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 an abbreviated programme of **in vitro** tests or studies in animals, as required by EU guidelines. The non-clinical studies usually comprise repeat dose toxicity studies as well as **pharmacokinetic** and **pharmacodynamic (PK/PD)** studies in an appropriate animal model, together with local tolerance testing. The PK/PD parameters for these studies, as well as the predefined level of similarity of these parameters, need to be scientifically justified in order to support comparability with the reference product. The aim of these studies is to further support comparability or to detect potential differences between the biosimilar and reference products.

- **Third Step – Clinical Comparability (Comparative clinical studies)**

The clinical trials are also comparative

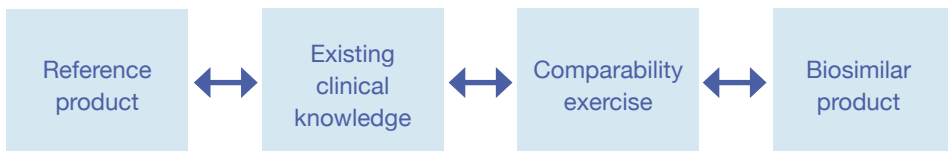
in nature in the case of a biosimilar development. However, clinical testing is not required to the same extent as would be needed for a new active substance due to the clinical experience acquired from the use of the reference product, accumulated over many years. The design of the clinical development 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 testing in animals, the more an abbreviated 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. Abbreviated clinical trials help to ensure that unnecessary human testing does not take place and that the very high development costs associated with clinical trials can be reduced.

The clinical comparability exercise usually begins with pharmacokinetic and/or pharmacodynamic studies. As a further step, these studies can be followed by

comparative clinical efficacy and safety trial(s) in one or more representative indications. 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 PLACE OF THE COMPARABILITY EXERCISE

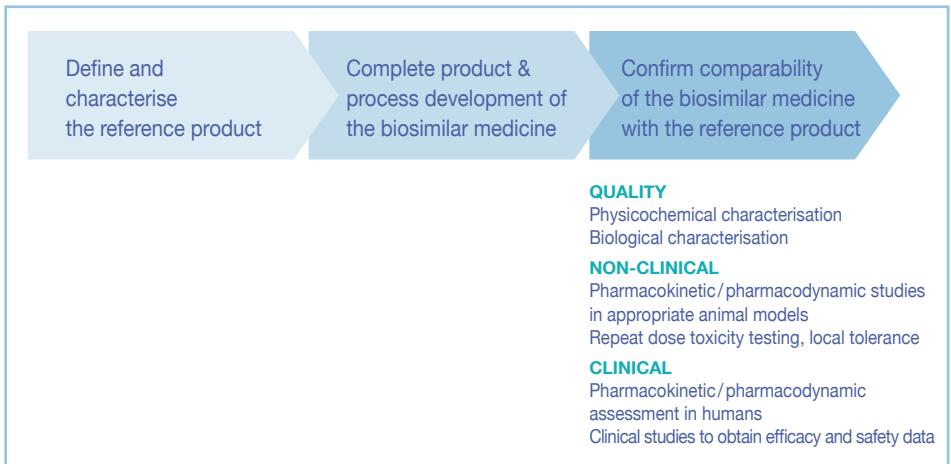


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The primary purpose of the assessment of a biosimilar product is not the characterisation of the benefit/risk profile of the product as such, but the qualitative and quantitative evaluation of the comparability (similarity) of the product to the reference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

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FIGURE 6 > STAGES OF DEVELOPMENT OF A BIOSIMILAR MEDICINE



EXTRAPOLATION OF INDICATIONS

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

This fact has been acknowledged by the European regulators and therefore they have included a provision for this in the European regulatory framework for biosimilar medicines, which states that “in certain cases it may be possible to extrapolate the therapeutic similarity shown in one indication to other indications of the reference medicinal product”⁵.

The scientific basis for this extrapolation of indications is the proven, in-depth comparability between the biosimilar and the reference product at quality level. This quality comparability is established with regards to molecular structure as well as with regards to functionality and must be demonstrated with comprehensive analytical characterisation, relevant receptor binding studies, bioassays and appropriate animal studies, all to be performed with the biosimilar and the reference product in a rigorous comparative manner.

Only when this quality comparability is achieved, is it justified for a biosimilar product dossier to cross-refer to the clinical data obtained through the extensive experience with the reference product, which is described in the literature and in publicly accessible health authority documents.

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

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 biosimilars 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.



“

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 approval 10 to 20 years earlier.

”

regulation of biosimilar medicines

SCIENTIFIC GUIDELINES

The EU is 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 2004⁶.

With the legal framework for biosimilars having been 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), releases specific guidelines to deal with all aspects of the development, production, testing and regulation of biosimilar medicines. This is done after consultation with all the relevant stakeholders, which include national regulatory bodies, scientific advisory groups, industry, clinicians, and patient groups.

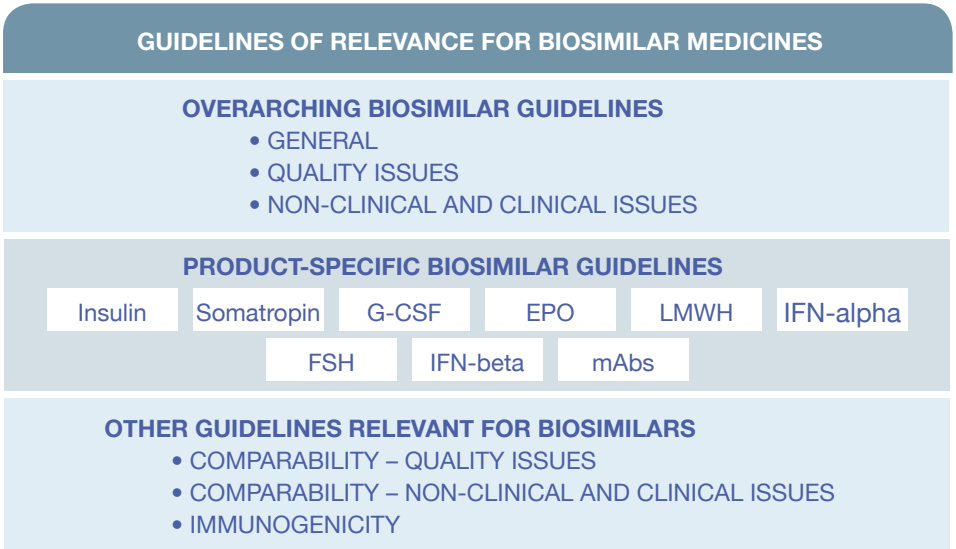
The initial guidelines, published in 2005 and 2006, comprise an overarching guideline as well as other more general

guidelines concerning the product quality, clinical and non-clinical issues. Product-specific guidelines listing the non-clinical and clinical requirements are also available, and the EMA is in the process of developing additional guidelines (see the detailed list of all the guidelines in the Appendix at the end of this handbook). Existing guidelines also evolve over time to take into account the scientific and technological developments, as well as the accumulated experience with marketing authorisation applications and marketed medicinal products.

| EMA building in London



FIGURE 7 > SCHEMATIC OVERVIEW OF CURRENT BIOSIMILAR 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 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 administration⁷. 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 these data are 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

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:

- 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

Most of the above data would be presented as a comprehensive comparability exercise with the reference product.

NON-CLINICAL DATA

The registration dossier for biosimilar medicinal products will usually include comparative non-clinical data.

The amount of non-clinical data required is specific to the product, and will be determined on a case-by-case basis.

Usually the following non-clinical tests are included:

- A short-term toxicological repeated dose study (typically 4 weeks)
- Pharmacokinetic/pharmacodynamic studies in an appropriate animal model
- Local tolerance testing

CLINICAL DATA

The registration dossier for a biosimilar medicinal product will usually include clinical data, summarising the results of clinical trials conducted in patients and healthy volunteers with the biosimilar product. For most biosimilar medicines, extensive comparative trials have been conducted, often including several hundreds of patients.

Companies applying for a marketing authorisation must submit all the results from their trials, both positive and negative. Immunogenicity data are required.

PHARMACO-VIGILANCE

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. The Risk Management Plan also includes the description of the routine pharmacovigilance system, which requires the submission of Periodic Safety Updates Reports (PSURs).

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 about the medicinal product, known as a 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. 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 EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine and the batch number must

be included in the ADR report. This allows linking a suspected adverse reaction 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.



introduction 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.

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 product⁸.

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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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.
”



SUBSTITUTION

Substitution or substitutability (i.e. the ability to substitute) refers to the pharmaceutical practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level and without requiring consultation with the prescriber. The term ‘automatic substitution’ refers to the practice whereby the pharmacist is obliged to dispense one medicine for another equivalent and interchangeable medicine due to national or local requirements. Substitution is governed by national laws, which vary from country to country and which may take both scientific and other factors into account. In practice, automatic substitution is very rare for medicines in general, and at the time of writing in 2010, does not take place for biopharmaceuticals, including biosimilar medicines, in the EU.

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Substitution refers to the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without requiring consultation with the prescriber.

Automatic substitution refers to the practice whereby a pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or local requirements.

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the future and evolving landscape of biosimilar medicines

THE EU BIOSIMILAR REGULATORY FRAMEWORK CONTINUES TO EXPAND

The following guidelines have been released for consultation in the course of 2010.

- Guideline on Similar Biological Medicinal Products containing recombinant follicle stimulation hormone
- Guideline on Similar Biological Medicinal Products containing monoclonal antibodies
- Guideline on Similar Biological Medicinal Products containing interferon beta

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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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BIOSIMILAR MONOCLONAL ANTIBODIES: THE NEXT FRONTIER

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.

TABLE 3 > EXAMPLES OF CURRENTLY LICENSED MONOCLONAL ANTIBODIES

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

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 the assessment of numerous biosimilar applications. Existing, overarching EU guidelines for biosimilar medicines are applicable for the development of biosimilar mAbs. In addition, there are specific guidelines on biosimilar monoclonal antibodies 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. 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, biosimilar guidance was finalised and issued in Canada, with the first biosimilar medicine having been already approved there in 2009, using the earlier draft guidelines. In the USA the Biologics Price Competition and Innovation Act (BPCI Act) has been adopted in 2009. 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 biosimilars has been embedded in the March 2010 US healthcare law, i.e. the Patient Protection and Affordable Care Act (PPACA).

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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.

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WHO GUIDELINE

The World Health Organization (WHO) published the final guidelines on evaluation of similar biotherapeutic products (SBPs) in April 2010⁹. 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.

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

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further information

Some information on the issues summarised in this short guide can be found at the following links:

TABLE 4 > USEFUL WEBSITE LINKS

European Medicines Agency (EMA)	http://www.ema.europa.eu/
World Health Organization (WHO)	http://www.who.int/en
European Commission, Directorate General Enterprise and Industry	http://ec.europa.eu/enterprise/index_en.htm
European Commission, Directorate General Health and Consumer Affairs	http://ec.europa.eu/dgs/health_consumer/index_en.htm
European Generic medicines Association (EGA)	http://www.egagenerics.com/



contributors

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- STADA Arzneimittel AG www.stada.de/
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DISCLAIMER

The information in this handbook contains the views of the EGA-EBG 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 one of its committees or working parties.

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.

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, e.g. to 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 the 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

Substitution/Substitutability

→ (i.e. the ability to substitute) refers to the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level and without requiring consultation with the prescriber. The term 'automatic substitution' refers to the practice whereby the pharmacist is obliged to dispense one medicine instead of another equivalent and interchangeable medicine due to national or local requirements



acronyms and abbreviations

BMWP	Working Party on Similar Biological Medicinal Products (EMA)
BPCI Act	Biologics Price Competition and Innovation Act
BWP	Biotechnology Working Party (EMA)
CHMP	Committee for Medicinal Products for Human use (EMA)
EC	European Commission
EEA	European Economic Area
EGA	European Generic medicines Association
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

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- 2 Scrip-World Pharmaceutical News–17 September 2007 (Ref. S00970766)
- 3 European Commission: Interim EPC-SPC, Joint Report on Pensions, Brussels 21/4/2010, ARES save number (2010)221924
- 4 EGA estimation based on IMS data
- 5 EMEA/CHMP/BMWP/42832/2005: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues: quote “In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on, e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.”
- 6 European Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC
- 7 Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (Doc. Ref: EMEA/CHMP/BMWP/14327/06, publication date: Jan. 2008; effective date: Apr. 2008)
- 8 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
- 9 The WHO SBP Guideline was adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization, 19–23 October 2009 and published in the WHO Technical Report Series

appendix

EUROPEAN GUIDELINES OF RELEVANCE FOR BIOSIMILAR MEDICINES

OVERARCHING BIOSIMILAR GUIDELINES

TOPIC	REFERENCE NUMBER	PUBLICATION DATE (PD) EFFECTIVE DATE (ED)
Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	Adopted guideline CHMP/42832/05	PD: Feb 2006 ED: Jun 2006
Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues	Adopted guideline CHMP/49348/05	PD: Feb 2006 ED: Jun 2006
Similar biological medicinal product	Adopted guideline CHMP/437/04	PD: Sep 2005 ED: Oct 2005

Source: *European Medicines Agency's website*

PRODUCT-SPECIFIC BIOSIMILAR GUIDELINES

TOPIC	REFERENCE NUMBER	PUBLICATION DATE (PD) EFFECTIVE DATE (ED)
Similar biological medicinal products containing recombinant follicle stimulation hormone	Concept paper EMA/CHMP/ BMWP/94899/2010	Release for consultation Mar 2010
Similar biological medicinal product containing recombinant interferon beta	Concept paper CHMP/ BMWP/86572/10	Release for consultation Mar 2010
Similar biological medicinal products containing monoclonal antibodies	Draft guideline EMA/CHMP/ BMWP/403543/2010	Release for consultation Nov 2010
Similar biological medicinal products containing recombinant erythropoietins	Adopted guideline EMA/CHMP/ BMWP/301636/08	PD: Apr 2010 ED: 30 Sep 2010
Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues – Guidance on similar medicinal products containing recombinant erythropoietins (superseded by EMEA/CHMP/BMWP/301636/08)	Adopted guideline CHMP/94526/05	PD: Mar 2006 ED: Jul 2006

Similar biological medicinal products containing low-molecular-weight heparins	Adopted guideline CHMP/ BMWP/118264/07	PD: Apr 2009 ED: Oct 2009
Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha	Adopted guideline CHMP/ BMWP/102046/06	PD: Jun 2009 ED: Apr 2009
Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues — Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor	Adopted guideline CHMP/31329/05	PD: Feb 2006 ED: Jun 2006
Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues — Guidance on similar medicinal products containing somatropin	Adopted guideline CHMP/94528/05	PD: Feb 2006 ED: Jun 2006
Annex to Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical Issues — Guidance on similar medicinal products containing recombinant human insulin	Adopted guideline CHMP/32775/05	PD: Feb 2006 ED: Jun 2006

Source: European Medicines Agency's website

OTHER GUIDELINES RELEVANT FOR BIOSIMILAR MEDICINES

TOPIC	REFERENCE NUMBER	PUBLICATION DATE (PD) EFFECTIVE DATE (ED)
Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use	Draft guideline EMA/CHMP/ BMWP/86289/2010	Release for consultation Nov 2010
Comparability of biotechnology-derived medicinal products after a change in the manufacturing process — non-clinical and clinical issues	Adopted guideline CHMP/ BMWP/101695/06	PD: Jul 2007 ED: Nov 2007
Immunogenicity assessment of biotechnology-derived therapeutic proteins	Adopted guideline CHMP/ BMWP/14327/06	PD: Jan 2008 ED: Apr 2008
Comparability of medicinal products containing biotechnology-derived proteins as active substance — quality issues (superseded by ICH Q5E - CPMP/ICH/5721/03)	Adopted guideline CPMP/BWP/3207/00 Rev. 1, CPMP/ ICH/5721/03	PD: Dec 2003 ED: Dec 2003
Comparability of medicinal products containing biotechnology-derived proteins as drug substance — non clinical and clinical issues (superseded by CHMP/BMWP/101695/06)	Adopted guideline CPMP/3097/02	PD: Dec 2003 ED: Jun 2004
Development of a CPMP guideline on comparability of biotechnology-derived products	Concept paper CPMP/BWP/1113/98	PD: Jun 1998 ED: -

Source: *European Medicines Agency's website*

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