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 innovative pharmaceuticals.

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);
  - Patient file: indication of trade name or PZN, 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.

- No automatic substitution in the future either.

- No economically-driven prescription guidance.

- The therapeutic decision should be made solely by the physician, based primarily on medical considerations in adherence to economic efficiency, taking the patient into account and with appropriate detailed product documentation.
Content

Executive Summary ................................................................. 1
Content ....................................................................................... 2
A) Basic situation ........................................................................ 3
B) Biosimilars in Germany – Status quo ................................. 4
C) vfa/vfa bio: Position ............................................................... 5
    Studies are required before and after biosimilar marketing authorization .......................................... 5
    Product-specific prescription and documentation in patient files as well as unique identifiability including traceability in case of reported side effects are necessary ................................................................. 5
    No automatic substitution in pharmacies but preservation of the physician’s therapeutic freedom ....... 7
    The Law for More Safety in the Supply of Pharmaceuticals (GSAV): Planned automatic substitution of biopharmaceuticals in pharmacies ........... 8
D) vfa/vfa bio: Recommendations ................................................. 9

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

Appendix II: The process for manufacturing biopharmaceuticals is very time-consuming and complex and requires a high level of technical know-how
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 concluded a revision of the EC pharmaceutical legislation at the end of March 2004 in which it 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. The active ingredient of biopharmaceuticals – original products and biosimilars – is of biological origin and is 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. Biosimilars are similar, but not identical, to the biopharma-
aceutical originals, since the complete imitation of the complex manu-
ufacturing process and mere referencing of the original manufacturer's
documents is not possible. Instead, each new producer of a biophar-
maceutical, 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 biosimi-
lars ensuring their quality, efficacy and safety.

If the biosimilar manufacturer has proven the biosimilarity of its prod-
uct to the reference product for one indication and there are no ob-
jections 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 extrap-
olation.

The following products must be distinguished:

- **Biopharmaceutical original products**
- **Biosimilars**
- **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) Biosimilars in Germany – Status quo

The EU's stipulations and standards for marketing authorization of
biosimilars are high and have proven themselves
(https://www.ema.europa.eu/en/human-regulatory/overview/biosim-
ilar-medicines-overview).

An increasing number of biosimilars are approved every year in Eu-
rope. For a detailed overview of the biosimilars authorized in Europe
and their reference products: www.vfa-bio.de/biosimilars.

Biosimilars are showing very strong growth in Germany and are al-
ready gaining significant market share in just the first year following
their market launch. For the prescription share of biosimilars, critical
factors include the date of market entry, the relevant substance
group, the difference in price compared to the original product and
the number of available biosimilar products. Rituximab biosimilars,
available for rheumatism and cancer therapy in Germany since April
2017, have reached a share of more than three-quarters of all pre-
scriptions since their market launch approximately two years ago.
And Adalimumab biosimilars reached a market share of around 50% just one year after market launch.

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.

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). 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 or PZN; 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 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 Vor-schriften“: In case of reports of side effects for biologicals all biologicals clearly should be identified via documentation of the product brand name and batch number. A “must” provision instead of a “should” provision and a change in the pharmaceutical prescription regulation (see above) would be the next logical and necessary steps.
No automatic substitution in pharmacies but preservation of the physician's therapeutic freedom

Up to now, 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 (e.g. low molecular weight heparins) should also be excluded from automatic substitution. Appendix 1 to the framework agreement between the GKV Spitzenverband and the Deutsche Apothekerverband should be updated and the relevant products should be included.

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 take the patient into account and with appropriate detailed product documentation. 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. Furthermore, the automatic substitution of biopharmaceuticals in pharmacies would be diametrically opposed to the central role of the physician in making therapy decisions, and, in accordance with law and due to the regulatory requirements surrounding pharmacovigilance, is not permitted in Germany up to now (see also Appendix I).

In addition, biopharmaceuticals are sophisticated products in terms of the necessary and helpful devices frequently required by the patient for self-administration of drugs against chronic illnesses. These devices generally differ from product to product. This is another reason that the consultation between physician and patient regarding the specific pharmaceutical is especially important.

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 pure economic aspects.

The Law for More Safety in the Supply of Pharmaceuticals (GSAV): Planned automatic substitution of biopharmaceuticals in pharmacies

According to the GSAV, which took effect in August 2019, following the substitution instructions for physicians, the G-BA is also to prepare specific information for the eligible substitution of reference drugs by biosimilars in pharmacies, which will take effect in August 2022 at the latest. Because the physician would not be informed which biopharmaceutical the patient actually received in the pharmacy in the event of a substitution, the legally prescribed documentation including unequivocal identifiability and traceability would be disrupted. The automatic substitution of biopharmaceuticals in pharmacies would thus be diametrically opposed to both the patient’s safety and therapeutic freedom.

In addition, automatic substitution in conjunction with discount agreements for generics has contributed to the generics supply in Germany becoming largely dependent on other countries, which may be linked to possible supply shortages for patients. An aut idem regulation for biopharmaceuticals could have detrimental effects on the production of biopharmaceuticals in Germany and Europe in the medium and long term.

The competition between original biopharmaceuticals and biosimilars in Germany is already in full swing and is now gaining even more momentum as patents for high-revenue biopharmaceuticals expire. Consequently, no further interventionist measures are necessary that would additionally aggravate drug safety and the conditions for production in Germany and Europe. The central role of the physician for the initial prescription of a biopharmaceutical as well as for switching is and will remain the essential prerequisite – with the appropriate involvement of the patient – for the quality-assured use of biopharmaceuticals.

With the GSAV, legislators have also approved amendments to the import subsidy clause. The inception of this new feature in the GSAV, which exempts biotechnologically manufactured drugs and additionally parenteral anti-cancer agents from the import subsidy clause, is regulated with the Implant Registry Establishment Act: “Biotechnologically manufactured drugs and additionally antineoplastic medicinal products for parenteral use are exempted from the obligation to supply low-priced imported medicinal products due to their special requirements, especially with regard to storage and transport. Due to higher transport risks with longer delivery routes,
the quality and efficacy of these drugs are considered compromised.”
This measure is expressly supported by vfa and vfa bio.

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 pharmaceuticals.

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);
  
  ▪ Patient file with indication of trade name or PZN 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.

▪ **No automatic substitution in the future either** (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 an explicit prescription 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.

▪ The **therapeutic decision should be made solely by the physician**, based primarily on medical considerations in adherence to economic efficiency, taking the patient into account and with appropriate detailed product documentation. This can be differentiated as follows:
Due to the market launch of biosimilar products, the physician has a greater selection to choose from for the initial prescription of a biopharmaceutical and the product most suitable for the patient should be prescribed.

When a switch is made from a reference product to a biosimilar, from one biosimilar to another corresponding biosimilar, or from one biosimilar to the reference product: The decision to switch a well-controlled patient to another biopharmaceutical should be weighed between the physician and the patient on a case by case basis.

Cross-substance switch: A change in preparations should always be based on medical reasons.

Preservation of therapeutic freedom of the treating physician: Prescription controls that are purely economically driven, e.g. quotas must be rejected for biopharmaceuticals, 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.

The totality of evidence of all data including those from clinical trials is the basis for biosimilar approval. For the approval of biosimilars comprehensive comparative analytical, qualitative as well as non-clinical data should be provided also in the future. 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). Risk management plans have proven themselves in the established European approval framework also for biosimilars and should be maintained.

Status: December 2019
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: 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 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.