

Biosimilars in Germany: guidance of the Drug Commission of the German Medical Association

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Biosimilars have been available in Europe for more than 10 years, but their adoption in Germany has not been very successful. As their pharmaceutical quality, efficacy (particularly in extrapolated indications), safety (especially immunogenicity) and interchangeability with reference products have been controversially discussed by healthcare professionals, the Drug Commission of the German Medical Association developed a practical guidance for the therapeutic use of biosimilars.

Keywords: Biologicals, biosimilars, Germany, guidance, switching

Introduction

Biosimilars (biosimilar medicines) have been available in Europe for more than 10 years, which has made it possible to gain practical experience with these products, particularly in oncology, rheumatology and gastroenterology.

Nevertheless the adoption of biosimilars in Germany has not been very successful and still faces many concerns voiced by physicians about their pharmaceutical quality, efficacy (particularly in extrapolated indications), safety (especially immunogenicity) and interchangeability with the originator product [1]. These misconceptions cannot be explained medically or scientifically. The uptake of biosimilars in Germany has not been very high to date, as no approved biosimilar has achieved complete or at least high market penetration, even after 10 years of availability [2].

Position of the Drug Commission

In 2008, the Drug Commission of the German Medical Association (Drug Commission) released a statement about biosimilars, pointing out that they can be considered a therapeutic alternative to the reference (originator) products [3].

Given that the first biosimilar of a monoclonal antibody, i.e. infliximab (Remsima[®], Inflectra[®]), was approved in 2013 and the patents of many bestselling biologicals have already expired or will expire in the next few years, German physicians will continue to be confronted with an ever-increasing number of biosimilars in the near future [4].

As the substitution of biosimilars at the pharmacy level is not permitted in Germany, physicians are in the key position to increase the use of biosimilars. Therefore, physicians' information and education are the most critical factors impacting the integration of biosimilars into the treatment practice.

The Drug Commission has revised its statement to develop practical guidance for the therapeutic use of biosimilars. This guidance aims to acquaint clinicians with the concept of biosimilars. Furthermore, it provides an overview of the scientific principles guiding biosimilar development and regulatory requirements

and also outlines the differences between biosimilars and generic medicines. The extrapolation procedure is also highlighted, as it seems that there is not a thorough understanding of it among all physicians. Topics such as pharmacovigilance and immunogenicity are also addressed [5].

Particular attention was paid to the interchangeability of reference products and biosimilars. Switching from the reference products to biosimilars in patients who have already been treated with a biological medicine has been introduced on the basis of available switch studies focused on efficacy and safety, which demonstrated no (significant) differences between the patients who were switched and those who were maintained.

Guidance summary

The Drug Commission summarized the central points of its guidance to respond to the most frequently voiced concerns about biosimilars. Understanding the specifics of biological and biosimilar medicines and their manufacturing process and approval is crucial for the assessment of biosimilars.

Biological medicines are large, complex molecules (proteins) produced in living organisms, mostly by biotechnology. As biological medicines are manufactured in living cells or organisms, the final products regularly have the same amino acid sequence, but an inherent degree of minor variability (microheterogeneity), e.g. in glycosylation [1, 6]. Every single batch of a biological medicine is highly similar, but not identical to the other batches of the same biological medicine. Minor variability is often seen after changes in the manufacturing process. In the case of Remicade[®] (infliximab), there have been more than 30 changes in the manufacturing process since its approval in the EU in 2002 [7]. The version of Remicade[®] which is currently available is therefore highly similar (biosimilar), but not identical to the Remicade[®] used in the pivotal studies.

Minor variability does not critically affect the efficacy and safety of biological medicines as long as it is within an acceptable range defined during the approval process. Minor variability is constantly monitored using analytical tests, which are usually more sensitive than clinical studies in terms of detecting structural and functional differences. Following changes in the

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manufacturing process, companies producing biological medicines must continuously ensure that the post-change batches are as efficacious and safe as the pre-change batches. To date, there have been no cases of a biological medicine with minor variability within the acceptable range resulting in differences negatively affecting clinical efficacy and safety [1]. The scientific principle of comparability is also applied for the approval of biosimilars.

A biosimilar is a biological medicine containing a version of the active substance of an already approved biological medicine (reference product). Biosimilarity is established based on the totality of evidence from physicochemical, structural and functional tests, as well as from clinical studies (comparability exercise) [8, 9]. The scientific principles used are the same as those applied to demonstrate comparability after a change in the manufacturing process of an already licensed biological medicine [8, 9]. The designation 'highly similar' marks the acceptable range for minor variability in biosimilars in the same way it does for every post-change batch of a reference product.

The first biosimilar in the European Union (EU) was approved in 2006. Over 10 years of clinical experience with biosimilars have not revealed any clinically meaningful differences between biosimilars and reference products in terms of clinical efficacy and the type, severity and incidence of side effects. In August 2017, there were 35 approved biosimilars in the EU and 24 of them are already available in Germany [10].

Drug Commission's perspective: FAQs about biosimilars

1. Are there any differences between biosimilars and reference products with regard to quality, efficacy and safety?

Biosimilars are developed and approved in the EU according to scientifically sound principles and carefully monitored to ensure their pharmaceutical quality. The strict requirements for establishing biosimilarity are the same as those applied for demonstrating comparability after a change in the manufacturing process of already approved biological medicines. As the therapeutic efficacy and safety of biosimilars are comparable to the therapeutic efficacy and safety of their reference products, biosimilars offer a safe and efficacious alternative to originator biologicals. Functionally irrelevant differences (minor variability) are not higher within biosimilars than they are within different batches of reference products. Over 10 years after the approval of the first biosimilar in the EU, no important differences between biosimilars and reference products have been demonstrated.

2. Should biosimilars, when available, be given to treatment-naïve patients?

Biosimilars and reference products are therapeutically comparable. Biosimilars can be prescribed with consideration of the approved indications, the availability of an adequate monodose formulation to avoid costs associated with drug disposal and the availability of suitable pharmaceutical preparations (pre-filled pens or syringes or powder for solution for injection).

3. Should patients already treated with a biological medicine be switched to a biosimilar, when available?

With regard to switching between reference products and biosimilars, the Drug Commission adheres to its opinion from 2008. Switching is possible when followed by adequate clinical

monitoring. The same clinical aspects taken into account for treatment-naïve patients should also be considered before switching. All switch studies have confirmed the therapeutic equivalence of biosimilars and reference medicines [11].

4. Should biosimilars be used in approved indications for which no clinical studies have been conducted?

The pivotal studies with biosimilars do not aim to establish the clinical efficacy of the active substance per se, as this has already been done for the reference product. Clinical studies are carried out to examine the biosimilar product and to ensure that there are no clinically meaningful differences between the biosimilar and the reference product which negatively affect efficacy, safety and immunogenicity. For this purpose, an indication of the reference product is chosen, which is most suitable for detecting any differences in therapeutic effect. The scientific principles of data extrapolation used for biosimilars approval are not a special arrangement for biosimilars, as extrapolation occurs also with other regulatory procedures as, e.g. when establishing line extensions. The comparability exercise used to evaluate the biosimilarity of a biological investigational medicinal product (IMP) is the same as that applied to establish comparability following changes in the manufacturing process of all biological medicines. Therefore, biosimilars can be considered therapeutically comparable to their reference products in all approved indications [9].

5. What should be taken into consideration when monitoring therapy with biosimilars?

There are basically no differences between the pharmacovigilance of biosimilars and their reference products. Spontaneous reporting of suspected side effects is crucial for the monitoring of the medicines' safety. As biologicals are highly complex drugs manufactured in living cells resulting in a minor degree of variability, traceability is an important issue for both reference medicines and for biosimilars. If patients treated with biological medicines, regardless of whether they are originator biologicals or biosimilars, experience side effects, the brand name and batch number should be reported to guarantee the traceability of the product in the case of safety issues.

6. What should German statutory health insurance (SHI)-contracted physicians consider when prescribing biosimilars?

Twenty-four biosimilars are already available in Germany and can be prescribed by SHI-contracted physicians. Biosimilars are usually cheaper than reference products. It has already been shown that the availability of biosimilars strengthens economic competition in the pharmaceutical market and provides opportunities for cost reduction [12, 13]. This supports the financial sustainability of the national solidarity-based health insurance system in Germany. The prescribing of any given medicine in Germany must adhere to the efficiency principle based on § 12 SGB V (Social Code V, § 12). This also applies when prescribing biosimilars. In order to increase the uptake of biosimilars, regional target agreements were concluded. Regional biosimilar prescription quotas should assist German physicians to improve prescribing efficiency.

7. How could patients be involved when prescribing biosimilars?

A major point to consider when prescribing biosimilars or switching between reference medicines and biosimilars should

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be to ensure that the patients are well-informed. This is supported by independent publications, e.g. by the European Medicines Agency (EMA) or the European Commission [6]. To ensure patients' adherence to therapy, it is crucial to respect and to address any fears and concerns they may have. Following the recommendations in this guidance will help to improve access to biological therapy and reduce costs. The decision to use biosimilars in treatment must be made by a physician. From the Drug Commission's perspective, the use of biosimilars requires detailed patient information and consultation in addition to the consideration of approved indications, availability of an adequate mono-dose formulation and suitable pharmaceutical preparations. In light of the fact that a non-medical switch or an automatic substitution (which is not permitted in Germany) could not satisfactorily fulfil these requirements, the Drug Commission strongly rejects this procedure.

The future: perspectives and challenges

The mission of the Drug Commission is to provide physicians with independent, scientific information about medicines. By emphasizing the relevance of biosimilars for the sustainability of the healthcare system, the Drug Commission aims to assure German physicians of the benefits of biosimilars.

Biosimilars offer a safe and efficacious therapeutic alternative to originator biologicals. There is plenty of evidence supporting the use of biosimilars in clinical practice and there are no grounds to believe that the use of biosimilars carries more risk than the use of reference biologicals. To date, no data have been published revealing any disadvantages of biosimilars either when starting therapy or when switching patients from reference medicine to a biosimilar. Switch studies have not indicated any reasons for physicians not to prescribe biosimilars.

Biosimilars approved in the EU and used for years have proven to be safe and efficacious. Bridging the information gap on biosimilars should minimize unfounded fears and concerns among clinicians to assist them in making evidence-based, appropriate and cost-effective treatment choices for their patients. As healthcare costs are constantly rising in Germany, biosimilars offer an opportunity to reduce costs without compromising the right of German patients to efficacious and safe medicines in a national solidarity-based health insurance system. Assisting physicians to get acquainted with biosimilars could effectively and consistently deliver the best health care for patients while retaining physicians' freedom to prescribe.

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