vfa/vfa bio Position Paper

Biopharmaceuticals – Original Products and Biosimilars

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 broadens the financial scope for the health care system, which in turn can be utilized for innovative pharmaceuticals.

Executive Summary

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 generic market can therefore not be simply transferred to biopharmaceuticals; 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 patients at all times:

- The therapeutic decision should be made solely by the treating physicians, based primarily on medical considerations in adherence to economic efficiency, taking the patients into account and with appropriate detailed product documentation.
- 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.
- No economically-driven prescription guidance.
- No automatic substitution in the future either.

Basic Situation

Biopharmaceuticals are biological drugs which are manufactured with the help of 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. 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.

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 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 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.

Biopharmaceuticals vs. Biosimilar vs. Bioidentical

The following products must be distinguished:

- **Biopharmaceutical original products (reference 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 the devices (application aids) and their respective handling.

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/biosimilar-medicines-overview).

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-bio.de/biosimilars.

Meanwhile, treating physicians are mostly prescribing biosimilars very speedily and frequently in Germany. This is why biosimilars show very strong growth in Germany. For their prescription share, 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. In Germany, biosimilars are now gaining significant market shares of up to 60% in the first year after launch, with bevacizumab even approaching 80%. The current market share of biosimilars was high for many products in November 2021 (based on

daily doses, overall pharmacy and hospital market): 70% for infliximab, 73% for adalimumab, 78% for trastuzumab, 80% for etanercept, 85% for bevacizumab, and even 87% for rituximab biosimilars[1].

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.

Consequently, 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. The overall analysis of available evidence is critically important in this connection, especially since there is growing trend towards fewer clinical trials for biosimilars.

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

1. 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). This is necessary because the international non-proprietary name (INN) alone does not usually indicate which biopharmaceutical is involved. Because, while most biosimilars have INNs identical to the reference product, the products among themselves are not identical to each other. Therefore, physicians should be obliged to prescribe biopharmaceuticals via brand names or PZN; a corresponding change of the drug prescribing regulation is required.

2. Product-specific documentation of biopharmaceuticals in patient files:

The prescribed biopharmaceutical should be specifically documented by the physicians 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.

A product-specific documentation for all epoetin products has been requested by EMA since 2009

[1] IQVIA Arzneimittelverbrauch (AMV) Datenbank: hospital market data from IQVIA DKM® (German hospital market), pharmacy market data from IQVIA PharmaScope® National

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.“).

3. 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“ (effective since end of 2016): 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.

Although electronic patient records (ePA) are being gradually introduced since 2021, uninterrupted documentation of the biopharmaceuticals that patients receive is not guaranteed. The use of this ePA is voluntary for patients, which also means that patients decide for themselves which documents are included and who has access to the files for how long.

4. Differences in labeling regarding the black triangle for biopharmaceuticals with similar active ingredients

In EU member states, drugs that are subject to additional monitoring are being labeled with a black triangle since 2013. Drugs labeled in this way are to be given particular attention to more quickly recognize potential unknown side effects and thus improve patient safety. Every newly approved biologic is labeled with the black triangle for a period of five years. This means that not all biopharmaceuticals with similar active ingredients bear this label. For these products, automatic substitution in the pharmacy should therefore be omitted, also to avoid unsettling patients through the different labeling.

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 existing legal rules 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). Biopharmaceuticals - original products and biosimilars - may only be switched among each other after corresponding prescription from the treating 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.

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 including 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 as long as no sufficient evidence is available.

A product change without sufficient documentation would make the attribution of side effects to a product impossible, especially when side effects arise later during treatment. Therefore, and also because the treating 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.

Furthermore, biopharmaceuticals are sophisticated products in terms of the necessary and helpful devices frequently required by the patient for self-injection of drugs against chronic illnesses. These devices generally differ from product to product. In addition, there may be differences among the devices in terms of being needle-free or needing cold storage, which can also impact adherence and product safety. These are other reasons that the consultation between physician and patient regarding the specifically to be administered biopharmaceutical is especially important.

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

In accordance with the GSAV (effective since August 2019), the G-BA has established substitution indications for doctors: They state that, in the future, physicians prescribing biopharmaceuticals are required to switch them multiple times for non-medical reasons, which is refused by many health care stakeholders, especially physicians and patients as well as their associations, with regard to pharmacovigilance aspects and patient adherence. In addition to that, 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 not be realizable. 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. Automatic substitution of biopharmaceuticals could have detrimental effects on the production of biopharmaceuticals in Germany and Europe in the medium and long term. This would contradict the declared goal of the EU and the German government of strengthening the locations of Germany and Europe as well as of achieving greater autonomy.

The competition between original biopharmaceuticals and biosimilars in Germany is already in full swing and is now gaining even more momentum as more and more 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.

It is also questionable whether additional scientific insights were actually gained over the last three years (as stipulated in the GSAV explanatory statement) that, going forward, allow the G-BA to reliably assess – with regard to the corresponding drug substances – the risks involved with automatic substitution by pharmacists.

vfa / vfa bio: Recommendations

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Good reasons against automatic substitution in the pharmacy

Consequently, the corresponding passage in the GSAV regarding the automatic substitution of biopharmaceuticals should be deleted from the law – as demanded by the majority of stakeholders in the health care system:

- To maintain the physician's freedom to choose therapies!
- To ensure a resilient high-tech production location in Germany and Europe!
- To provide the maximum security of supply for biopharmaceuticals for patients!

use of biosimilars broadens the 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 generic market can therefore not be simply transferred to biopharmaceuticals; 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:

- **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. A cross-substance switch in preparations should always be based on medical reasons.
- **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.
- **No economically-driven prescription guidance:** 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.
- **No automatic substitution in the future either** (exception: bioidenticals): 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 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.

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