BIO DEUTSCHLAND

Background Paper by BIO Deutschland

on

Biosimilars

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I. Introduction

1. Definition

Biological medicinal products ("biologics") are made from a living system or organism. Similar biological medicinal products ("biosimilars") are follow-on versions of original biotechnological compounds. They are developed independently following expiry of the original products' patents, generally by companies other than the original manufacturer. A genetically modified cell line usually forms the base material for most biologics. Each manufacturer uses its own, characteristic and unique cell line (host cell) with which it then develops a unique manufacturing process in order to produce the drug in question.

A biosimilar should have exactly the same effect as the reference medicinal product and treat the same diseases as the innovator product. However, biologics have a lower bioavailability than classical (chemically produced) medicines because of their molecular size. As a result, they must be administered parenterally[1]. Because of the size of their molecules, the human body's reaction to the presence of xenobiotics (the "immunogenic response") must be carefully tested and monitored to ensure that patients can enjoy the intended product benefits safely. These ongoing validations and tests during the complex manufacturing process and the administration of biotechnological medicinal products are time-consuming and necessary. The aim is to provide the maximum level of patient safety[2] as the highest priority.

On account of the special features that characterise a biological medicinal product, the European Union has decided that the designation and authorisation procedure of follow-up products of biological medicinal products ("biosimilars") should be different than that applicable to chemical medicines ("generics").

The definition, authorisation and marketing of similar biological medicinal products are the topics of an intense debate. The discussion focuses on the difference between similar biological medicinal products and the generic copies of standard chemical medicines. As chemical medicinal products, generics are clearly defined in terms of structure and contain identical copies of the original active substance. From a pharmaceutical perspective, the original and generic compounds can hardly be distinguished from each other. They meet the strict criteria of "equivalence" in the organism, particularly as regards safety and effect. This equivalence between the original and generic product must be proved in a critical trial (proof of "bioequivalence"). In contrast, the above-mentioned definitions cannot be used for the follow-up products of biological medicinal products due to their individual features and the complexity of their manufacturing process.[3] Analytical and preclinical trials are not enough to prove equivalence or an identical character between two biological products.

2. Differences between biologics and chemicals

Biological medicines differ from standard chemical medicines in various ways. Size is one immediately apparent difference: the molecules in a biological medicinal product are much larger, have a far more complex spatial structure and are more diverse ("more heterogeneous") than the small molecules found in chemical medicines. A biological medicine is usually a protein that consists of a chain of several hundred amino acids in a complex three-dimensional structure (see Table 1: molecular weight as an indicator of structural complexity). This makes it more difficult to characterise biological medicines precisely, as the analytical methods used for chemically produced medicinal products are not sufficient for biologics. Unlike biological medicinal products, chemical compounds have relatively simple components and a clearly defined molecular structure that is easier to identify and can also be reproduced in exactly the same way.

1 From the Greek for "bypassing the intestine", usually administered by injection, infusion or implantation.

2 Cf. recitals 4 and 15 of Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

3 The European legislature also makes this clear in Article 10, paragraph 4 of the consolidated version of Directive 2001/83/EC.

Table 1: Comparison of the sizes of chemical and biological medicinal products

Chemical medicinal products	Molecular weight (daltons)	Biological medicinal Products	Molecular weight (daltons)
Glucophage®	166	Neupogen®	18,800
Aspirin®	180	Intron-A®	19,625
Prozac®	346	Humatrope®	22,125
Zantac®	351	Avonex®	22,500
Paxil®	375	Epogen®	30,400
Claritin®	383	Pulmazyme®	37,000
Zocor®	419	ReoPro®	47,615
Augmentin®	420	Enbrel®	75,000
Crixivan®	712	Zenapax®	144,000
Taxol®	854	Rituxan®	145,000

This difference can also be seen in the tests and trials needed to determine and ensure patient safety. A typical manufacturing process for a chemical medicinal product involves 40 to 50 critical tests, while a biological compound might be subject to 250 more tests.

Table 2: An overview of the differences between biologics and chemicals

	Biologics	Chemicals
Product structure	A complex structure – proteins from one or more chains of several hundred amino acids, which can lead to complex three-dimensional structures (hence the high molecular weight).	A less complex structure – usually a protein from a chain of several hundred amino acids in a complex three-dimensional structure (hence lower molecular weight).
	The large molecules are diverse and difficult to characterise.	The molecular structure is relatively simple and can be easily reproduced.
Variability	Higher variability, as they are made from living systems such as cell lines. As a result, each biological product is unique.	Extremely low variability due to chemical production.
Administration type	Usually injected[4] (but can also be administered via infusion and – rarely – as an implant)	Usually administered orally (tablets) All other administration types are conceivable.
Miscellaneous	Have the potential to trigger immune responses because of their composition and heavy molecular weight.[5]	The small chemical molecules cannot trigger an immune response because of their small size.
	Require special transport and storage conditions in order to guarantee their shelf life.	Usually do not require any special transport or storage conditions.

In contrast to generics, biosimilars are subject to far more stringent authorisation requirements and manufacturing processes. Hence, they cannot be subject to the price regulation mechanisms for generics.

The European Medicines Agency (EMA) has explicitly stated that biosimilars are not generics by definition and that the procedure applicable to generics is "scientifically not appropriate"[6] for these products. Biosimilars are biological medicinal products that are similar to an original biological product.

"*It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent*

4 Administering biologics orally would mean that the digestive system would rapidly separate the proteins into their amino acid components.

5 Hence, biologics can trigger an unwanted formation of antibodies against the therapeutic protein, as the body regards this protein as "foreign". The potential to trigger immune responses is a double-edged sword for all biologics. Vaccines use the immunogenic potential to trigger an immune response to a certain "invading" foreign substance. On the other hand, the aim of using most active substances based on recombinant proteins is not to trigger an immune response.

6 EMA – Guideline on similar biological medicinal products (CHMP/437/04) of 30 October 2005, p. 4.

until greater experience in their use has been established. Therefore, in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.[7]

3. Manufacturing of biologics

The manufacturing of biologics is far more complex than that of traditional chemical medicines. Biological medicines demonstrate a higher batch-to-batch variability than chemical medicines. There are many reasons for this, such as the nature of the base material and the high precision required in the manufacturing process. However, it should be noted that there is also a certain batch-to-batch variability in original medicinal products.

A genetically modified cell line is usually the base material for most biologics. Each manufacturer uses its own characteristic and unique cell line, with which it then develops a unique manufacturing process in order to produce the drug in question.

The biologics manufacturing process involves fermentation (an upstream process) and a cleaning procedure (a downstream process). The smallest modification during the process, for example, in temperature or pH, can lead to major changes in the clinical and pharmacokinetic properties of the biological product. As a result, it is essential that the manufacturing process is precisely controlled so that consistent results are obtained and product safety and efficacy is achieved. The control procedure involves bioassays to determine characterisation and stability evaluation. In addition to the chemical and physical tests, bioassays determine the identity and purity from batch to batch.

The unique base material and the complex manufacturing process mean that – unlike chemical medicines– it is not possible to reproduce a biological medicine exactly.

4. Biologics' intellectual property

By definition, biosimilars – just like generics – first appear on the market when the property rights for the original product have expired.

New original products benefit from patent protection. Patents protect new inventions as a reward for their publication and grant the patent holder the exclusive right to decide how his or her invention should be used. In general, the intellectual property (IP) of original products is protected for the period of the relevant patents (in Europe this is usually for 20 years from the time that the patent was registered). However, innovations also benefit from further exclusive rights such as data protection and market exclusivity. This means that a certain period of time[8] after authorisation is granted before a competitor can sell a follow-up product that is fully or partially based on the original manufacturer's safety and efficacy data in the authorisation procedure. In general, the authorisation procedure for a follow-up product is less time-consuming, less risky and less expensive, as it is based on existing documents prepared by the original manufacturer.

These possibilities to enjoy IP protection are of huge importance to originators who develop and manufacture innovative medicinal products in obtaining a return on investment (ROI). In turn, this fosters the motivation to continue investing in research and development on innovative medicines.

II. The regulatory requirements for biosimilars

The national authorities of the individual EU member states can approve chemical active substances. This is not the case for biologics, including biosimilars, which are subject to a centralised authorisation procedure conducted by the EMA. Marketing authorisation applications (MAA) submitted to the EMA are examined by the Committee for Medicinal Products for Human Use (CHMP), which votes in favour or against the application. If the EMA votes in favour, the European Commission issues marketing authorisation, which is then valid in all EU states.

Since 2004, the European Union has had a legal and regulatory guideline for the development and marketing of biosimilars. The directive on medicinal products for human use (the consolidated version of 2001/83/EC) describes the legislative process. The EMA has issued a series of regulatory guidelines[9] that describe the required data for the authorisation of a biosimilar. Apart from these general guidelines, the EMA has also published guidelines on quality, preclinical and clinical requirements, and product specifications for biologics

7 Idem.

8 Biological medicinal products are automatically granted data protection for eight years and marketing protection for ten years in Europe (Article 14, paragraph 11 of Regulation (EC) No 726/2004).

9 EMA Guidelines: CHMP/437/04*, EMEA/CHMP/BMWP/428327/2005* with three annexes, EMEA/CHMP/BWP/49348/2005*, EMEA/CHMP/BMWP/118264/2007*, EMEA/CHMP/BMWP/301636/2008, EMEA/CHMP/BMWP/14327/2006 and EMEA/CHMP/BMWP/101695/2006. (* These guidelines are currently being revised.)

that have already been authorised. These include guidelines on insulin[10], epoetin[11] and GM-CSF[12]. The EMA is currently working on guidelines for other products.

In its guidelines, the EMA upholds the principle that biosimilars are not generics by definition and that the authorisation procedure for generics cannot be applied to biosimilars because of scientific reasons.

In addition, the EMA stipulates in its Q&A document[13] that trials must be conducted in order to show that the biosimilar product is exactly as safe and effective as the biological reference product. Hence, the authorisation procedure for a biosimilar requires the manufacturer to prove that its medicine is similar to the reference product in terms of quality, safety and efficacy. This means that clinical trials must show that there are no meaningful clinical differences between the biosimilar and the reference product. Manufacturers of biosimilars must provide a preclinical and clinical set of data to prove the similarity between the biosimilar and the reference product. Furthermore, the similarity to the reference product must also include the formulation and concentration of the active substance, as well as the administration type of the medicine. The necessary data may come from preclinical, in vitro or in vivo experiments, as well as from clinical trials on healthy volunteers or patients. The EMA inspects the submitted data for each biosimilar on a case-to-case basis before deciding whether or not to grant marketing authorisation. Less data must be provided for a biosimilar than for the original biological product.[14]

In cases where a reference product is authorised for more than one indication, relevant tests and trials must show the efficacy and safety of the biosimilar for each individual indication. Under certain conditions, the EMA allows an indication to be extrapolated. For example, other indications of the reference product can be extrapolated in terms of safety and efficacy if a biosimilar has already demonstrated comparable safety and efficacy in a very sensitive indication. However, such extrapolation is only permitted if the same mechanism of action applies to all indications and if there are no scientific objections.

As is standard for all biopharmaceuticals, the EMA requires biosimilar manufacturers to provide a risk management programme (RMP) containing the safety specifications, a pharmacovigilance plan and a plan on risk minimisation activities. Preparing an MAA for a biosimilar is therefore much more time-consuming than an application for a generic.

III. Biosimilars – problems and challenges

1. Description

All therapeutic agents have both an international nonproprietary name (INN) and a brand name. Chemical pharmaceuticals have the same INN as the original product, as they are exact copies of the original. As explained above, biological therapeutic agents are mainly of a more complex nature. Furthermore, their size and complex structure can trigger immune responses (which is the specific aim of vaccines, but not the desired effect for active substances based on recombinant proteins). As biosimilars are not identical, but rather comparable to the original product, each biotechnological therapeutic agent needs its own INN.[15] This is in the interests of patient safety, as the INN clearly states which compound the doctor has prescribed and the patient has actually received. Hence, the medicine should only be changed by the patient's doctor.

In some countries, doctors are obliged or at least urged to prescribe on an INN basis. In cases where two biologics have the same INN, this can create the impression that the products are identical and can be switched without any problem, although there is no scientific reason for this. This type of switch could have negative clinical effects on patients. The two products may be similar, but they are not identical – and it is precisely these differences that can influence therapeutic efficacy.

In order to ensure that documentation is unambiguous, particularly as regards adverse effects, biosimilars must remain clearly identifiable. The European legislature therefore calls on the member states to check all

[10] Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant human soluble insulin. (EMEA/CHMP/BMWP/32775/2005)

[11] Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (EMEA/CHMP/BMWP/301636/2008)

[12] Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor. (EMEA/CHMP/BMWP/31329/2005)

[13] EMA – Questions and answers on biosimilar medicines (similar biological medicinal products). Doc. Ref. EMEA/74562/2006 Rev. 1 of 22 October 2008.

[14] Further information by the EMA is available at www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac058081bf0.

[15] Article 102(e) of the human medicinal products directive (consolidated version of Directive 2001/83/EC).

biological products very closely and provide clear documentation on them in order to improve pharmacovigilance.[16] The holder of marketing authorisation must therefore state the product name and batch number in reports on adverse effects.

2. Health economics and pricing

For several reasons, biosimilars are not subject to the same price competition as was the case when generics were introduced. On the one hand, biologics and biosimilars are very complex and expensive to produce; on the other hand, independent clinical trials are required for biosimilars, which is not the case for generics.

In addition, the regulatory requirements prior to authorisation and the monitoring of the medicinal product following market introduction are much stricter than those for generics, which leads to a further cost increase for biosimilars.

The exact pricing of biosimilars depends on various factors:

- the amount reimbursed in the various countries;
- competition between the various biosimilar producers and
- the development of new innovative and more effective products.

3. Immunogenicity aspects

Biologics have the potential to trigger unwanted immune responses. This potential is one of the main reasons why biologics are treated differently in general by the authorisation agencies and must be treated differently than regular chemical medicinal products.

Although much is already known about certain characteristics of biological products that can trigger an immune response, such as a high content of host cell proteins or a certain way of administering the medicine, it is currently not possible to accurately predict immunogenicity in humans. Only findings from non-clinical tests on animals are available. For this reason, the evaluation of immunogenicity via clinical trials plays a major role in the development of biologics. On the other hand, it is already known from the originator's trials which possible general adverse effects are to be expected. Hence, it is not the case that the safety risk is fundamentally higher in the development of biosimilars.

When a biosimilar is granted marketing authorisation, there is already a relatively large amount of information on the safety and efficacy of the product class and reference product. However, there remains a risk that the spectrum of immune responses will differ from product to product. For example, minor effects can only be ascertained if a sufficiently large number of patients is treated with the product in question. At the time of authorisation, the information on the safety of a product is still relatively limited. It is only during the extensive "field trial" following authorisation that information on the profile of adverse effects, safety problems and the appropriate patient population becomes clear.

Unlike generics, a risk management plan must be developed for biosimilars in order to take the biological characteristics into account. This plan defines and describes the pharmacovigilance activities with the aim of avoiding or minimising the product risks. It should also be noted here that a risk management plan must be produced and implemented for original medicinal products, too.

The potential of biologics to trigger immune responses is the main reason why biosimilars must be treated in exactly the same way as new biologics as regards the monitoring of the medicinal products following market introduction. As is the case for all medicinal products, patient safety is the main concern and guiding principle of the manufacturers (of biological medicinal products). As information on immunogenicity cannot be fully provided even by conducting clinical trials at the time of authorisation, the EMA requires the manufacturers of all biosimilars to implement a wide-ranging post-marketing pharmacovigilance programme, including a post-marketing safety study, and to present a post-marketing risk management plan. Unlike generics, which are not subject to such requirements, significant financial resources are needed for this.

4. Interchangeability

The interchangeability of medicinal products refers to the situation whereby one product can be exchanged for another during treatment of patients without the risk of adverse effects among the patients being treated.

Generics, which are regarded as bioequivalent, are also seen as therapeutically equivalent and therefore as interchangeable. When evaluating an MAA for a biosimilar and granting marketing authorisation, the EMA

[16] Loc. cit.; also cf. recital 17 and Article 23, paragraph 1(b) of Regulation (EU) No 1235/2010 of 15 December 2010.

does not examine the product's interchangeability or substitutability. In other words, marketing authorisation does not mean that a biosimilar can be exchanged for or replaced by the reference product.

To date, only a few clinical trials (comparisons of two original biosimilars and comparisons between the original and a biosimilar) have been conducted in order to find out which clinical consequences can be caused by the repeated change of a biological medicine[17]. The EMA recommends that "the decision to treat a patient with a reference or biosimilar medicine should be taken following the opinion of a qualified health professional".[18] In September 2007, the European Commission stated that interchangeability is a topic that must be dealt with by the authorisation agencies of the individual member states.

5. Substitution

Pharmacists work on the basis of substitution (aut idem) regulations in Germany. If there is an original compound and one or more generics for a certain active substance, they may interchange these compounds. For example, they are obliged to do so if the patient's health insurance company has a discount agreement with another manufacturer than the manufacturer whose product the doctor prescribed (article 129, paragraph 1, Fifth Book of the German Social Code). However, the doctor also has the option of preventing such substitutions by explicitly stating so on the prescription.

This is not the case for biopharmaceuticals and biosimilars. For these products, pharmacists may only dispense exactly what has been prescribed. Because of the differences between the original and biosimilar products (and between various biosimilars, as well as between various similar originals) it cannot be inferred that the patient will tolerate each compound equally well and that each will have an equally positive effect on him or her. This means that it is not possible to switch to another biopharmaceutical without the doctor having expressly requested this change and without his or her knowledge merely because the patient's health insurance company has a discount agreement with a certain manufacturer. Since 2011, pharmacists may switch products in exceptional cases if the switched product was authorised with respect to the reference product and is not different in terms of base materials and manufacturing process.[19] As a result of the different manufacturing processes (which generally involves using a different cell line than that used in the original) and the pharmacological differences that may result from this, biosimilars are not identical to the original in terms of active substance and are therefore not subject to the aut idem regulation contained in the Fifth Book of the German Social Code and in 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, paragraph 2 of the Fifth Book of the German Social Code.

In some countries it is compulsory to substitute a generic for a non-generic product under certain conditions, for example if a doctor prescribes by INN. Generic substitution is often linked with reimbursement. For example, some health insurance companies only reimburse the costs of generics. The result is that patients who reject generics in favour of the original must pay the price difference themselves.

Generic versions of a chemical pharmaceutical for which bioequivalence has been shown can be substituted without a risk to patient safety. The EMA's stance is as follows: "*Since biosimilars and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or biosimilar medicine should be taken following the opinion of a qualified health professional.*"[20] In addition, no convincing scientific data has proved so far that the repeated switching of a biological medicinal product will not have negative clinical consequences.

A range of countries such as France, Italy, Spain, the UK, the Netherlands, Sweden and Germany have legal regulations that either prohibit the automatic substitution of biologics or provide clear regulatory instructions for their use (including prescription by brand name). Patient safety is the justification for these measures.

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17 Romer et al, Effect of Switching Recombinant Human Growth Hormone: Comparative Analysis of Phase 3 Clinical Data, Biologics in Therapy of 16 December 2011.

18 EMA, Doc. Ref. EMEA/74562/2006 Rev. 1 of 22 October 2008.

19 Section 129, paragraphs 1 and 2 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, paragraph 2 of SGB V.

20 EMA, Doc. Ref. EMEA/74562/2006 Rev. 1 of 22 October 2008.

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The Biotechnology Industry Organisation Deutschland (BIO Deutschland) has set itself the objective of supporting and promoting the development of an innovative economic sector in Germany based on modern biosciences. The association currently has over 280 members, which include companies, BioRegions and sector service providers. **Dr Peter Heinrich** is Chairman of the Board of BIO Deutschland.

BIO Deutschland's supporting members and partner organisations are as follows: **berlinbiotechpark GmbH**, **Celgene GmbH**, **CMS Hasche Sigle**, **Commerzbank AG, Deutsche Bank AG, EBD Group, Ernst & Young AG, KPMG AG, Merck KGaG, Miltenyi Biotec GmbH, PricewaterhouseCoopers AG, Roche Diagnostics GmbH, Sanofi-Aventis Deutschland GmbH** and **TVM Capital GmbH**.

You are welcome to request further information on the activities of BIO Deutschland and its working groups from the association's office or at www.biodeutschland.org.

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