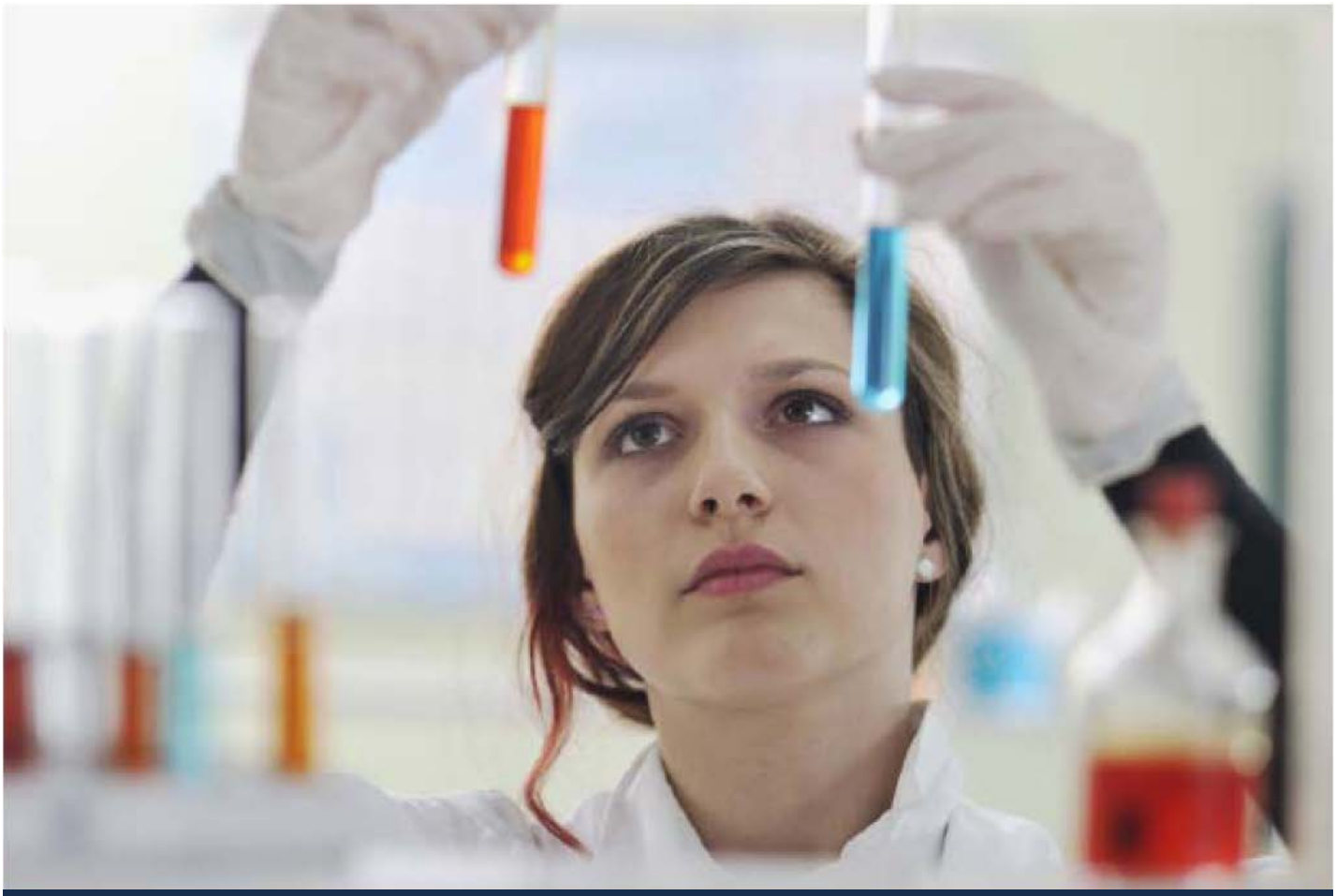

# vfa/vfa bio Position Paper

## Biopharmaceuticals – Original Products and Biosimilars

Die forschenden Pharma-Unternehmen

**vfa / vfa bio Position Paper**
**Biopharmaceuticals – Original Products and Biosimilars**

## EXECUTIVE SUMMARY

vfa and vfa bio represent biopharmaceutical companies with proven expertise in research, development and production of biopharmaceuticals – original products and biosimilars. The competition among biopharmaceutical therapy options is an essential element in improving patient care. The use of biosimilars can broaden financial scope for the health care system, which in turn can be utilized for innovation ("headroom for innovation").



Biopharmaceuticals are biological drugs that are manufactured with the help of genetically modified cells (e.g. microorganisms, animal cells or – more rarely – plant cells). When patent protection for biopharmaceuticals expires, increasing numbers of biosimilars are put on the market which are each similar but not identical to the original product. In the EU there are clearly defined stipulations and standards for approval of biosimilars ensuring their quality, efficacy and safety.

Because biopharmaceuticals are not chemical-synthetic drugs, biosimilars cannot be compared with generics. The instruments that regulate the market can therefore not be simply adopted by the generics segment; rather, they must be adjusted accordingly. vfa and vfa bio are committed to the following conditions for the quality-assured use of biopharmaceuticals – original products and biosimilars – whereby the focus must be on the patient at all times:

- Unequivocal identifiability incl. traceability by means of indication of batch numbers and trade names:
  - → Prescriptions for biopharmaceuticals: based on trade names or PZN (pharmaceutical registration number), where applicable;
  - → Patient file: indication of trade name or PZN, where applicable, and batch number when possible;
  - → Reported side effects: indication of trade name and batch number.
- A biosimilar should be identified as such in all product information provided to the physician and patient.
- Marking in the product information of biosimilars which applications were actually substantiated by clinical trials and which were derived from the biopharmaceutical of the original manufacturer without separate clinical data (via extrapolation).
- No automatic substitution in pharmacies.
- The therapeutic decision must always rest with the physician: The product decision is made first and foremost for medical reasons and with the patient's involvement; no economically-driven prescription guidance.

Hausvogteiplatz 13
10117 Berlin
Telefon 030 206 04-0
Telefax 030 206 04-222
www.vfa.de

## Content

## A) Basic situation

Biopharmaceuticals are biological drugs which are manufactured with the help of cells (e.g. microorganisms such as yeasts or bacteria like E. coli, animal cells derived for instance from the Chinese hamster or – more rarely – plant cells). In contrast to chemical-synthetic pharmaceuticals, their quality is essentially determined by the living organisms used and the manufacturing process. The process for manufacturing a biopharmaceutical is very time-consuming and complex. The biological effect of biopharmaceuticals depends on numerous factors, such as the growth conditions for host cells, solution additives, fermentation processes, temperature and other physical conditions. Even small modifications to the process may lead to differences in the product that can change the drug's efficacy or tolerability in a sustained manner. This also applies to low molecular weight heparins, since these products are complex drug substance mixtures whose characteristics are determined mainly through their production process and monitoring. That is why extensive pre-clinical and clinical studies are conducted to assess the therapeutic effect and safety of a biopharmaceutical.

With regard to the expiration of the first patents for biopharmaceuticals, the question arose in the EU of how approval of copycat products of biopharmaceuticals should be regulated. In this respect, the EU legislature coined the term "medicine which is similar to the biological reference medicine" (**biosimilar**), since a copycat biopharmaceutical can be similar but not identical to the original product. The term has quickly taken hold in the EU and is also used in other parts of the world, e.g. in the United States. Thus, biosimilars are copycat products of biopharmaceutical originals after patent expiration; their active ingredient is of biological origin and usually produced with genetic engineering. A biosimilar must prove that it is effective and safe compared to the reference product by means of detailed quality data as well as through non-clinical and clinical data.

For decades, there have been generic versions on the market of those pharmaceuticals whose active ingredient is manufactured chemically. These are drugs that are identical to the product of the original manufacturer and contain the same active chemical ingredient in the same amount. Such generic drugs can be granted marketing authorization after patent expiration based on a bioequivalence study without the company having to conduct its own trials for efficacy and safety, since it can refer to the corresponding documents of the original manufacturer (without knowing them). Since generic drug manufacturers save the lion's share of research and development costs for a new pharmaceutical of USD 1.0 to 1.6 billion this way, they can offer their drugs at much lower cost than the original manufacturers.

For a high-quality biopharmaceutical, on the other hand, extensive development work with regard to a suitable manufacturing process is required. Furthermore, to prove efficacy and tolerability, it is also

necessary to conduct elaborate pre-clinical and clinical trials. Biosimilars are similar, but not identical, to the biopharmaceutical originals, since the complete imitation of the complex manufacturing process and mere referencing of the original manufacturer's documents is not possible. Instead, each new producer of a biopharmaceutical, i.e. also those of a biosimilar, must conduct pre-clinical and clinical studies in the interest of patient safety. In the EU there are clearly defined stipulations and standards for approval of biosimilars ensuring their quality, efficacy and safety.

If the biosimilar manufacturer has proven the biosimilarity of its product to the reference product for one indication and there are no objections from a scientific viewpoint, the EMA can also authorize the biosimilar for all (or some) of the other indications of the reference product without additional clinical data. This process is called extrapolation.

The following products must be distinguished:

- **Biopharmaceutical original products**
- Biosimilars (copycat products of biopharmaceutical originals after patent expiration) that are similar but not identical to the original product and therefore cannot automatically substitute it
  - **Special case of biopharmaceuticals with multiple trade names (so-called secondary brands or bioidenticals)**: These come from one and the same production facility, are therefore identical with each other and are consequently also substitutable among each other. It is necessary to take into consideration whether two identical drugs differ from each other regarding applicators and their respective handling.

## B) Approved biosimilars in Europe – Status quo

The EU's stipulations and standards for marketing authorization of biosimilars are high and have proven themselves. An increasing number of biosimilars are approved every year in Europe. For a detailed overview of the biosimilars authorized in Europe and their reference products: www.vfa.de/biosimilars-uebersicht-originalpraeparate.pdf.

In the meantime, biosimilars are being frequently prescribed by many office-based physicians in Germany. According to information by the the National Association of Statutory Health Insurance Funds (GKV-GAmSi; data for January to September 2017: based on DDD, defined daily dose) epoetin biosimilars reached the highest prescribing share (88 %). Filgrastim biosimilars yielded in 75 % and infliximab biosimi-

lars showed about 50 % in the outpatient setting. Source: Bundesbericht GAmSi, GKV-Arzneimittel-Schnellinformation für Deutschland nach § 84 Abs. 5 SGB V, http://www.gkv-gamsi.de/gamsi_statistiken/gamsi_statistiken.jsp.

## C) vfa/vfa bio: Position

When patent protection for biopharmaceuticals expires, biosimilars – which are each similar but not identical to the original product – are increasingly put on the market. In the EU there are clearly defined stipulations and standards for that. Adequate approval requirements ensure the quality, efficacy and safety of the biosimilars approved in the EU.

### The process for manufacturing biopharmaceuticals is very time-consuming and complex and requires a high level of technical know-how

The manufacturing process for a biological active ingredient significantly defines the drug manufactured from it, since these processes are based on living cells – or, as in the case of the low molecular weight heparins, on biological material. In contrast to chemical products, biopharmaceuticals are heterogeneous at the molecular level, as a result of the variability of the live processes through which they are produced. The same is true for biosimilars, since these - like original biopharmaceutical products - are manufactured in living cells.

As with other medical products, the manufacturer of a biopharmaceutical - original products and biosimilars - is mandated according to pharmaceutical guideline 2001/83/EG (Article 23) to adapt the drug's manufacture and control to meet the relevant state of science and technology. All manufacturers must comply with this, meaning that procedural changes will become necessary over time. Possible effects of the changes made must be examined in detail by the manufacturer as part of the ***"comparability assessment"*** (comparison when changes are made to the same product of one and the same manufacturer; see below – Guideline EMEA/CHMP/BMWP101695/2006). In this connection, the regulatory authorities have increasing requirements to match the magnitude of the changes. For instance, Type I variations (e.g. administrative changes, changes to packaging materials or specification limits, etc.) and Type II variations (e.g. change in the manufacturing process or location) rarely require clinical data, in so far as they do not involve substantial changes, such as change to the cell line that produces the biopharmaceutical, or changes in the formulation. For such severe changes or for extensions of marketing authorizations (e.g. new clinical indications) clinical data are generally required.

For it, the manufacturer of a biopharmaceutical – original product as well as biosimilar – has a comprehensive data analysis available for all production steps and for all important intermediate products and

has established in-process controls and reference standards for its corresponding product. Modifications (process changes) that become necessary over the course of time will generally be small changes in a well-understood and comprehensively validated process. All other aspects of production remain unchanged. Often, the customized processes developed for the production of biopharmaceuticals are protected intellectual property or trade secrets. The manufacturer is in a position to compare the manufactured product before and after the change in order to demonstrate to the marketing authorization agency that the change has no negative impact on the product's efficacy and safety. To this end, the manufacturer may also have to submit new clinical data if necessary before the introduction of severe process changes. This depends on the results of the characterization studies for the product comparison, which are used to determine any effects on quality, efficacy and safety. Changes that become necessary during the manufacturing process equally affect manufacturers of original products and biosimilars.

According to WHO and EMA guidelines, the manufacturers of biosimilars must prove by comparative analytical tests that the biosimilar does not differ significantly from the reference product with regard to its physico-chemical and biological properties to obtain approval (***"similarity assessment"***, the comparison of similar products from different manufacturers with different manufacturing processes). Furthermore, pre-clinical and clinical data have to be provided. That is because, due to the complexity of biopharmaceuticals, it is not possible after the patent expiration of the original products to develop copycat products that are identical to the reference product. Therefore, it is not acceptable to only collect data on the quality and prove bioequivalence as is customary for chemical-synthetic generics.

## Studies are required before and after biosimilar marketing authorization

For its product, a biosimilar manufacturer must have a comprehensive data collection for all production steps, from its starting material such as its own cell banks, through to the manufacturing process, the most important intermediate products and the in-process controls as well as reference standards. In doing so, its own process needs to be developed, with which it must come to a result as close as possible to the product of the original manufacturer.

The similarity of the clinical properties of the biosimilar and its reference product normally has to be demonstrated via sufficiently big, comparative studies which analyze efficacy and safety as well as immunogenicity. Furthermore, biosimilars – like all other biopharmaceuticals – are also to be monitored in their broader application after marketing authorization in order to capture potential immunogenicity reactions and rare side effects.

To be consistent, marketing authorization applications of biosimilars must include detailed comparative data on the quality as well as non-

clinical and clinical data in order to demonstrate that a biosimilar is pharmaceutically and clinically similar in comparison to the original product in question. Efficacy trials are in particular required for complex molecules such as monoclonal antibodies or when validated surrogate parameters are missing. This is ensured by the well proven EU body of regulations for biosimilars, which also served as a model for the regulations in other countries.

## Product-specific prescription and documentation in patient files as well as unique identifiability including traceability in case of reported side effects are necessary

Product-specific prescription of biopharmaceuticals based on:

Unlike with chemical-synthetic drugs, the product-specific prescription of biopharmaceuticals and so avoiding uncontrolled product changes during therapy are essential to patient safety. Biopharmaceuticals should therefore only be prescribed with specification of the trade name or the PZN (pharmaceutical registration number) if applicable. That is necessary because some biopharmaceuticals have the same active ingredient name, but the products are not identical. Therefore, physicians should be obliged to prescribe biopharmaceuticals via brand names; a corresponding change of the drug prescribing regulation is required.

Product-specific documentation of biopharmaceuticals in patient files:

The prescribed biopharmaceutical should be specifically documented by the physician in the patient file using the trade name or PZN if applicable and with reference to the batch number when possible. Only then the biopharmaceutical the patient has been receiving (including the corresponding batch) can be traced back immediately, e.g. in case of severe side effects, for example. Based on this, physicians and authorities as well as marketing authorization holders can take adequate countermeasures.

EMA has been requesting product-specific documentation for all epoetin products since 2009 and is demanded for all biopharmaceuticals – original products and biosimilars – since August 2016 („Guideline on good pharmacovigilance practices “: „The product name and batch number of an administered biological should be recorded by the healthcare professional and be provided to the patient.“).

Product-specific documentation of biopharmaceuticals if side effects are reported:

According to Article 102 e of the Pharmacovigilance Directive 2001/83/EC the Member States shall ensure that "all appropriate 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 the medicinal product, in accordance with Article 1(20), and

the batch number". With regard to patient safety – especially in case of side effects or tolerability issues – it is critically important that biological medicinal products can be traced back unambiguously to one specific product and to the respective batch number, respectively. This is because different biological drug substances with identical non-proprietary names may show different side effect profiles. In Germany, this has been tackled within the scope of the „Viertes Gesetzes zur Änderung arzneimittelrechtlicher und anderer Vorschriften“: In case of reports of side effects for biologicals all biologicals clearly have to be identified via documentation of the product brand name and batch number. The corresponding change of the drug prescribing regulation would be the logical and required next step (see above).

## No automatic substitution in pharmacies but preservation of the physician’s therapeutic freedom

Automatic substitution in pharmacies between the original product and biosimilar (in the same way as with substitution of different original products or different biosimilars between each other) is prohibited by law in Germany (exception: bioidenticals which are listed in Appendix 1 of the master agreement between the German National Association of Statutory Health Insurance Funds and the German Pharmacists' Association; see also Appendix I). Biopharmaceuticals - original products and biosimilars - may only be switched among each other after instruction from the physician and with involvement of the patient.

Original products and copycat products of biological drugs that are approved as biosimilars but not genetically engineered should also be excluded from automatic substitution. There is currently a gap in regulation in the framework agreement according to Section 129 SGB V that could compromize with the traceability of biological drugs according to § 62 Abs. 2 Sent. 4.

The therapeutic decision about which biopharmaceutical to administer must rest with the physician and should be primarily medically based. In addition, the choice of therapy should only take place on the basis of medical considerations and with consultation of the patient. Since the human body can recognize biological medicines as “foreign”, the possibility inherently exists that – due to their composition and molecular size – they may induce undesirable immune reactions and impact efficacy and/or safety. Medically unjustified product switching is to be avoided with biopharmaceuticals if no adequate evidence is available. In addition, a product change without sufficient documentation could make the attribution of side effects to a product impossible, especially when side effects arise later during treatment.

Therefore, and also because the physician assumes liability for the prescription, biopharmaceuticals are not to be switched without the physician's approval and not without involvement of the patient. This

is why automatic substitution in pharmacies is not allowed in Germany (see also Appendix I).

With regard to the physician's therapeutic freedom, quotas for biopharmaceuticals should be declined, since the prescribing decision must always rest with the physician. Furthermore, quota requirements ignore the time and effort needed for information and integration, adjustment and surveillance of patients as part of a prescription switch. Quotas also deprive physicians of part of their necessary medical decision-making freedom and shift the decision-making focus from medical to economic aspects.

## D) vfa/vfa bio: Recommendations

vfa and vfa bio represent biopharmaceutical companies with proven expertise in research, development and production of biopharma-ceuticals – original products and biosimilars. The competition among biopharmaceutical therapy options is an essential element in improving patient care. The use of biosimilars can broaden financial scope for the health care system, which in turn can be utilized for innovation ("headroom for innovation").

Because biopharmaceuticals are not chemical-synthetic drugs, biosimilars cannot be compared with generics. The instruments that regulate the market can therefore not be simply adopted by the generics segment; rather, they must be adjusted accordingly. vfa and vfa bio are committed to the following conditions for the quality-assured use of biopharmaceuticals – original products and biosimilars – whereby the focus must be on the patient at all times:

- **Unequivocal identifiability incl. traceability** by means of indication of batch numbers and trade names:
  - → No prescriptions for biopharmaceuticals based on INN (international non-proprietary name); rather, they should be based exclusively on trade names or PZN (pharmaceutical registration number), where applicable;
  - → Patient file with indication of trade name or PZN, where applicable, and batch number when possible;
  - → Trade name and batch number indicated in the event of reported side effects.
- **A biosimilar should be identified as such** in all product information (summary of product information, package inserts and EPAR) provided to the physician and patient.
- **Marking in the product information of biosimilars** which applications were actually substantiated by clinical trials and which were derived from the biopharmaceutical of the original manufacturer without separate clinical data (via extrapolation).

- **No automatic substitution in pharmacies** (exception: bioidenticals, see Appendix I): A switch from the original product to the biosimilars, from the biosimilar to the original product as well as between different original products or different biosimilars must not be made unless there is express consent of a physician and stringent medical supervision. Also for patients with a new prescription, a change of product in the pharmacy is not permitted, since the treatment decision has to be made by the physician in consultation with the patient.
- **Change of therapy primarily on the basis of medical considerations and with consultation of the patient.** Medically unjustified product switching is to be avoided with biopharmaceuticals.
- **Preservation of therapeutic freedom of the treating physician (no economically-driven prescription guidance such as quotas):** Quotas for biopharmaceuticals must be rejected, since the decision regarding the prescription in question must always remain with the physician and must be primarily based on medical reasons. Quotas also deprive physicians of part of their necessary medical decision-making freedom and shift the decision-making focus from medical to economic aspects.

For the approval of biosimilars comprehensive comparative analytical, qualitative as well as non-clinical data should be provided also in the future. The totality of evidence of all data including those from clinical trials is the basis for biosimilar approval. In addition – as for all biopharmaceuticals, observational studies are required, including participation in existing registers after marketing authorization of biosimilars, in order to determine potential immunogenicity reactions and rare side effects (pharmacovigilance studies). This is specified in the established European approval framework including risk-management plans also for biosimilars which has proven itself and which should be maintained.

Stand: December 2017

## Appendix I: Properties of the active ingredients of biopharmaceuticals (original products and biosimilars)

- They have proven biological activity/activities.
- They have a high molecular weight and a highly complex structure compared to most chemical-synthetic active ingredients.
- They are heterogeneous in terms of their molecular structure. The heterogeneity of the molecular structure and the respective impurity profile can have impacts on the efficacy, action profile and safety of biological drugs.
- Their quality can be influenced by differences of the biological or genetic starting material, the master cell bank, the expression system and the manufacturing process, which leads to different posttranslational modifications and therefore microheterogeneities of the molecule.
- Since the human body can recognize biological medicines as “foreign”, the possibility inherently exists that – due to their composition and molecular size – they may induce undesirable immune reactions and impact efficacy and/or safety.
- They may be very sensitive in their biological activity to physical conditions (temperature, light, shear forces, phases), enzyme activities in the manufacturing process (sensitivity toward process changes) and changes in the formulation; this places special demands on storage and transportation.
- They may require very specific formulation conditions (e.g. excipients, conjugation or special chemical and physical conditions) to develop the specific and full biological activity upon administration.
- They require (a) bioassay(s) for characterization and stability assessment in addition to the chemical and physical tests to determine the identity and purity from batch to batch. The number of tests is much higher than with chemical-synthetic medications.
- Especially monoclonal antibodies are highly complex molecules which are used for very different areas of applications in patients with severe diseases with different and in some cases not fully clarified pathomechanisms and with potential different co-medications and co-morbidities.
- The low molecular weight heparins are special in that their drug substances are not produced via genetic engineering. They are composed of heterogeneous mixtures of highly sulfated, differently long polysaccharide chains with still not fully understood structure-function-relationship.
- Bioidenticals are secondary brands, come from one and the same production facility and are therefore identical with each other. This

is also defined in the master agreement between the German National Association of Statutory Health Insurance Funds and the German Pharmacists' Association (DAV): biotechnology drugs with the same active ingredient must not differ as regards their starting materials and manufacturing process. Only for these products, which are listed separately in Appendix 1 to the master agreement, does the pharmacy have to choose a low-cost biopharmaceutical that corresponds to that prescribed and has the same active ingredient (automatic substitution).

## Appendix II: Marketing authorization of biosimilars in the EU – rules and standards

As part of the revision of EC pharmaceutical legislation concluded at the end of March 2004 in the EU, a regulation for biological medicines similar to a biological reference medicine (biosimilars) was also included among others**. Article 10 paragraph 4 of the amended Directive 2001/83/EC** reads:

"Where a 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 analyses or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines."

The criteria for registration of a biosimilar product have to be applied for biopharmaceuticals, because their drug substances are manufactured based on genetic engineering. Furthermore, they have to be used for low molecular weight heparins, since these products are complex drug substance mixtures whose characteristics are determined mainly through their production process and monitoring. Several product-specific guidelines or annexes have already been adopted by the EMA (see below).

According to Annex I, Part II "Specific Marketing Authorization Dossiers and Requirements" Item 4: "Similar Biological Medicinal Products," information to be supplied for a marketing authorization for a biological medicinal product which refers to an original medicinal product shall not be limited to pharmaceutical, chemical and biological data as well as data on bio-equivalence and bio-availability. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case-by-case basis in accordance with relevant scientific guidelines. Due to the diversity of biological medicinal products, the need for identified studies foreseen in Module 4 (Pre-clinical Reports) and Module 5 (Re-

ports on Clinical Studies) shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

Marketing authorization of each new medicinal product, including biosimilars, comprises an individual risk management plan. This plan outlines measures to support the safe use of the pharmaceutical and to answer questions for which – at the time of approval – data were not yet sufficiently available. That is because some risks cannot be judged appropriately in submission studies because they are very rare and the number of patients in the comparative studies too low or because the unwanted effects occur only later.

The revised Directive 2001/83/EC including Annex I became effective at the end of 2005. Since October 2005, **the Guideline on Similar Biological Medicinal Products (CHMP / 437 / 04**; so-called "overarching" guideline) is to be applied, which contains the concept of biosimilars, the basic principles, e.g. for choosing the reference product, and information regarding the relevant guidelines. This guideline has now been updated and is valid in the revised version (CHMP/437/04 Rev 1) as of April 2015.

Furthermore, the following additional guidelines by the EMA have to be applied:

- ***Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance – Quality Issues (EMA / CHMP / BWP / 247713 / 2012)***
- ***Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance – Non-Clinical and Clinical Issues (EMEA / CHMP / BMWP / 42832 / 2005 Rev 1)***
- ***Product-specific guidelines for***
  - ***Epoetins***
    *(EMEA/CHMP/BMWP/301636/08)*
  - ***FSH products*** (follicle stimulating hormone)
    (EMA/CHMP/BMWP/671292/2010)
  - ***G-CSF products*** *(granulocyte- colony stimulating factor)*
    *(EMA/CHMP/BMWP/214262/2015)*
    *currently under revision*
  - ***Insulins and insulin analogs***
    (EMEA/CHMP/BMWP/32775/2005 Rev 1)
  - ***Interferon alpha and pegylated Interferon alpha products***
    *(EMA/CHMP/BMWP/693108/2015)*
    *currently under revision*
  - ***Interferon beta products***
    *(EMA/CHMP/BMWP/652000/2010)*

- ***Monoclonal antibodies***
  *(EMA/CHMP/BMWP/403543/2010)*
- ***Low molecular weight heparins***
  *(EMEA/CHMP/BMWP/118264/2007 Rev. 1*)
- ***Somatropin***
  (EMEA/CHMP/BMWP/94528/2005)

Furthermore, in April 2008, the specific **Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006; currently under revision)** became effective, in which it was explicitly pointed out that studies on immunogenicity are also required for biosimilars. In addition, the **Guideline Regarding Immunogenicity of Monoclonal Antibodies (EMA/CHMP/BMWP/86289/2010)** entered into force on December 1, 2012.

Since November 2007, the Guideline **EMEA/CHMP/BMWP/101695/2006 ("Guideline on comparability of biotechnology-derived medicinal products after a change in the manufacturing process – non-clinical and clinical issues")** has been effective, in which the comparability of a biopharmaceutical after a change in the manufacturing process at a manufacturer's production facility or that of a subcontractor is described. Such changes in production process become necessary during the development of a drug and after its marketing authorization. Since the process changes are made at the same manufacturer, who already has comprehensive experience with the active substance, the data requirements for comparability ("comparability assessment") are usually lower than for the proof of similarity ("similarity assessment") between a biosimilar and the biopharmaceutical original, since these products come from different manufacturers.

## Appendix III: Differences in the active ingredient names of biopharmaceuticals

Presently, the name of the active ingredient alone (INN = international non-proprietary name; the abbreviated name issued by the WHO) is not always sufficient to determine which biopharmaceutical is concerned. This fact is illustrated in the following table by the example of the epoetin, infliximab and rituximab products.

**Epoetin: original products**

- Aranesp
  INN: Darbepoetin alfa
- ERYPO
  INN: Epoetin alfa
- Mircera
  INN: Methoxy polyethylene glycol-epoetin beta
- NeoRecormon
  INN: Epoetin beta
- One product with two trade names:
  Biopoin and Eporatio
  INN: Epoetin theta

**Epoetin: biosimilars**

- One biosimilar with three trade names:
  Abseamed, Binocrit, Epoetin alfa HEXAL
  INN: Epoetin alfa
  Reference product: ERYPO
- One biosimilar with two trade names:
  Retacrit, Silapo
  INN: Epoetin zeta
  Reference product: ERYPO

**Infliximab: original product**

- Remicade
  INN: Infliximab

**Infliximab: biosimilars**

- One biosimilar with two trade names:
  Inflectra, Remsima
  INN: Infliximab
- One biosimilar with one trade name:
  Flixabi
  INN: Infliximab

**Rituximab: original product**

- MabThera
  INN: Rituximab

**Rituximab: biosimilars**

- One biosimilar with four trade names:
  Truxima, Blitzima, Ritemvia, Rituzena
  INN: Rituximab
- One biosimilar with two trade names:
  Rixathon, Riximyo
  INN: Rituximab

Against this background, indication of the trade name or PZN, where applicable, is required for prescriptions of biopharmaceuticals and in documentation in the patient file. Indication of trade names and batch numbers is already mandated EU-wide for possible reported side effects with biopharmaceuticals.

The World Health Organization has already initiated a discussion regarding a so-called biological qualifier (BQ), a 4-letter code as a suffix to the active biological substance.

In January 2017, the FDA (US regulatory authority) published a Guidance for Industry on the topic of "Nonproprietary Naming of Biological Products", in which they speak out in favor of a four-letter suffix for active ingredients ("Under this naming convention, the nonproprietary name designated for each originator biological product, related biological product, and biosimilar product will be a proper name that is a combination of the core name and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.").

## Appendix IV: Regulations in other countries

In the United States, biological/biotechnological products governed by the Public Health Service Act are exempt from the regulations of the Federal Food Drug & Cosmetic Act for generic marketing authorization (ANDA). The FDA has now finalized the first documents on biosimilar approval (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm 290967.htm), in particular the guidance for Industry „Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" (December 2016) and the draft guidance for Industry „Considerations in Demonstrating Interchangeability With a Reference Product" (January 2017). Six biosimilars (Adalimumab-atto, Etanercept-szzs, Filgrastim-sndz, Infliximab-abda, Infliximab-dyyb, Infliximab-qbtx) have meanwhile been approved by the FDA, several others are in the approval process.

The WHO guideline for biosimilars (Guidelines on evaluation of similar biotherapeutic products, World Health Organization, 2009) basically

follows the same principles as are prevalent in the EU and is meant to serve as a guidance for those countries that do not yet have any biosimilar legislation.

Almost all guidelines that have either been passed or are being discussed in other parts of the world (e.g. Switzerland, Turkey, Malaysia, Australia, Japan, Mexico, Taiwan, Korea) have taken the WHO guideline as a basis and therefore largely correspond to the European body of regulations for biosimilars.