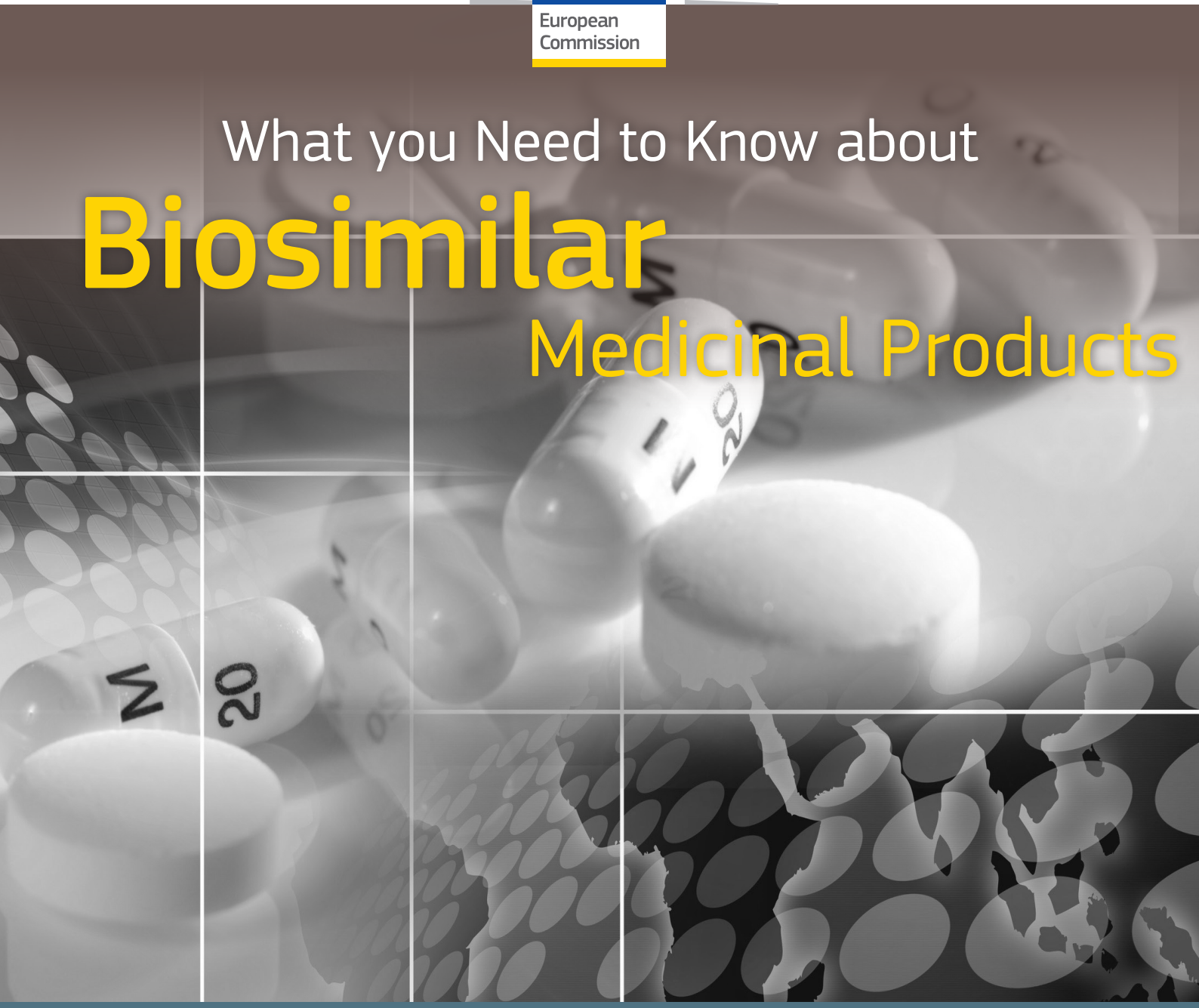
European Commission

What you Need to Know about Biosimilar Medicinal Products



Process on Corporate Responsibility in the Field of Pharmaceuticals Access to Medicines in Europe

A Consensus Information Document

Enterprise and Industry

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The present document is without prejudice to any existing or future EU / national and international legislation.

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List of Acronyms

ADR	Adverse drug reaction
AIM	Association Internationale de la Mutualité
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use (EMA)
CPME	Standing Committee of European Doctors
DDD	Defined daily dose
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGA	European Generic medicines Association
EMA	European Medicines Agency
EPF	European Patients Forum
EPAR	European public assessment report
EPO	Erythropoietin
ESAs	erythropoiesis-stimulating agents
ESIP	European Social Insurance Platform
EU	European Union
EV	EudraVigilance
EuropaBio	European Association for Bio-industries
G-CSF	Granulocyte colony-stimulating factor
GDP	Good Distribution Practice
GIRP	European Association of Full-line Wholesalers
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HGF	Human growth factor
HOPE	European Hospital and Healthcare Federation
INN	International Non-Proprietary Name
MAT	Moving annual total
MIA	Manufacturer's and importer's authorisation
NO	Norway
PAES	Post-authorisation efficacy studies
PAG	Policy Advisory group (EPF)
PASS	Post-authorisation safety studies
PhVWP	Pharmacovigilance Working Party
PI	Product information
PIL	Package information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PRCA	Pure red cell aplasia
RMP	Risk management plan
SmPC	Summary of product characteristics
WDA	Wholesaler distributor's authorisation
WHO	World Health Organization

In September 2010, the European Commission launched the Process on Corporate Responsibility in the Field of Pharmaceuticals[1] focusing on, amongst others areas, non-regulatory conditions for better access to medicines following their marketing authorisation.

Under its Platform "Access to Medicines in Europe", Member States, EEA countries and relevant stakeholders were invited to a project group on biosimilar medicinal products in order to take stock of the availability of biosimilar medicinal products in European national markets, and to define the necessary conditions for an informed uptake and adequate patient access to these products.

In accordance with the project group's Terms of Reference, the group looked into topics related to improving information on the concept of biosimilar medicinal products and the science and process behind the approval. All these are relevant to decision makers including scientific societies, healthcare professionals and competent authorities, as well as patients and patient organisations.[2] All aspects related to interchangeability and/or substitution remained outside of the group's scope.

In order to provide the different target groups with adequate information on biosimilar medicinal products, the project group, in close co-operation with the Commission services, decided to prepare this information paper including a specific Question & Answer part targeting patients, physicians and payers. The European Medicines Agency contributed to the paper within their responsibilities and competence.[3]

The paper is a consensus document agreed by the project group Market Access and Uptake of Biosimilars[4] and adopted by the Steering Group of the Process for Corporate Responsibility in the field of Pharmaceuticals.

[1] Press Memo - Process on Corporate Responsibility in the Field of Pharmaceuticals - 24/09/2010

[2] For more information about the project group's other deliverables please consult our dedicated Webpage "Access to Medicines in Europe"

[3] The present information paper should not be considered as authored or endorsed by the EMA.

[4] The paper represents the consensus outcome from discussions of a multi-stakeholder subgroup (named "Information" group) and was formed by volunteers from the European Patients Forum (EPF), Standing Committee of European Doctors (CPME), European Social Insurance Platform (ESIP), Association Internationale de la Mutualité (AIM), European Generic medicines Association (EGA), European Federation of Pharmaceutical Industries and Associations (EFPIA), European Association for Bio-industries (EuropaBio) and Austria. The paper was adopted by the project group with the following members: AT, BE, CZ, DK, ES, FR, HU, IE, IT, LT, NL, NO, SE, EPF, CPME, ESIP, AIM, EGA, EFPIA, EuropaBio, European Association of Full-line Wholesalers (GIRP) and European Hospital and Healthcare Federation (HOPE). The project group was chaired by Denmark and the European Commission.

Key Messages

- A biosimilar medicinal product is a biological medicine which is similar to another biological medicine that has already been authorised for use, the "reference medicinal product".

- A biosimilar medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile. Biosimilar medicinal products are authorised either for all or selected indications of the reference medicinal product on a case by case basis.

- The development and the manufacturing process of biosimilar medicinal products are more complex and expensive than generics of chemical (small molecule) products.

- Biosimilar medicinal products follow the specific provisions of EU legislation (the so-called "biosimilar pathway") which include defined high standards of quality, safety and efficacy.

- Standards of the EU Good Manufacturing Practice (GMP) apply to the manufacture of biosimilar medicinal products in the same way as for any other biological medicinal product. Compliance with the EU GMP Guidelines is verified during routine GMP inspections by the EU national competent authorities.

- Biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006 and their market share has been growing at different rates across both EU Member States and product categories.

- Biosimilar medicinal products may offer a less-costly alternative to existing biological medicinal products that have lost their exclusivity rights.

- The availability of biosimilar medicinal products enhances competition, with the potential to improve patient access to biological medicines and to contribute to the financial sustainability of EU healthcare systems. Thus, their availability offers potential economic benefit to EU healthcare systems while addressing the issue of new treatment options brought about by advances in medical science.

- EMA provides detailed information on centrally authorised biosimilar medicinal product on their website.[5]

- *"The decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of the EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions".*[6]

[5] See dedicated EMA biosimilar medicines webpage
[6] See page 33/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011_March 2013

- *"For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist".*[7]

[7] See question: Can a biosimilar and its reference medicine be used interchangeably ? in EMA Questions and answers on biosimilar medicines (similar biological medicinal products)_EMA/837805/2011_September 2012.

1. INTRODUCTION

Biotechnology has enabled the development of treatments for a variety of serious diseases. Worldwide, many million patients have already benefited from approved biological medicines. These medicines help treat or prevent many rare and severe diseases including cancers, heart attacks, stroke, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases.

Given that the first biological medicinal products produced by DNA recombinant techniques were approved in the 1980s, the exclusive rights (patents and other data protection) for several biological medicinal products have reached their expiration and many more will expire in the coming decade. Consistent with this expiry, similar biological medicinal products, or biosimilar medicinal products ("biosimilars") as they are now commonly called, are being developed and several are already available on European markets, with the first approved and marketed in 2006.

2. BIOLOGICAL MEDICINAL PRODUCTS

2.1. What are biological medicines and how do they work?

Biological medicines[8] (also called "biopharmaceuticals") are comprised of proteins such as hormones (growth hormones, insulins, erythropoietins), enzymes that are naturally produced in the human body, or monoclonal antibodies, but also blood products, immunological medicinal products such as sera and vaccines, allergens, and advanced technology products such as gene and cell therapy products. Like all medicines, biological medicines work by interacting with the body to produce a therapeutic outcome, but the mechanisms by which they do this may vary from product to product and across indications. Biopharmaceuticals can be tailor-made to fit the desired target. Therefore the role of the physicians in treatment of patients with these complex medicinal products is particularly important.

2.2. How are biopharmaceuticals produced and distributed?

Biotechnology uses living systems (plant or animal cells, bacteria, viruses and yeast) and modern technologies to produce biological medicines to treat diseases and genetic disorders in humans. Many, but not all biological medicines, are made using genetically-modified cells. Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes. It is noted that some biological medicines are produced by non-Biotechnology methods and are therefore not necessarily authorised through the centralised procedure. This consensus information document only addresses centrally authorised biotechnology-derived medicinal products[9]. (see also 3.1)

[8] See definition in Part I of Annex I of Directive 2001/83/EC (as amended by Directive 2003/63/EC): a biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physic-chemical-biological testing together with the production process and its control.

[9] This chapter and the whole information consensus document only focuses on biological medicinal products, including biosimilar medicinal products, that are biotechnology-derived medicines and which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion

The production of biological medicines involves processes such as fermentation and purification. The manufacturing processes for biological medicines are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final product. The production of biological medicines is a complex process which requires a very high level of technical expertise with typically about 250 in-process tests being conducted compared to about 50 tests for a small molecule medicine. Manufacturers and importers of medicines approved in the European Union, including biosimilar medicinal products, are legally obliged to hold a valid Manufacturer's and Importer's Authorisation (MIA)/ GMP certificate issued by an EU national competent authority. An MIA/GMP certificate will only be granted if the manufacturing/importing site complies with the EU Guidelines on Good Manufacturing Practice (GMP), which also include specific provisions for biological medicinal products (Annex 2 of the Volume 4 of EudraLex).

To verify compliance with GMP, manufacturers and importers in the EU are subject to regular GMP inspections by the supervisory authorities. The EU national competent authorities also inspect manufacturers located outside the EU that export to the EU. For biopharmaceuticals which are centrally assessed and authorised for marketing in the whole European Union, the EMA coordinates inspections related to the medicine's scientific assessment and conducted by the EU national competent authorities.

Importers, manufacturers and wholesale distributors are obliged to comply with Good Distribution Practice (GDP) standards. According to the GDP Guidelines, specific conditions for storage and transport (e.g. refrigeration) must be ensured. Wholesale distributors are legally obliged to hold a valid wholesaler distributor's authorisation (WDA) issued by an EU national competent authority. Wholesale distribution by manufacturers, importers and distributors is equally subject to supervision by EU national competent authorities.

2.3. How do biological medicines differ from small molecule medicines?

Biopharmaceuticals differ in many ways from small molecule medicines, including for example the manufacturing techniques, their molecular size and complexity, or their stability. Because proteins are affected by the digestive system when taken orally, most biopharmaceuticals must be administered by injection or infusion.

Small molecule medicines are typically manufactured by chemical synthesis, whereas most biopharmaceuticals are made in living systems such as microorganisms or animal cells and purified through a complex manufacturing process. Therefore their exact characteristics are subject to inherent variability and biopharmaceuticals are defined as mixtures of many different forms of the same protein. Another source of variability in certain biopharmaceuticals is the type and length of sugar or carbohydrate group attached to the protein backbone (glycosylation).

Small molecule medicines generally have well-defined chemical structures and can usually be analysed to determine all the various components. This is not the case for biopharmaceuticals, where the inherent variability in the molecules means they are

adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

more difficult to characterise than small molecule medicines and most cannot be exactly reproduced, even between batches of the same product (irrespective of whether it is a reference medicinal product or biosimilar medicinal product). This inherent variability of all biopharmaceuticals is tightly controlled by manufacturers and regulators and must remain within accepted and pre-defined limits.

Biological medicines have the potential to be recognised by the body as "foreign" and therefore have the inherent potential to induce unwanted immune reactions, due to their composition and large molecular size. Chemical medicines, on the other hand, are usually too small to be recognised by the immune system.

This potential to induce an immune reaction in the body (immunogenicity) is a double-edged sword for biological medicines. Vaccines specifically exploit their immunogenic potential by provoking an immune response that recognises and "fights of" an "invader" substance. However, for some medicines based on proteins, stimulating an immune response is regarded as undesirable. Most of the immune responses that occur are mild and do not have negative effects on the patient. However in rare cases, unwanted immune reactions can lead to severe and detrimental effects on the health of a patient. An unwanted immune response in treated patients can be influenced by numerous factors such as the disease state, drug-related factors (product-and process related factors), patient-related factors (age, sex, genetic background, etc.) and treatment-related factors (concomitant drugs, route of administration, etc.).

3. REGULATION OF BIOLOGICAL MEDICINES IN EUROPE, INCLUDING BIOSIMILAR MEDICINES

3.1. What is the EU legal and regulatory pathway?

In the European Union, marketing authorisation applications for biotechnology-derived medicinal products, including biosimilar medicinal products, are by law reviewed centrally by the European Medicines Agency (EMA). The European Commission issues the Decisions concerning the authorisation of these medicinal products on the basis of the scientific opinions from the EMA. The resulting marketing authorisation is valid in all EU Member States.

The EU is the first region in the world to have set up a legal framework and a regulatory pathway for "similar biological medicinal products", more commonly called "biosimilars". The EU regulatory framework inspired many countries around the world e.g. Australia, Canada, Japan, Turkey, Singapore, South Africa, Taiwan, USA etc. as well as the World Health Organisation (WHO). The concept of a "similar biological medicinal product" was adopted in EU pharmaceutical legislation in 2004[10] and came into effect in 2005. The first biosimilar medicine was approved by the European Commission in 2006.[11]

The legislation did not introduce a definition of a biosimilar medicinal product per se. Rather it laid down the legal basis of the "biosimilar pathway". It states that "*where a*

[10] Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC

[11] Biosimilars Marketing Authorisation status as of January 2013: 22 Marketing Authorisation Applications (MAAs) reviewed (14 positive, 7 withdrawn, 1 negative); 12 biosimilar medicines currently hold a valid MA; (1 somatropin, 5 epoetin, 6 filgrastim); 5 biosimilar MAAs are currently under review (2 follitropin alfa, 2 infliximab, 1 filgrastim) - source: EMA website, Medicines under evaluation.

biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided."

Since biosimilar medicinal products are biological medicinal products, they also fall under the EU legal definition of a biological medicinal product. Consequently they have to follow the general scientific guidelines related to biological medicinal products and undergo the same rigorous regulatory assessment by the relevant regulatory authorities, like all other biopharmaceuticals.

In the course of 2012, the EMA included a definition of a "biosimilar" in an EMA procedural guidance document[12]: "*A similar biological medicinal product, also known as "Biosimilar", is a product which is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". The active substance of a biosimilar medicine is a known biological active substance and similar to the one of the reference medicinal product. A similar biological medicinal product and its reference medicinal product are expected to have the same safety and efficacy profile and are generally used to treat the same conditions."* The reference medicinal product[13], to which the application for marketing authorisation for a biosimilar medicinal product refers, "*is a medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data"* and in accordance with the provisions, applicable to originator medicinal products.

As mandated by law and in order to give guidance to industry, the EMA has developed overarching and product-class specific scientific guidelines on biosimilar medicines, thus providing a robust regulatory process in which to be able to grant marketing authorisations for biosimilar medicinal products. These guidelines are revised on a regular basis to reflect the experience gained with biosimilar applications and approvals, and to take into account evolving science and technology. In addition, a number of other scientific guidelines are relevant for biosimilar medicinal products, such as immunogenicity and comparability guidelines. All these guidelines are posted on a dedicated page of the EMA website.[14]

3.2. What is the scientific rationale behind approval of biosimilar medicines?

What is comparability?

Comparability between the reference and the biosimilar medicinal product is the core principle of a biosimilar development. The scientific concept of "comparability" is well

[12] See page 5/33 : EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications EMA/940451/2011, March 2013
[13] See page 8/33 : EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications EMA/940451/2011, March 2013
[14] See EMA biosimilar medicines webpage

established.[15] The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological medicinal product and for development of a biosimilar medicinal product are the same. However, as recognised by Weise et al in a scientific journal [16], data requirements for biosimilar medicinal products are higher than when assessing a process change for the same product. *"…It should be noted that a comparability exercise is also required for originator biological medicinal products when changes to the manufacturing process are made. Indeed, such changes are frequently introduced throughout a product's lifecycle (e.g., to improve the quality or to increase the yield of the product). As a consequence, the quality profile of the biological product may evolve over its life cycle but would still be considered as comparable to the product before changes were made as long as relevant impact on safety and efficacy has been excluded with sufficient confidence. The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product[17] and for the development of a biosimilar product[18] are the same. Even so, data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent manufacturing processes, some differences between the biosimilar and the reference product can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone...."*

What is biosimilarity?

"Biosimilarity" is the regulatory term used in the European Union to denote the comparability between a biosimilar and its reference medicinal product. The marketing authorisation of a biosimilar medicinal product is based upon a regulatory assessment that the applicant has demonstrated the product's similarity to the reference medicinal product by the means outlined in the Committee for Medicinal Products for Human Use (CHMP)/EMA specific "scientific guidelines on biosimilar medicines".

Biosimilar medicinal products are systematically developed to be highly similar to the reference medicinal product with regards to quality, safety, and efficacy. The biosimilar development is started with the definition of the molecular characteristics and quality attributes of the target product profile of the biosimilar medicinal product and its comparability with the reference medicinal product.

This is followed by a comparability exercise performed in several steps:

[15] See guidelines:
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMA/CHMP/BWP/49348/2005
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BWP/42832/2005

For updates and ongoing revisions please go to scientific guidelines on biosimilar medicines at the EMA dedicated biosimilar medicines webpage

[16] Nature Biotechnology, Biosimilars – why terminology matters, Volume 29, Number 8, Aug. 2011, page 690

[17] Not quoted by Weise et al, but see also: ICH Topic Q5E: Comparability of Biotechnological/Biological Products: Note for guidance on biotechnological/biological products subject to changes in their manufacturing process (CPMP/ICH/5721/03)

[18] Not quoted by Weise et al, but see also guidelines:
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues EMA/CHMP/BWP/49348/2005
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMA/CHMP/BWP/42832/2005

1. first step - quality comparability (physicochemical and biological comparability)
2. second step - non-clinical comparability (comparative non-clinical studies)
3. third step - clinical comparability (comparative clinical studies)

Quality comparability is established with regard to the molecular structure as well as with regard to the functionality and must be demonstrated with comprehensive analytical characterisation, relevant receptor binding studies and bioassays, all to be performed with the biosimilar and the reference medicinal product in a rigorous comparative manner.

The non-clinical and clinical comparability then provides the confidence that any differences observed at the quality level have no impact on the safety and efficacy of the biosimilar medicinal product when compared to the reference medicinal product.

The comparability exercise is consequently based on a robust head-to-head comparison between the biosimilar and the reference medicinal product at the levels of quality, safety and efficacy.

Every biosimilar medicinal product application is assessed on an individual basis.

What is the scientific rationale for extrapolation of indications?

Biopharmaceuticals are often used in more than one therapeutic indication. Extrapolation of clinical efficacy and safety data to other indications of the reference medicine that are not specifically studied during the clinical development of the biosimilar medicine is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate scientific justification. This includes at least one clinical study in the most sensitive patient population measuring the most sensitive[19] clinical endpoint(s).

If pivotal evidence for comparability is based on pharmacodynamics, and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. Biosimilar medicinal product applicants should also support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.

Only when quality and non-clinical and clinical comparability is achieved, is the new medicinal product accepted as a biosimilar and is it justified for the biosimilar medicinal product to cross-refer to the clinical data obtained through the extensive experience of the reference product. This is described in the relevant scientific literature and in publicly accessible health authority documents. Whether extrapolation to multiple indications is acceptable (or not) is decided on a case-by-case basis by the CHMP/EMA.

[19] Sensitive meaning most likely to show differences between the biosimilar and the reference medicine, if these exist.

3.3. Naming and identification of biological medicines, including biosimilar medicines

As required by EU law, every medicine will either have an invented (trade) name, or the name of the active substance together with the company name/trademark. The approved name, together with the batch number, is important for clear identification to support adverse drug reaction reporting and monitoring of the safe use of the medicine (see also 3.5.).[20]

3.4. Public EMA information on biosimilar medicines

As with any other medicinal product scientifically assessed by the EMA and authorised by the European Commission, the EMA publishes a defined set of official documents on its website for each biosimilar medicinal product. The dedicated webpage on biosimilar medicines can be found under Special Topics section of the EMA website.

The dedicated webpage above also contains a link to a list of all centrally authorised biosimilar medicines.

By clicking on the approved name of a biosimilar medicine on the list, a number of documents collectively known as the European public assessment report (EPAR) can be found:

- The package (information) leaflet [P(I)L] and the summary of product characteristics (SmPC) are found together in a product information (PI) that is available in all EU languages.
    - The package (information) leaflet [P(I)L] document is primarily intended to summarise information on the medicine for patients. It is also contained within each pack of the medicine.
    - The summary of product characteristics (SmPC) summarises information on the medicine for healthcare professionals and is more detailed than the package leaflet on specific characteristics of each medicine, such as pharmacokinetic, pharmacodynamic properties, preclinical and clinical data and pharmaceutical particulars.
- Assessment reports, including the reports on initial evaluation and major variations
- Summary of the European public assessment report (Summary EPAR) for the public which is a short document in lay language that explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the studies performed to reach its recommendation on how to use the medicine.

[20] See content of the individual case safety report: Article 28 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012.
The Management and reporting of adverse reactions to medicinal products is described in the Guideline on good pharmacovigilance practice (GVP) Module VI.

3.5. Pharmacovigilance

Every pharmaceutical company must have a pharmacovigilance system in place which is used by the marketing authorisation holder to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance. This pharmacovigilance system is subject to inspections by the regulatory authorities. Every company is required to submit a risk management plan (EU-RMP) together with the marketing authorisation application. The EU-RMP describes in detail the risk management system which the company will introduce for the medicine concerned once it is marketed. The EU-RMP describes the safety profile of the medicine and outlines how the manufacturer will further monitor and fill any potential or known gaps in knowledge regarding both safety and efficacy. The EU-RMP also describes the measures the applicant intends to introduce to prevent or minimise any potential risks when using the medicinal product, including the measurement of their effectiveness in clinical practice.

Under the new EU pharmacovigilance legislation, a marketing authorisation can be granted subject to the condition to conduct post-authorisation safety (PASS) and/or post-authorisation efficacy studies (PAES).[21] Such studies will be part of the pharmacovigilance plan of the EU-RMP. The aim of a PASS is to identify, characterise or quantify a safety hazard or to confirm the safety profile of the medicine, or to measure the effectiveness of the risk management measures during its lifetime. Immunogenicity is an example of a key safety concern of any biological medicine to be addressed in the EU-RMP. PAES will be required when there are concerns relating to some aspects of the efficacy of a medicinal product which can only be resolved after the medicine has been marketed. The European Commission will, in separate delegated acts, further define the situations in which PAES may be required.

The EU-RMP for a biosimilar medicinal product is product-specific and has to be approved by the competent authorities before the medicine is marketed. Every biosimilar medicine on the market has an EU-RMP in place with information on the RMP included in the Assessment Report published on the EMA website. The EU-RMP for a biosimilar medicinal product should take into account the known safety profile of the reference medicinal product.

For all medicinal products, a standard text will be included in the summary of product characteristics and in the package leaflet encouraging healthcare professionals and patients to report any suspected adverse reaction in accordance with national spontaneous reporting systems, which should allow for different ways of reporting, including electronic reporting by means of web-based forms. For adverse reaction (ADR) reporting relating to all biological medicines including biosimilar medicines, the clear identification of the medicine is of particular importance. Therefore EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine, as approved, and the batch number should be included in the ADR report.[22] For the same reason, and as mandated by the new EU pharmacovigilance legislation, "*the Member States shall ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate*

[21] Directive 2010/84/EU, Reg. (EU) 1235/2010

[22] A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in VI. Appendix 1 of the Guideline on Good Pharmacovigilance Practice (GVP)
Module VI – Management and reporting of adverse reactions to medicinal products

measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of medicinal product (…) and the batch number."[23]

The new EU pharmacovigilance legislation has also introduced a new approach which consists in publishing a list of medicines subject to additional monitoring for a set period. The EMA and the Member States will work together on this public list and further steps have been taken in the course of 2012. Medicinal products subject to additional monitoring are to be identified as such by a black symbol and an explanatory statement will be added to the summary of product characteristics and in the package leaflet. The European Commission has adopted further Implementing Measures for the new pharmacovigilance legislation and a whole set of Guidelines on good pharmacovigilance practice (GVP) have been developed and adopted by the EMA during the course of 2012.

The implementation of the new EU legislation has consequently strengthened pharmacovigilance for all medicines and increases transparency, communication and confidence.

4. ECONOMIC CONSEQUENCES

Biological medicines are an indispensable part of today's medical armamentarium for treating a variety of serious and debilitating diseases. Biological medicines are generally more expensive than small molecule medicines, and managing their use is a challenge for payers. Like the originator reference medicines, biosimilar medicines are generally more difficult and more expensive to develop than small molecule generic medicines.

The budgetary implications of biological medicines have been growing over the years and managing their use has become more and more important for payers. Biosimilar medicines may offer a less-costly alternative to existing biologic medicines which have lost their exclusivity rights (e.g. patents, data protection, etc.) and enhance competition. As a result, the availability of biosimilar medicines may improve access to biological medicines for more patients and contribute to the financial sustainability of healthcare systems. Thus, their availability offers potential economic benefit to healthcare systems while addressing the issue of new treatment options brought about by advances in medical science.

Once approved and authorised for sale, biosimilar medicines introduce an important element to existing price competition to the EU market. It should be recognized that the price differentials (at the point in time of publication of this consensus information document) between biosimilar medicinal products and their reference medicinal products have not been as substantial as experienced in the classical small-molecule generic medicine market. It remains to be seen how the future market will develop, however, it is expected that several new classes of biosimilar medicines will be approved in Europe over the next few years.

EU authorised biosimilar medicines have been launched in nearly every EU market and have thereby given European physicians and patients new treatment options. As a result, market competition has been enhanced by the addition of biosimilar medicines. Indeed,

[23] Directive 2001/83/EC, as amended; Article102, 1st paragraph, point (e)

market data from mid-2011 shows that all biosimilar medicines are growing in terms of sales and at the same time, decreasing the cost of treating patients with these medicines. Sales growth varies across EU markets and by product class indicating that market dynamics are different for each product class.[24] Overall, biosimilar medicines are starting to provide the benefits that they were expected to bring – giving physicians and patients an additional treatment option while affording payers a broader range of tools to better manage healthcare expenses.[25]

According to a study conducted in mid-2011 by the firm IMS[26], biosimilar medicines were a relatively small segment of the EU pharmaceutical market, but they have strong annual growth. It is important to note that this market data does not always show the whole picture. This is because in addition to biosimilar medicines, their reference products[27] and so-called "non-referenced" products[28], there is sometimes an additional class of products to be considered. This class comprises long acting, patent protected biological medicinal products which treat the same disease as short-acting products. These long-acting medicines are also a potential alternative to treat patients for similar diseases as biosimilar medicines and their reference medicines. It is fully expected that when the exclusivity rights of these medicines expire they too will face direct biosimilar competition.

It is important to note that biosimilar market uptake has been possible despite the fact that substitution between the biosimilar and its reference medicinal product is not practiced at the pharmacy level. The decision on whether to substitute a biological medicinal product lies outside the remit of the EMA/CHMP and is the responsibility of the relevant competent authorities within each EU Member State.[29] Since October 2011, pharmacists in Germany may substitute, within the framework of the aut idem substitution, biotechnologically manufactured products among each other which (a) have been approved with reference to the same reference product and which (b) have been produced by the same manufacturer with the same manufacturing process. The only difference between such substitutable products is their trade name.[30] At the point in time of publication of this consensus information paper, no country has explicitly authorized the substitution of biological products from different manufacturers, and a number of EU Member States have put legal, regulatory, and political provisions in place that prevent this practice.

The overall experience to date therefore suggests that the most important conditions for market uptake of biosimilar medicines are driven by factors in the commercial market

[24] The data is taken from a study commissioned by the European Commission project group Market Access and Uptake of Biosimilars. It was presented to the project group in Copenhagen on 18 April 2012 and is entitled "Biosimilar Accessible Market: Size and Biosimilar Penetration."
[25] EMINet report 2011

[26] Link to full IMS study
[27] IMS definition of reference product: Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has been referenced (in a biosimilar application)
[28] IMS definition of non-reference(d) product : Original product, granted market exclusivity at the start of its life, exclusivity is now expired and the product has never been referenced or may have been referenced but the referencing biosimilar has not launched
[29] See page 33/33 EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

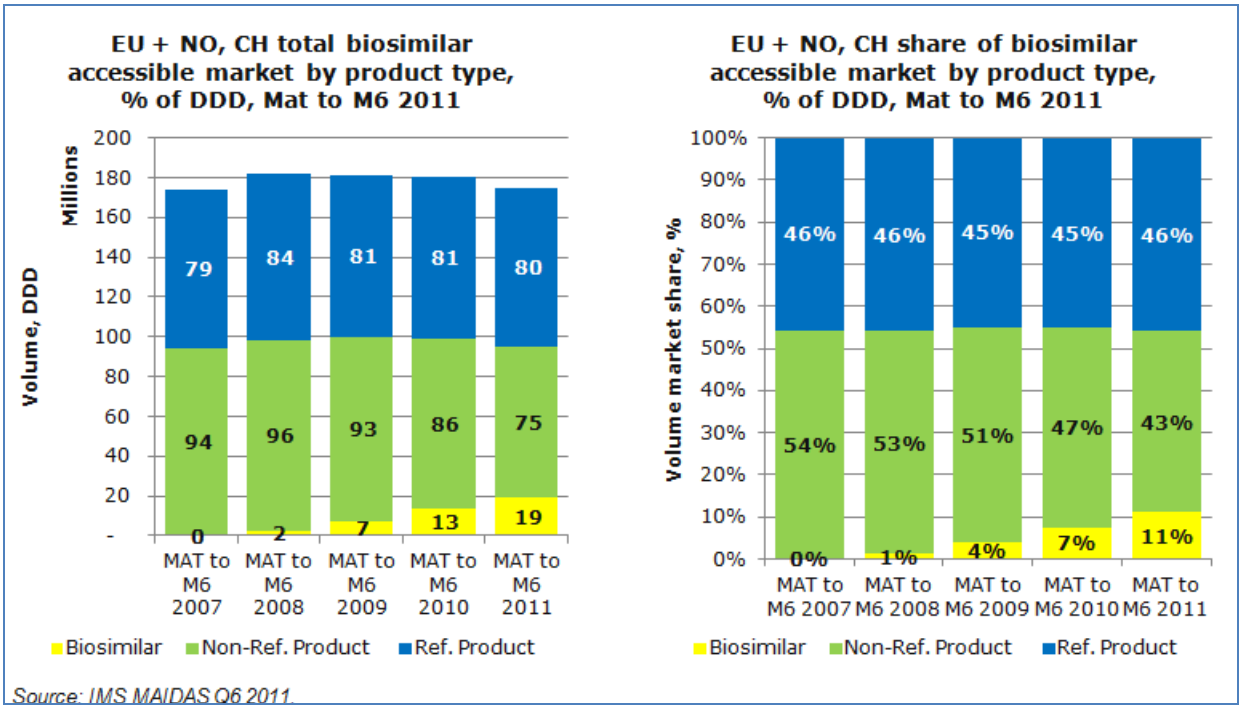
[30] Section 129, subsection 1 of the Fifth Book of the German Social Code (SGB V) in connection with the framework agreement between the National Association of Statutory Health Insurance Funds and the German Pharmacists' Association on the supply of medicinal products in the version of 1 February 2011, which is based on section 129, subsection 2 of SGB V.

place. Differences across European Member States in national healthcare systems, structures and processes impact biosimilar medicines' uptake. Such differences may be any or all of the following:

- Physician perception of biosimilar medicines
- Patient acceptance of biosimilar medicines
- Local pricing and reimbursement regulation
- Procurement policies and terms

It is thus essential that physicians and patients share a thorough understanding of biological medicines, including biosimilar medicines, and express confidence in using either type of therapy. This can be achieved by maintaining a robust regulatory framework and effective risk management, transparency with regard to biological medicinal products, and continued education on biological medicines, including biosimilar medicines.

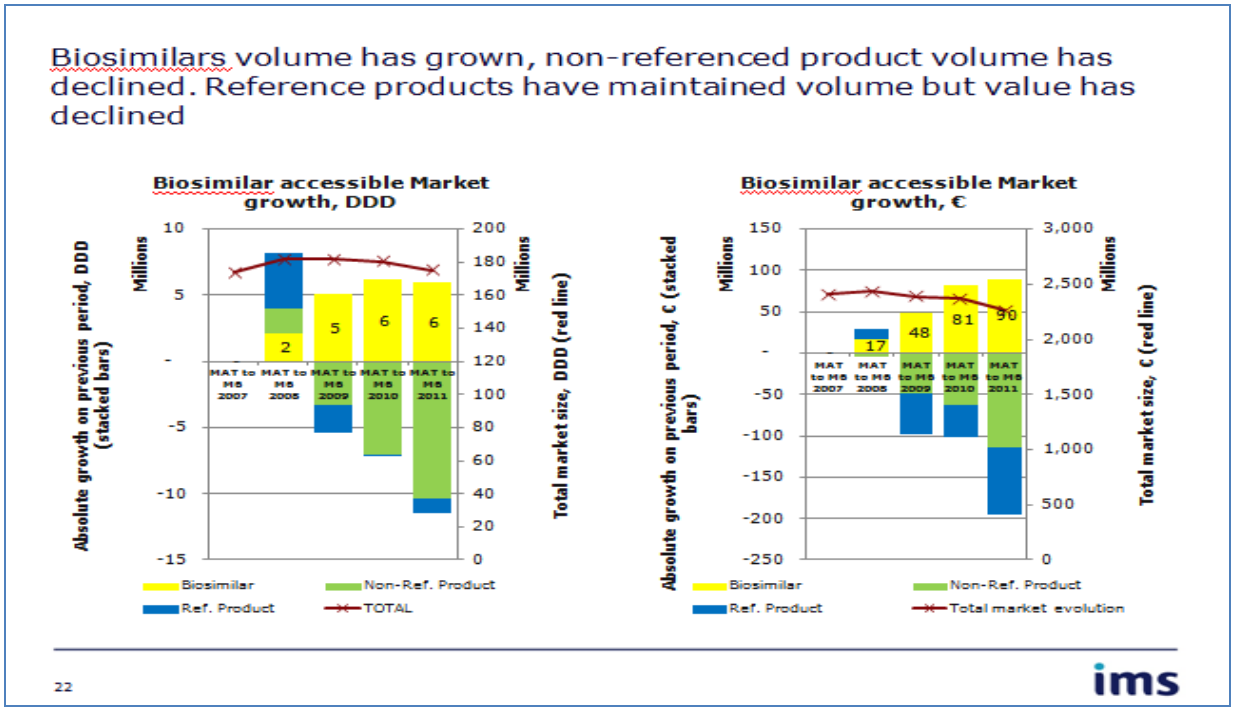
Figure One: Biosimilars Have Steady Growth With 11 percent of Total EU Biologics Sales



Source: IMS MAIDAS Q6 2011.

- Data in the IMS report is up to the end of 2Q2011 and includes sales throughout EU countries as reported by IMS with the addition of Norway and Switzerland.
- The market data in the report shows total EU sales for the 3 classes of biosimilar products available in the EU: HGF (Human Growth Factor), EPO (short-acting erythropoetin) and GCSF (daily GCSF). Long-acting EPO and GCSF are not included in the market analysis as these medicines are still protected by their patents and supplementary protection certificates.
- DDD, or defined daily dose, is a World Health Organization definition that assumes average maintenance dose per day for a drug used for its main indication in adults.
- Drug consumption data presented in DDDs provide an outline estimate of consumption but this is not an exact picture of actual use.
- All figures are for the 12 month period from July 2010 to June 2011 (MAT – moving annual total – 2Q2012)
- In the 12 month period, biosimilar products represent 19 million, of a total market estimate of 175 million DDD- approximately 11 percent by total patient volume.

Figure Two: Biosimilars Have Enhanced Existing Market Competition and Helped Stabilize Health Care Costs



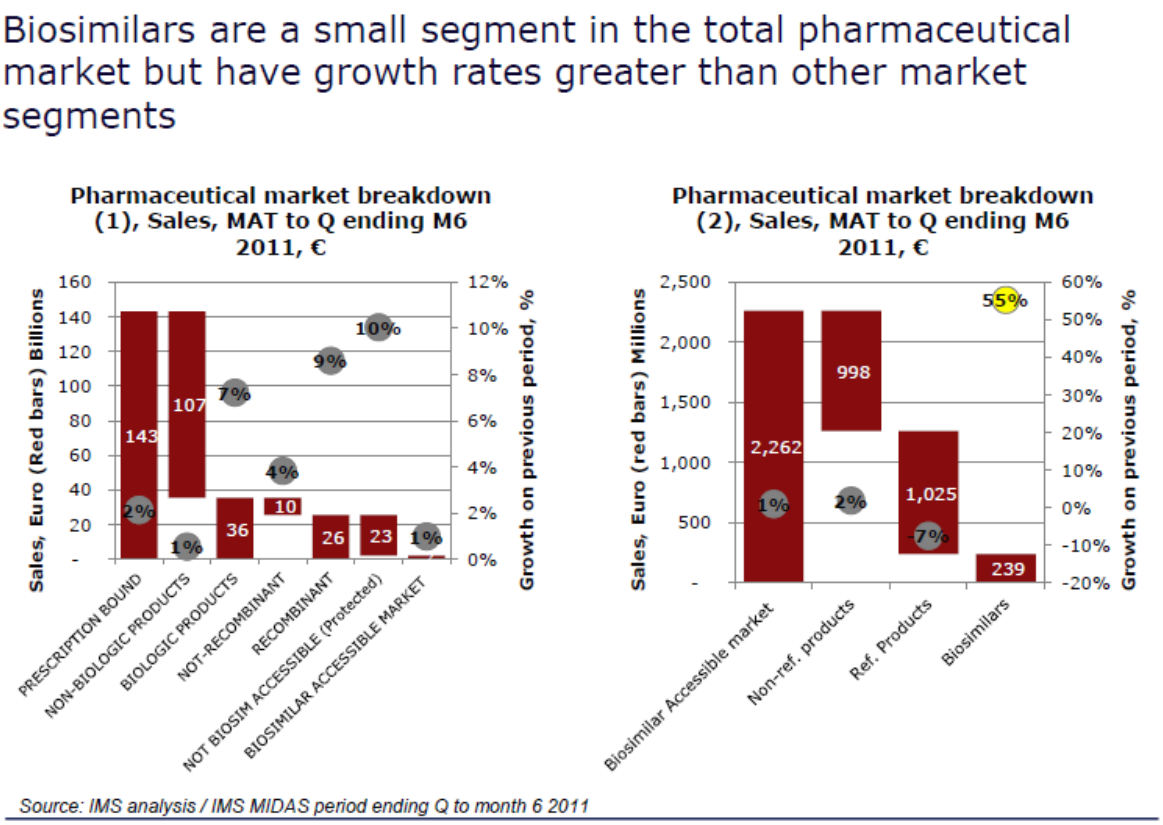
- The IMS data shows that as the number of marketed biosimilar products in Europe has increased, the total size of the market has decreased.

- The left hand chart demonstrates that, since their introduction, biosimilar products have grown steadily. At the same time there has been an increasing reduction in the DDD consumption of short-acting originator biological products, regardless of whether they have direct biosimilar competition or not.

- The right hand chart shows a gradual decline in market value (sales) as biosimilar products gain share from short-acting originator biological products, regardless of whether they have direct biosimilar competition or not.

- It is important to note that factors other than the introduction of biosimilar products may have contributed to the decline of the overall market, including safety concerns in the use of EPO in oncology patients and trends toward the use of longer acting products.

Figure Three: At This Stage Biosimilars Are a Small (but rapidly growing) Part of the EU Pharmaceutical Market



- These IMS data show total EU prescription pharmaceutical sales for the 12 month period to 2Q2011 (left chart) and total biosimilar accessible market sales for the 12 month period to 2Q2011 (right chart).

- Recombinant biological medicines account for 18 percent of total EU pharmaceutical sales.

- The majority of these sales are from biological medicines that do not yet have biosimilar competition (for example monoclonal antibody therapies) and are currently protected by patents and supplementary protection certificates.

- Sales for the 12 month period up to 2Q2012 for segment of the recombinant biological medicines market that is accessible to biosimilar products were €2.3 billion – around 8% of the total recombinant biological market.

- The "accessible market" is defined by the market of originator medicinal products which have been referenced in biosimilar applications and originator medicinal products which have lost their market exclusivity but have not yet been referenced.

- For the year to June 2011, biosimilar products accounted for ~10% of the "accessible market" with an approximate sales value of €240M of the total €2.3B. This represented a 55 percent increase from the previous period.

Q&A FOR PATIENTS

The Questions and Answers section refers only to biotechnology-derived medicines that are centrally assessed by the European Medicines Agency and authorised by the European Commission.

Introduction: questions identified from the patients' perspective

Patients' knowledge of biosimilars and biologics generally varies greatly from low to sophisticated. The questions in this document include even very basic questions that may seem obvious to an expert reader, but are real concerns based on feedback received from the EPF Policy Advisory Group.[31]

The relationship between patient and healthcare professional is key to ensuring the best treatment/care decisions and health outcomes for each patient. Patients often do not receive enough information from healthcare professionals that they understand, whereas many health professionals overestimate the amount and quality of information they provide. It is crucial that all available therapeutic options are discussed thoroughly and that healthcare professionals ensure that patients understand the options, relative benefits and risks. Prescription decisions should be based on mutual agreement (*concordance*).[32]

Patients tend to ask questions directly relevant to their own situation and in their own words, which do not always reflect medical terms and language.

The aim of the Q&A is to answer basic questions in a simple and easily understandable manner. The reader should then be able to read and understand the main paper, if they wish to have more detailed information. Other sources of good quality, understandable information, including that produced by the EMA, are given in the core document.[33]

The basics:

1. What is a biological medicine?

"*A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source. Some of them may already be present in the human body. Examples include proteins such as insulin, growth hormone and erythropoietin*"[34] (hormone for producing red blood cells).

2. How are biological medicinal products made?

[31]The EPF Policy Advisory Group (PAG) is a group of 14 representatives of different EPF member organisations (as of December 2012) .The questions included in this document were validated by the PAG. The draft answers were reviewed by a panel of 6 patient representatives, based on an open call for interest.

[32] Concordance is a term that describes the relationship between patient and prescribing doctor, and the degree to which the prescription is based on a joint agreement. Concordance means that the beliefs and preferences of both the doctor and the patient are taken fully into consideration but the patient's views take precedence. (Sources: Horne, R: Compliance, adherence and concordance: implications for asthma treatment. Chest, 2006;130;65-72; Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R&D, December 2005.)

[33] Part of the wordings used in some of these questions has been 'recycled' from the EMA Questions and Answers document on biosimilar medicines (similar biological medicinal products)(EMA/83780572011) dated 27 September 2012. Where this is the case, the EMA document is cited as a reference and the text is in italic.

[34] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

"Classical" medicines are typically manufactured by a process called chemical synthesis, whereas most biological medicines are made from living organisms such as genetically-modified cells. These cells have received a gene (obtained from gene banks or via a manufacturer's artificial gene production) to enable them produce a specific protein. The production of biological medicines involves processes such as fermentation and purification. Each manufacturer has its own unique cell lines and develops its own manufacturing processes.

3. How are biological medicines different from "classical" medicines?

Like all medicines, biological medicines work with the body to produce a therapeutic outcome, but the mechanisms by which they do this may be different from product to product and depending on the condition to be treated.

The active substances of biological medicines are larger and more complex than those of non-biological medicines. Only living organisms are able to reproduce such complexity. Their complexity as well as the way they are produced may result in a certain degree of variability in molecules of the same active substance, particularly in different batches of the medicine.[35] Such variability is natural for biological medicines. For more detailed information see question 4 as well as section 2.3 of the core consensus information document.

4. *What are biosimilars?*

A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the "reference medicine"). Biosimilars are not the same as generics. Generics have simpler chemical structures and are considered to be identical to their reference medicines.

"The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, this variability and any differences between the biosimilar and its reference medicine will have been shown not to affect safety or effectiveness".

"*Biosimilars are usually authorised several years after the approval of the reference medicine. This is because the reference medicine benefits from a period of exclusivity, during which biosimilars cannot be authorized".*[36]

[35] See question: What is a biological medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012
[36] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012_Questions and answers on biosimilar medicines (similar biological medicinal product)_September 2012

5. *What does "similar" mean?*

No two cell lines, developed independently, can be considered identical. This is why biotechnology-derived medicines cannot be fully copied. In recognition of this, the European Medicines Agency (EMA) has established the term "biosimilar".

A biosimilar medicine is developed to be highly similar to its reference medicine in terms of quality, safety and efficacy. "*The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods*". [37]

"*A biosimilar and its reference medicine are expected to have the same safety and efficacy profile and are generally used to treat the same conditions".* [38]

6. *Are biosimilars generics?*

Biosimilar medicines are not generic medicines. "A generic medicine[39] is a medicine that is developed to be the same as a small-molecule (chemical) reference medicine". *"Generic medicines have simpler chemical structures."*[40] (See also question 5)

7. *What is a reference product (may also be called branded medicine)?*

The reference product is a medicine which has been granted a marketing authorisation by a Member State or by the European Commission. Marketing authorisation is granted on the basis of submitted quality, pre-clinical and clinical data, gained through laboratory studies and clinical trials. The application for marketing authorisation for a biosimilar refers to the data submitted for the reference product.[41]

8. *Are biosimilars "personalised medicine"?*

No. "Personalised medicine" is a targeted treatment approach that uses modern diagnostic tools to tailor medical care closer to the needs of individual patients. By sorting patients into subgroups of responders based on certain characteristics - such as a genetic mutation - it aims at predicting their likelihood to benefit from a specific treatment. "Personalised medicine" is also sometimes called "stratified medicine", "targeted therapies" or "personalised healthcare".

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[37] See question: What is a biosimilar medicine? in EMA/837805/2011-27/9/2012- Questions and answers on biosimilar medicines (similar biological medicinal product)_September 2012

[38] See page 5/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

[39] The legal definition of a generic medicinal product can be found under Article 10(2)(b) of Directive 2001/83/EC, as amended. The simplified definition can be found in the EMA "Questions and Answers on generic medicines" dated 17 March 2011-EMA/393905/2006 Rev. 1 and in the glossary of this consensus information document.

[40] See question: What is a generic medicine? in the "Questions and Answers on generic medicines" developed by the European Medicines Agency_EMA/393905/2006 Rev1_March 2011.

[41] See page 8/33 of EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications_EMA/940451/2011, March 2013

9. Do biosimilars have anything to do with "parallel imports"?

No, not specifically. Parallel import, also called parallel distribution or parallel trade, is a legal form of trade within the European Union where any pharmaceutical product that is authorised for marketing in one Member State and distributed therein may subsequently be distributed in another Member State, in which the product is also authorised for marketing. Parallel trade exists for example when there are significant price differences between Member States.

Quality and safety

10. Is the approval process different from generic medicines? Who authorises biosimilar medicines for use in the EU?

The legal and regulatory pathway for approval of biosimilar medicines is different from generic medicines. Since 1995, all biotechnology-derived medicines must be assessed centrally by the European Medicines Agency (EMA). In case of a positive scientific opinion adopted by the scientific committee, the European Commission makes a formal decision for marketing. Since 2003 a specific legal and regulatory pathway exists for the development and approval of biosimilar medicines. The general principles of drug development and review by the European authorities apply to biosimilar medicines in the same way as to the reference biological medicines.

11. Is there any difference in safety between the biosimilar and the reference product?

No, an approved biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile.

EU legislation defines the studies that need to be performed for the biosimilar medicine to demonstrate similarity in quality, safety and efficacy (therapeutic effect) in relation to its reference medicine, and that there is no significant clinical difference to the reference medicine.

Based on the information published on the EMA website, no specific safety issue has been identified for approved and marketed biosimilar medicines at the time of publication of this consensus information document.

12. Is switching between a reference medicine and a biosimilar medicine (and vice versa) safe?

There is relatively little published data available on the number of patients that have been switched between biopharmaceuticals in clinical practice. "*For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist*"[42].

[42] See question: Can a biosimilar medicine and its reference medicine be used interchangeably? in EMA/837805/2011_Questions and answers on biosimilar medicines (similar biological medicinal products)_September 2012

13. Are biosimilar medicines likely to cause more adverse reactions than the reference medicines?

No, once approved, a biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile, which includes the same level of adverse reactions.

Biological medicines in general have the potential to be recognised by the body as "foreign" and may cause unwanted immune reactions. This is called immunogenicity and it is due to their composition and large molecular size, compared to chemical medicines.[43] However, there is no evidence or scientific rationale to suggest that biosimilar medicines are likely to cause more immune reactions than their reference medicines. (see also questions 10 and 11)

14. What should I do if I suspect I have an adverse reaction to a medicine?

It is important that patients report any suspected adverse reactions; this helps in the continuing assessment of the quality and safety of medicines. Adverse drug reactions (or "side effects") can sometimes appear a long time after a person has been taking a medicine, or even after stopping it.

In the first instance, if you suspect an adverse reaction to any medicine, or if you think the medicine is not having any effect, you should speak with a healthcare professional such as your prescribing doctor or a pharmacist.

In order to report suspected reactions, your healthcare professional is expected to identify the medicine correctly, and document the trade ("brand") name of the medicine prescribed in your patient file. For the same reason you as a patient should make sure you have been given information about the trade name, the international non-proprietary name (INN)[44] of the medicine, the manufacturer's name, and the batch number of the prescribed medicine.

Under the new EU pharmacovigilance legislation, patients themselves can also report suspected side effects directly to the national authorities.[45] This is not intended to replace contact with a healthcare professional, but is of great value for the collection of data on adverse reactions. For information on medicines safety data collected by the European Medicines Agency, please visit www.adrreports.eu. (This website is not for reporting adverse reactions.)

[43] Vaccines specifically exploit their immunogenic potential by provoking an immune response that recognises and "fights off" an "invader" substance. However, for some medicines based on proteins, stimulating an immune response is regarded as undesirable. Most of the immune responses that occur are mild and do not have negative effects on the patient; but in rare cases, unwanted immune reactions can be severe. This is why monitoring the impact of the medicine on the patient, by the patient themselves and their healthcare professional, is of crucial importance.

[44] International Non-proprietary Names identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name. (Source: WHO Guidance on INN, www.who.int)

[45] More information can be found in the EPF guidance document for patient organisations on the new EU legislation

15. *Is there any difference in quality and efficacy between biosimilar medicines and their reference medicines?*

No, a biosimilar medicine and its reference medicine are expected to have the same safety and efficacy profile.[46] Biosimilar medicines are made following the same standards as other biological medicines. Before the European Commission takes a decision to authorise a biosimilar medicine to be marketed in the EU, the European Medicines Agency, through its Committee for Medicinal Products for Human Use (CHMP), evaluates whether the new biosimilar has a comparable efficacy (therapeutic effect), quality and safety profile to its reference medicine.

The studies that need to be performed for a new biosimilar medicine include comparisons on several aspects of the biosimilar and its reference medicine, such as the structure and activity of the molecules. Targeted studies are performed to show that the products are comparable. Scientific guidelines exist to determine the extent of clinical data required, and the decision is taken on a case-by-case basis. Detailed information on all biosimilar medicines approved in the EU is available on the EMA website.

16. *Is there evidence that the biosimilar medicine is at least as effective as the branded medicine in treating all the same conditions as the branded medicine? Or has this just been assumed given its high similarity?*

Biological medicines are often authorised to treat more than one condition (indication). However, the mechanism of action can be the same. Therefore, it may be possible that the biosimilar can be scientifically justified to be used in other conditions. The decision whether to extend the efficacy and safety data from a condition for which the biosimilar has been clinically tested to other conditions for which the branded product is approved is known as “extrapolation”. The decision on whether to require new comparative clinical studies is taken on a case-by-case basis by the scientific committee (CHMP) at the EMA. The committee always makes its decision based on a thorough review of the scientific evidence.

The scientific basis for this extrapolation of indications is that the product has the same mode of action as its reference product; that the biosimilar and the reference medicine are proven to be comparable at the quality and biological level; and that there is conclusive evidence of similar safety and efficacy in at least one indication of the reference medicine. An authorised biosimilar medicine should be used at the same dose to treat the same conditions as the reference medicine.

17. *How is the safety of the biosimilar monitored after authorisation?*

As with all medicines, monitoring patients’ response and reporting any suspected adverse reactions (unwanted negative effects) is important to ensure safety and efficacy of the treatment.

Biosimilar medicines, like all biological medicines, must be continually monitored after authorisation for adverse events. The monitoring of adverse reactions is a part of “pharmacovigilance” (the system in place for monitoring the safety and risk-benefit

[46] See page 5/33 in EMA Procedural advice for users of the centralised procedure for similar biological medicinal products applications EMA/940451/2011_March 2013

balance of authorised medicines). All manufacturers are required to set up a system to monitor side effects for their medicines.

Patients often react individually to medicines, whether chemical or biological. They themselves are often in the best position to assess the effects of a medicine on their body and their life. A patient should be able to be fully involved in the decision to take any biological medicine following a thorough discussion with their prescribing doctor of all the treatment options. They should understand the medicine and the potential reactions they may experience – both positive and negative - and be aware of the importance of taking it correctly and carefully monitoring their response. Moreover, patients need to feel confident in discussing any suspected side effects with their healthcare professional.

In order to report suspected reactions and identify the medicinal product correctly, patients on any biological medicine, including biosimilar medicines, should always have information about the trade ("brand") name of the medicine, the international non-proprietary name (INN) which is the name of the active substance, the manufacturer's name, and the batch number of the prescribed medicinal product. The patient may find this information on the package leaflet, or get it from their pharmacist or prescribing doctor.

The new EU pharmacovigilance legislation makes it mandatory for all member states to allow direct patient reporting of adverse reactions to their national authority. Ideally, patients should feel comfortable to discuss any suspected adverse reactions with their healthcare professional, but sometimes this is not the case.

The new EU pharmacovigilance legislation has also introduced a new approach which consists in publishing a list of medicines subject to additional monitoring for a set period. The European Medicines Agency and the Member States will work together on this public list and further steps have been taken in the course of 2012. An inverted black triangle symbol will identify those medicinal products which are subject to additional monitoring. An explanatory statement will be added to the package leaflet, encouraging patients to report any suspected side effects.

For information on medicines safety data collected by the European Medicines Agency, please visit www.adrreports.eu. (This website is not for reporting adverse reactions.)

18. Are biosimilars more likely to be counterfeited/falsified than any other medicine?

No. There is no evidence that biosimilar medicines are more likely to be counterfeited/falsified than any other medicines.

Use of biosimilars

19. Why have biosimilars been introduced?

Biological medicines offer treatment options for disabling and life-threatening diseases, such as cancer, infectious diseases like hepatitis, autoimmune disorders, neurodegenerative diseases and rare diseases. However, treatment with a biological medicine can be expensive compared to a "classical" chemical medicine.

Biosimilar medicines are introduced when exclusivity rights (e.g. patents, data protection, etc.) of the reference medicine have expired. They may offer a less-costly alternative to existing biological medicines and enhance competition. As a result, the availability of biosimilars may improve access to biological medicines for more patients and help the financial sustainability of healthcare systems. Thus, their availability offers potential economic benefit to healthcare systems while supporting patients' access to new treatment options brought about by advances in medical science.

20. Will I have the choice whether I will be prescribed the reference medicine or the biosimilar medicine?

It is important to have a thorough conversation with your prescribing doctor about all the available therapeutic options, their safety, benefits and risks, and the differences between the medicines, before coming to a decision concerning treatment. Policies regarding the use of biological medicines, including substitution, are the responsibility of the authorities of each EU Member State. If you have any concerns about a medicine that has been prescribed to you, you should discuss this with your doctor.

21. If the reference medicine is withdrawn from the market, will the biosimilar be withdrawn as well?

It depends on the reason for the withdrawal of the reference medicine. Each medicinal product approved on the market in the EU has its own marketing authorisation and each medicinal product is assessed independently. If the reference medicine is withdrawn for safety reasons, then that may be taken into consideration when assessing the biosimilar medicine. If there are serious safety concerns regarding the active substance of the reference medicine, the new Pharmacovigilance Risk Assessment Committee (PRAC) at the EMA will assess if other medicines with the same active substance are also concerned. Regulatory authorities investigate and take action as appropriate.

22. Can I take a biosimilar medicine in exactly the same way (after food, etc.) as the reference drug? Is there anything I should know about how to store a biosimilar medicine?

All biological medicines, including biosimilar medicines, can be less stable than chemical medicines, requiring more precautions in their production, transport and storage. When prescribing a new medicine, your doctor should advise you concerning any specific issues that should be taken into account with that particular medicine, which may be important to ensure its effectiveness and correct use.

Most biological medicines must be administered by injection or infusion, therefore except for products that must be taken with meals, such as mealtime insulins, the intake of food does not affect the product safety or efficacy. In general, a biosimilar medicine has to be taken exactly the same way as the reference medicine.

23. Where can I find more information?

- European Medicines Agency on biosimilar medicines
- European Medicines Agency on medicines safety monitoring

- Guidance document for patient organisations on the EU pharmacovigilance legislation

Q&A for PHYSICIANS

1. ***What is your responsibility as physician regarding prescription of biosimilar* medicines?**

As with prescriptions for medicinal products in general, it is the responsibility of the treating physician to take the individual patient's age, gender, stage of disease, co-morbidities and concomitant medications, as well as overall medical history into consideration when prescribing a medicinal product. In addition, as physician, you need to know that a biosimilar medicine is similar to a biological medicine that has already been authorised, the so-called "reference medicinal product". An approved biosimilar and its reference medicinal product are expected to have the same safety and efficacy profile but the biosimilar may not necessarily be authorised for all indications approved for its reference medicinal product. As with any medicine, physicians should choose carefully when prescribing.

2. ***What were the scientific steps taken to demonstrate similarity of safety and efficacy of a biosimilar to the reference medicine prior to a* marketing authorisation *being granted?***

The aim of a biosimilar development programme is to establish "biosimilarity". This is done through a stepwise "comparability exercise" in a tailor-made development programme which takes into account the safety and efficacy established for the reference medicinal product. This exercise is done in several steps: first step - quality comparability (physicochemical and biological comparability), second step - non-clinical comparability (comparative non-clinical studies) and third step - clinical comparability (comparative clinical studies). Every biosimilar application is assessed on a case-by-case basis. The comparability exercise is consequently based on a robust head-to-head comparison between the biosimilar and the reference medicinal product at the levels of quality, safety and efficacy. Comparability between the reference and the biosimilar medicine is the core principle of a biosimilar development.

3. ***Biosimilar medicines, like any biological medicine, are very sensitive to changes during their manufacturing process, transport and storage. How can a physician be sure that minor changes have not had an impact on the quality, efficacy and safety of the biosimilar medicinal product?***

The manufacturing processes for any biological medicine are very sensitive and it is vital that these are precisely controlled in order to obtain consistent results and to guarantee the safety and efficacy of the final medicinal product.

Manufacturers and importers of medicines approved in the European Union, including biosimilar medicinal products, are legally obliged to hold a valid manufacturer's and importer's authorisation (MIA)/GMP certificate issued by an EU national competent authority. An MIA/GMP certificate will only be granted if the manufacturing/importing site complies with the EU Guidelines on Good Manufacturing Practice (GMP) which also include specific provisions for biological medicinal products (Annex 2 of the Volume 4 of EudraLex).

To verify compliance with GMP, manufacturers and importers in the EU are subject to regular GMP inspections by the supervisory authorities. The EU national competent

authorities also inspect manufacturers located outside the EU that export to the EU. For biopharmaceuticals which are centrally assessed and authorised for marketing in the whole European Union, the EMA coordinates GMP inspections related to the medicine's scientific assessment and conducted by the EU national competent authorities.

Importers, manufacturers and wholesale distributors are obliged to comply with Good Distribution Practice (GDP) standards. According to the GDP Guidelines, specific conditions for storage and transport (e.g. refrigeration) must be ensured. Wholesale distributors are legally obliged to hold a valid wholesale distributor's authorisation (WDA) issued by an EU national competent authority. Wholesale distribution by manufacturers, importers and distributors is equally subject to supervision by EU national competent authorities.

4. Where can I find updated information[47] on the pharmacokinetics, safety, immunogenicity, and interchangeability studies on biopharmaceuticals and biosimilar medicines?

This information for each centrally authorised medicine is published by the European Medicines Agency (EMA) on their website: www.ema.europa.eu. Upon approval, a collection of documents known as the European public assessment report (EPAR) is published on the website, which contains scientific and technical information on the development of each medicinal product. Information on pharmacokinetics, efficacy and safety, as well as immunogenicity is also contained within the EPAR. Since decisions on interchangeability and substitution are not within the remit of the EMA/CHMP, and interchangeability studies are not part of the registration requirements, such information may not be included in the EPAR.

If the name of the biosimilar medicine is known, the updated EPAR can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**Biosimilar medicines**".

5. Are the pharmacovigilance requirements different for biological medicines than for the non-biological ones?

In general, yes. This is because biological medicines have a higher risk of being recognised by the body as "foreign" and therefore have the inherent potential to induce unwanted immune reactions, due to their composition and large molecular size. Chemical medicines, on the other hand, are usually too small to be recognised by the immune system.

The potential to induce an immune reaction in the body (immunogenicity) is a significant safety element assessed during the exploratory and confirmatory development of an innovator biological medicinal product, and is supported in clinical trials by extensive testing and characterisation of short and long term anti-product immune responses. The results of these studies will have an impact on the design of post-authorisation follow up studies and risk management plans to ensure that rare immune-related safety issues can

[47] Please note that the "scientific discussion" document of the initial marketing authorisation reflects the data available at the time of approval and is not updated in the post authorisation phase.

be detected by collecting safety information for a longer period and from larger numbers of patients. In order to monitor long-term immunogenicity and safety, marketing authorisation holders are required to collect post-authorisation safety data for all biological medicines, including biosimilar medicines. This is part of the risk management plan (RMP) agreed at approval.

Information on risk management plans for all medicinal products approved through the EU centralized procedure (including all biotechnology-derived medicines and novel synthetic medicines) will be made accessible in line with EU Regulation 1049/2001 on access to documents. Under the same provision, the Agency will make available post-authorisation obligations e.g. registry studies, continuation of pre-approval trials and post-marketing safety studies.

The clear identification of the medicine is of particular importance for adverse reaction reporting relating to all biological medicinal products, including biosimilar medicinal products. Therefore, EU legislation requires that for every adverse reaction report of a biological medicine, the name of the medicine (trade name), as approved by the regulatory authorities, and the batch number should be included in the adverse drug reaction (ADR) report.[48]

As per the new pharmacovigilance legislation, any biological medicinal product authorised after 1 January 2011 will be included in the additional monitoring list. For all medicines on this list, marketing authorisation holders shall include in the SmPC an inverted Black Triangle symbol and the statement: "*This medicinal product is subject to additional monitoring*" together with a standardised explanatory sentence as well as a standard text asking healthcare professionals to report any suspected adverse reaction.

6. Since the first initial authorisation of a biosimilar medicine in the EU (2006), have there been adverse effects reported following switching between the reference medicine and biosimilar medicines?

There is relatively little data available on the number of patients that have been switched between biopharmaceuticals in clinical practice. There are several publications describing such switches, but it remains unclear how often these occur. Moreover the studies reported in the literature were generally too short to show the possible long term side effects of switching.

The European Medicines Agency (EMA) adopts a scientific opinion as a basis for a European Commission decision on the need for an update of product information (the summary of product characteristics and the package leaflet) when deemed necessary following review of reported adverse event arising from the use of any medicinal product. Safety related updates to the product information can include changes to prescribing information, additions to the list of observed side effects and additions to the precautions and warnings for use. The current versions of the product information documents are available on the EMA website, as is the history of amendments to the product information since first authorisation of the product. Review of these regulatory information resources for all currently approved biosimilar medicines to date shows that there has been no

[48] See content of the individual case safety report: Article 28 of Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012

safety related updates to their respective product information documents which have been as a consequence of reports of adverse effects following product switching or substitution.

As with all medicines, adverse event for biosimilar medicines are reported through approved pharmacovigilance mechanisms. Suspected adverse event can be obtained by searching from EudraVigilance[49] on the EMA website and in all official European Union (EU) languages. Furthermore, there is a dedicated "Patient Safety" page which lists major changes made to the authorisation of medicines, which have been recommended by the Committee for Medicinal Products for Human Use (CHMP) to improve safety for patients. From October 2009 to July 2012 there have been also monthly reports of the CHMP Pharmacovigilance Working Party (PhVWP)[50]. The cumulative Index of PhVWP Monthly Reports provides an overview of all safety concerns. No specific safety concern has been identified for approved and marketed biosimilar medicines at the time of publication of this consensus information document.

Work has been done on switches from an originator reference medicine to a biosimilar medicine that was undertaken by Skåne University Hospital (Malmö, Sweden) in 2009. Ninety-eight paediatric patients who were receiving human growth hormone were selected for a switch from a reference medicine to a biosimilar medicine, out of a larger population of 130 patients. 15 children experienced an adverse event in the course of the switch (most commonly pain at the injection site), though none were deemed "serious" by hospital personnel. Four children were switched back to the originator reference medicine.

7. Are there any studies showing differences in survival-time, efficacy and side-effects of treatment over long term?

No, but manufacturers routinely collect long term data from post-approval clinical trials, patient registry studies and long term follow up of patients who participated in the pre-approval clinical trials. For all biosimilar medicines it is a condition of authorisation that a pre-determined risk management plan (RMP) is executed which comprises some or all of the above measures. This is necessary to establish that the safety profile of a biosimilar medicine is still comparable to that of its reference medicine in a much larger patient population than has been assessed in the relatively small numbers of patients in the pre-approval clinical investigations. These larger patient numbers and longer treatment exposures allow the greater statistical sensitivity required to capture low frequency events and to enable reliable safety signal detection. It is the obligation of the manufacturers to report the findings of these RMP derived data to the EMA and to propose changes to the product information if necessary. Review of regulatory information resources at the time of publication of this consensus information document, shows that there have been no such changes required by the EMA.

8. What provisions for traceability do doctors need to follow?

[49] EudraVigilance is the EU database that holds adverse reaction reports related to all medicinal products authorised in the EU. The European Medicines Agency has launched its Website on suspected side-effect reports for medicines authorised in the European Economic Area (EEA) in all official European Union (EU) languages (http://www.adrreports.eu/)

[50] Following the implementation of the new pharmacovigilance legislation, the Pharmacovigilance Working Party (PhVWP) has been replaced by the Pharmacovigilance Risk Assessment Committee (PRAC) which is now responsible for assessing and monitoring safety issues for human medicines.

As required by EU law, every medicine will either have an invented (trade) name, or the name of the active substance together with the company name/trademark. The approved name, together with the batch number, is important for clear identification to support adverse drug reactions reporting and monitoring of the safe use of the medicine.

For example, to ensure the identification and traceability of all erythropoietin products, the EMA has taken specific steps in this area as a result of several cases of pure red cell aplasia (PRCA) that started in the nineties – prior to the approval of any biosimilar medicine. In December 2009 the Pharmacovigilance Working Party (PhVWP) within the EMA "*considered it important that accurate medication histories are maintained for patients treated with epoetins, i.e. recording the trade name or the scientific name with the name of the manufacturer in the patient file*". The identification and traceability of epoetin products used in patients will help to assess if PRCA cases and other reported cases of adverse reactions are related to any quality specifications of a certain epoetin product. As a result of the PhVWP's recommendations, the summary of product characteristics (SmPCs) for all erythropoietin products (originator and biosimilar) have been updated to include the following special warning: "In order to improve the traceability of erythropoiesis-stimulating agents (ESAs), the trade name of the administered ESA should be clearly recorded (or stated) in the patient file".

Another example is a similar statement that has been introduced in the SmPC of an originator monoclonal antibody product (containing the active substance rituximab) at time of publishing of this consensus information document.

9. Is the cost of a biosimilar medicine consistently lower than that of the reference medicine?

While in general biosimilar medicinal products are introduced to the market at a lower price than their originator reference medicinal product, price is determined through market forces, by national competent authorities, and competition between originator and biosimilar medicines' manufacturers.

10. Since the first biosimilar medicine authorised in the EU, have there been adverse effects reported following changes in manufacturing process, transport and storage?

Review of regulatory information resources for all currently approved biosimilar medicines to date shows that there have been no safety related updates to their respective product information documents which have been the consequence of reports of adverse effects following changes in manufacturing process, transport and storage.

The European Medicines Agency (EMA) updates product information (the summary of product characteristics and the package leaflet) when deemed necessary following review of reported adverse events arising from the use of any medicinal product. Safety related updates to the product information can include changes to prescribing information, additions to the list of observed side effects and additions to the precautions and warnings for use. The current versions of the product information documents are available on the EMA website, as is the history of amendments to the product information since first authorisation of the medicinal product.

11. Where can I find information for which of the biosimilar medicines' approved indications clinical trials have been done and which ones have been extrapolated?

If prescribers wish to identify which indications have been extrapolated and for which ones head to head comparative clinical trials have been performed against the reference product, this information is published by the European Medicines Agency (EMA) on their website: www.ema.europa.eu.

The relevant information can be found in the European public assessment report (EPAR) pages of each authorised medicine. If the name of the biosimilar medicine is known, this information can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**biosimilar medicines**".

All approved indications of a medicine, whether extrapolated or not, are always approved based on scientific evidence. If questions remain regarding the approved indications of a biosimilar medicine, prescribers are reminded that the primary purpose of a biosimilar development is not to demonstrate the safety and efficacy of a known biological active substance; this has been done before for the reference medicinal product. The primary purpose of a biosimilar development programme is to demonstrate "biosimilarity" (please refer to question 2 and to the core-text).

12. Where can I find information about the clinical trials that have been conducted with the biosimilar medicine?

The EU Clinical Trials Register website contains information on interventional clinical trials on medicines. Information that appears on the EU Clinical Trials Register website is originally provided by the company or organisation responsible for the clinical trial.

Information on the assessment of the trials can be found in the European public assessment report (EPAR) pages of each authorised medicine. If the name of the biosimilar medicine is known this information can be found on the EMA homepage by going to "**Find Medicine**" and then to "**Human medicines**". Alternatively, the EPAR pages for all centrally-authorised biosimilar medicines can be found on the home page by going to "**Special topics**" and then "**biosimilar medicines**".

Q&A for PAYERS

1. Why are biosimilar medicinal products important to payers?

The availability of biosimilar medicinal products enhances competition and this potentially leads to lower prices. Lower prices may create savings for healthcare systems and payers and improved access for patients. These savings can be used to finance further advances in healthcare.

2. If biosimilar medicinal products cost less than originator medicinal products*, are they inferior?*

No, biosimilar companies have to adhere to the same high standards as originator companies in order to receive marketing authorisation. Biosimilar medicinal products can only be sold if the marketing authorisation holder has proven that their quality, efficacy and safety are similar to that of the originator medicinal products.

3. How much cheaper are biosimilar medicinal products than originator medicinal products?

Prices are not determined at the EU level and vary in the individual countries, not only in absolute amounts but also in relation to the price of the originator medicinal products. In addition, originator companies may respond to competition and prices may be subject to locally negotiated contracts. Although it is difficult to give an exact figure, biosimilar medicines have the potential to contribute to overall cost savings.

4. Originator medicinal product or biosimilar medicinal product - Who decides which brand will be dispensed?

Dispensing is not regulated at the EU level. It is up to each Member State to define who decides: doctor or pharmacist, and how patients are involved in the decision-making process. "*The EMA evaluates* biosimilar medicines *for authorisation purposes. The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine"*.[51]

5. Is the trade name of the biosimilar medicinal product important?

The trade name of the medicinal product is not important for the efficacy of a biosimilar or originator medicinal product.

The Europe-wide marketing authorisation procedure ensures similar efficacy and safety for biosimilar medicinal products for those indications for which both the reference medicinal product and the biosimilar medicinal product have been approved. Although the route of administration must be the same for the reference medicinal product and the respective biosimilar medicinal products, different brands may have different injection devices.

However, the trade name and the batch number are important for identifying the medicinal product for administrative and pharmacovigilance purposes.

[51] See question: Can a biosimilar medicine and its reference medicine be used interchangeably? in EMA/837805/2011-27/9/2012- Questions and answers on biosimilar medicines (similar biological medicinal product)_ September 2012

Physicians, hospitals and healthcare centres have many years of experience in treating patients with different brands of biological medicinal products in the same indications. Since all products have received European Union marketing authorisation[52], additional factors may be taken into consideration when making the choice (e.g. price, ease of use, patient factors, etc.).

6. Where can I find more information about biosimilar medicinal products?

Healthcare professionals (in particular doctors and pharmacists) will answer all questions that patients have about their treatment, including the reasons for the choice of product. On the Internet, the most authoritative source of information is the European Medicines Agency (www.ema.europa.eu). National competent authorities also have websites and may have a special webpage dedicated to biosimilar medicinal products and explaining which medicinal products are reimbursed and the rules that apply.

[52] This consensus information document only focuses on biological medicinal products, including biosimilar medicinal products, that are biotechnology-derived medicines and which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

Glossary

Active substance: Active ingredient or molecule which goes into a specific medicine and which provides this medicine with properties for treating or preventing one or several specific disease(s).

Adverse event / side effect: Any unintended or unfavourable event following the administration of a given medicine. WHO defines an adverse event as follows: “An injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.”

Antibody (pl: antibodies): Antibodies (also known as immunoglobulins, abbreviated to Ig) are large proteins that are found in blood or other body fluids. Antibodies are used by the immune system to identify and neutralise foreign objects, such as bacteria and viruses.

Autoimmune disease: A disease caused by the body producing an inappropriate immune response against its own substances or tissues. Thereby, the immune system ceases to recognise one or more of the body's normal constituents as "self" and will create auto-antibodies that attack its own cells, tissues, and/or organs. Inflammation and tissue damage are common symptoms of autoimmune diseases.

Biopharmaceuticals / Biotechnology-derived medicines: A medicinal product or a vaccine that consists of, or has been produced by the use of living organisms. Often recombinant DNA (a form of DNA that does not exist naturally and which combines DNA sequences that would not normally occur together in order to establish new functions) forms the basis for biotechnologically manufactured products. Examples include therapeutic proteins such as antibodies, insulins or interleukins; but also vaccines, nucleic acid or tissues and cells. This document only refers to biotechnology-derived medicines which, since 1995, must be assessed centrally by the European Medicines Agency (EMA) and in case of a positive scientific opinion adopted by the scientific committee, are subject to a formal decision process for marketing by the European Commission.

Biosimilar medicine: A biological medicine that is developed to be similar to an existing biological medicine (the “reference medicine”). Biosimilar medicines can only be marketed following the patent expiry of the reference medicine (also called originator product in the document, for more details, please see the consensus document or the EMA Q&A on biosimilar medicines).

Biotechnology: Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. An example is the reproduction of human hormones like insulin.

Cell line [including master cell line]: A well-established, living system of cultured (grown in a laboratory) cells that will continue to grow and produce new cells indefinitely, so long as the cells receive nourishment and have space to develop.

Cell therapy: The infusion or transplantation of whole cells into a patient for the treatment of an inherited or acquired disease. (American Society of Gene and Cell Therapy)

Extrapolation of indications: The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the branded product is approved, is known as "extrapolation".

Generic medicine: A medicine that is developed to be the same as a medicine that has already been authorised (the "reference medicine"). According to Directive 2001/83/EC "generic medicinal product" is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. A generic medicine can only be marketed after the loss of market exclusivity of the reference medicine (also called "originator product" in the document) (for more details, please see EMA Q&A on generic medicinal products).

Gene therapy: Gene therapy is an experimental technique for treating disease by altering the patient's genetic material. Most often, gene therapy works by introducing a healthy copy of a defective gene into the patient's cells. (Talking Glossary of Genetic Terms from the National Human Genome Research Institute)

Glycosylation: The type and length of any sugar or carbohydrate groups that are attached to a given molecule, e.g. a protein.

Immune system: The collection of mechanisms (or collection of biological substances and processes) within the body that protect against disease by identifying and killing pathogens (e.g. viruses and bacteria) and tumour cells.

Immune reaction/response: A defence mechanism by the body that leads to the production of antibodies by the human body in response to an invading substance (i.e. antigen) e.g. to viruses and substances recognized as foreign and possibly harmful.

Immunogenicity: The potential or ability of a substance or antigen to cause an immune reaction/response (see above).

Indication: A medical condition, disorder or disease.

INN: International Non-proprietary Name which identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary name is also known as a generic name. (Source: WHO Guidance on INN, www.who.int)

Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.

Marketing authorisation: The permission granted by a regulatory authority to a company to market a medicinal product in accordance with the indications described in the product information, following the company's submission of required documentation and data in line with the regulatory and legal framework.

Molecule: The smallest particle of a substance that has all of the physical and chemical properties of that substance. Molecules are made up of one or more atoms held together by strong chemical bonds. If they contain more than one atom, the atoms can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins, can be made up of many thousands of atoms.

Molecular: Of a molecule

Patent: A patent is a set of exclusive rights granted by a state (national government) to an inventor or their assignee for a limited period of time in exchange for public disclosure of its invention. Typically, however, a patent application must include one or more claims defining the invention which must be new, non-obvious, and useful or industrially applicable.

Pharmacovigilance: Science and safety control procedures to which medicines are subject before, during and after their approval by regulatory authorities with the aim of detecting, assessing and understanding the benefit: risk profile of a medicinal product. Pharmacovigilance activities cover the whole life-cycle management of medicines in relation to safety.

Protein: Large organic compounds made of amino acids arranged in a chain. Proteins are essential parts of organisms and participate in virtually every process within cells. e.g. erythropoietin is a protein.

Reference product (medicine): A medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a biosimilar product refers.

Risk management plan: A detailed description of the risk management system (see below) implemented by the manufacturer for a given medicine.

Risk management system: Set of pharmacovigilance activities and interventions which are designed to identify, characterise, prevent or minimise risks relating to a medicine, including assessment of the benefit: risk profile of a given medicine.

Side effect / adverse reaction: Any unintended or unfavourable event following the administration of a given medicine. WHO defines and adverse event as follows: “An injury related to medical management, in contrast to complications of disease. Medical management includes all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care. Adverse events may be preventable or non-preventable.”

Substitution: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

Vaccine: A biological preparation which is used to establish or improve immunity to a particular disease. Apart from such prophylactic vaccines, there also exist therapeutic vaccines.

What you Need to Know about Biosimilar Medicinal Products

Process on Corporate Responsibility in the Field of Pharmaceuticals
Access to Medicines in Europe

A Consensus Information Document

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