

## **Biosimilars – Position Paper**

**Updating position statement from the European League Against Rheumatism (EULAR) Standing Committee of People with Arthritis/Rheumatism in Europe (PARE)  
August 2018**

**EULAR PARE (People with Arthritis/Rheumatism in Europe) published a position paper “Biosimilars – what do patients need to consider” in RMD Open in November 2015. Since then, more biosimilars for rheumatic diseases have been approved by the European Medicine Agency (EMA) and have entered the market in several European countries. New studies and data regarding the use of biosimilars, as well as feedback received from patient organisations and in particular from PARE organisations, indicate a need to update EULAR PARE’s 2015 position paper.**

PARE considers it desirable that safe and effective therapies are available for all people with rheumatic diseases. Those patients with rheumatic diseases for whom a treatment with biotechnological drugs means an additional health benefit, and which improves their quality of life, must be given the opportunity to have access to these drugs. We are aware of the fact that biological therapies are significant cost factors for the healthcare system and that biological therapies have to be affordable, what is seen as difficult in various countries. But optimal quality healthcare is enormously important for the individual patient (e.g. fewer sick days, less hospitalisation, less disabilities), prevents early retirement and thus saves costs and contributes to a country’s economic and social system.

***For all regulatory decisions on biosimilars the health and safety of patients must be paramount for regulatory authorities, policy makers and healthcare providers and must always take precedence over pricing policy considerations.***

### **1. What is a biosimilar?**

By biosimilar we mean, as defined by EMA and the World Health Organisation (WHO), a biologic that is a similar copy of an already authorised biotechnological drug. A biosimilar has demonstrated in pre-clinical and clinical studies similarity to the original product (often referred to as a reference product or original biologic) in quality, biological activity, safety and efficacy. The similarity should, if at all, be associated with very small deviations between biosimilar and original product that have no clinical relevance.

***Biosimilars are similar but not identical to the original product.***

### **2. Variability of biologics**

The production of biologics (originals and biosimilars) requires living cells or organisms. In the case of biologics, not only the chemical composition is important, but also the three-dimensional folding of the structure and the assembly of several molecules are relevant for the mode of action. In addition, after assembly of the molecule (i.e. the precursor of the biological drug) by the living cell, the molecule is subject to chemical modifications. These so-called post-translational modifications can significantly alter the properties of the biologic and differ depending on the cell type / organism that makes the molecules. Immunogenicity, that is, the ability of a substance to trigger an immune response in the human body, is inherent in all biologics.

The developers of biosimilars usually have no access to the development data of the original manufacturers. The manufacturing process needs to be reinvented by biosimilar manufacturers. This may result in the use of other cell types or organisms for the manufacturer of a biosimilar, or the separation and purification processes may be different. Biosimilars therefore cannot be identical to the original product.

Even if it has been shown in pre-clinical studies that the **mode of action** is the same, this does not mean that the efficacy and the side-effect profile of the biosimilar match the original product. Therefore, additional studies are mandatory before market approval.

***To confirm the safety of biosimilars, patients wish to have more studies after market approval by EMA.***

### **3. Regulatory pathways / organisations**

Appropriate marketing authorisation for biologics (including biosimilars) is mandatory in the European Union (EU) and regulated centrally by the EMA.

Manufacturers must demonstrate in direct comparative studies that their biosimilar product is equivalent with the original product in terms of quality, safety and efficacy. This requires extensive comparative tests and studies. The EMA regulations state that when deciding on the scope of studies, it is necessary to weigh unnecessary and sufficient studies and that this must be decided on a case-by-case basis for each biotechnologically manufactured product.

The approval of each biosimilar must give a coherent justification as to why the indication in question makes use of **extrapolation** instead of carrying out a comparative study in each case.

### **4. Transferability of study data to other indications (extrapolation)**

The concept of extrapolation means that the results of clinical studies, investigating a certain biosimilar, in one indication can be transferred to another indication, where only the original product was investigated, without performing additional clinical studies with the biosimilar in the other indication due to the similarity of the biosimilar and the original product. But, biosimilars may differ slightly compared to the original product (bio-originator); there are theoretical concerns that these differences may impact on efficacy or safety in certain indications, which are not predictable under the principle of extrapolation. Extrapolation is particularly critical to PARE if a given biosimilar has only been clinically tested in a non-rheumatic indication (e.g. inflammatory bowel disease). In order to address the concerns of extrapolation in other areas in general, the EMA has developed relevant informative criteria.

So far, there is limited experience with biosimilars in extrapolated indications. Therefore, PARE is cautious of the use of biosimilars in extrapolated indications, as disease processes of rheumatic diseases are complex and often not fully understood. Accordingly, patient organisations are deeply concerned and encourage EMA to mandate more studies.

Several prior studies suggest that extrapolation is a procedure that can be reasonably applied without undue expense of patient safety (based on the efficacy and safety of biosimilars). An international working group of 25 members (including patient representatives) came to the same conclusion.

***At this time, PARE takes a conservative position and is of the opinion that further double-blinded, randomised controlled studies with a sufficient number of participants are necessary in order to substantiate the extrapolation procedure, especially when extrapolating from a non-rheumatic to a rheumatic indication.***

***Indications that have not been tested in the context of the approval of a biosimilar, but have been licensed by extrapolation, should be indicated in the package leaflet.***

### **5. Labelling of biosimilars**

Biosimilars must have an active substance clearly distinguishable from the original product and competing biosimilars, so that it is clear to patients, doctors and pharmacists, which product the patient is receiving.

Until now, manufacturers of biosimilars have had the option of applying to WHO for a new International Nonproprietary Name (INN), i.e. the name of the active substance, or to adopt the INN of the active substance of the original product. If the same INN is adopted, it may be impossible to distinguish between biosimilar and original product. This is a matter of concern to PARE.

The INN assigned must be clear and distinguishable so that the prescribing practitioner/rheumatologist can clearly communicate to the pharmacist which product he has prescribed. Only in this way can confusion be avoided. The unique INN of the active substance is also of particular importance in the case of undesirable side effects in order to clearly identify the corresponding causative product.

Thus all biological products should be identifiable and traceable. This counts for original products as well as for biosimilars.

***In order to be able to assign side effects it is essential that the INN, the name of the manufacturer, the name of the product (tradenname) and batch number are available. The INNs of the biosimilars must be clearly assignable.***

## **6. Monitoring of biosimilars**

The inclusion of biosimilars in registries makes it possible to trace unwanted side effects directly, but also to facilitate a clear distinction regarding safety and efficacy between various biosimilars.

There are however not yet registries available for all diagnoses nor are such facilities available in all countries. Close monitoring after marketing authorisation, which will specifically include the name of the active substance, the name of the product and the batch number, must be mandatory for all biosimilars (and original products) in all indications in order to detect undesired side effects at an early stage. Especially for indications for which the biosimilar has been approved by extrapolation, very close monitoring after market approval must be carried out in order to immediately detect any side effects. In order to record rare side effects or side effects of long-term therapy, international networking of independent registries is useful.

***Close monitoring of the effects and especially of the side effects of all biosimilars and original products in registries must also be ensured after market authorisation.***

## **7. Start of a therapy with a biological DMARD (original product / biosimilar)**

Generics are often 30-50% cheaper than the original product. However, biosimilars exemplify specific manufacturing process issues and therefore cannot be directly compared to generics; neither in their production (similar – not identical), testing or interchangeability and most likely therefore, also not in their price reduction (compared to the respective original).

Nevertheless, in most countries biosimilars offer more cost-effective access to biologic therapy. This probably leads to a situation – depending on the country's health system – whereby more patients can benefit from biologics.

Previous studies have shown that biosimilars and originator products are comparable in terms of efficacy and safety, and it is appropriate that 'therapy-naïve' patients can start treatment with a biosimilar. However, when starting a therapy the individual characteristics of the patient and the current state of research must be taken into account with regard to efficacy and patient safety.

***If so-called 'naïve' patients (patients who have not taken a biologic so far) should take a biologic, the less expensive biologic (either originator or biosimilar) can be used – as long as there are no***

***contraindications, the patient has been informed and the decision is based on a shared decision between rheumatologist and patient.***

PARE has a critical oversight of the prescription of biosimilars, including if the biosimilar has not been clinically tested for a specific indication but has been approved only by extrapolation. Although the results so far suggest the safety of the principle of extrapolation, the routine use of biosimilars in such indications should, if possible, only occur when studies have shown that the effect and safety profile for this particular indication are indistinguishable from the original product.

***The prescription in extrapolated indications requires the patient's agreement and close monitoring by the doctor.***

## **8. Switching from an original product to a biosimilar**

In almost 30 studies of various indications, the one-time switch of therapy (also referred to as 'switch' or transition) from the respective original product to its biosimilar (Flixabi®, Inflectra® / Remsima®, Benepali®) has been investigated.

***Overall, studies suggest that the one-time switch of therapy from the respective original product to its biosimilar has no effect on efficacy and safety.***

The one-time switch of therapy may be medically necessary. The doctor may however also consider the change of therapy for cost reasons in terms of lowering costs for the respective country's health system. If patients are already undergoing treatment with a biologic and considering a change from an original product to a biosimilar for one of the two reasons, the current situation of efficacy and safety of a drug change must be taken into account when deciding whether or not to change the patient's therapy. In addition, the individual situation of the patient must be taken into account when deciding on the biologic. The safety of the patient must be the first priority in the decision. The patient must be informed and have agreed to the switch based on a shared decision-making process.

***No patient should be switched from an original product to a biosimilar against the patient's decision just to reduce costs-. A switch should always be based on a shared decision between patient and doctor.***

## **9. Relevance of pharmaceutical form of application**

The available pharmaceutical dosage forms of a biosimilar may differ from the original product. The profile and the needs of the patient must be taken into account. Before a switch of therapy, the patient must be made familiar with a possibly different dosage form in order to avoid medication errors. A change in the dosage form (for example, from an injection to infusion) can also mean a loss of independence and cause logistical problems for those affected.

***The patient must agree to both, the biosimilar drug and the pharmaceutical dosage form.***

## **10. Single switch between biosimilars ('cross-switching')**

Each biosimilar comprises its own medicinal product whose similarity in the approval process has been demonstrated only in comparison to the original product. So far, there are no studies investigating the safety and efficacy of a therapy switch from one biosimilar to another biosimilar ('cross-switching'). In addition, results

from studies investigating the switch from the original product to its biosimilar are neither transferable to other biologics nor to other biosimilars of the same original product.

***As long as no studies exist, a switch between different biosimilars is not recommended.***

#### **11. Multiple therapy switches between original product and biosimilars ("repetitive switch", "reverse switch", "multiple switching")**

Due to their chemical nature, biologics may have immunogenic potential. Switching therapy may trigger the formation of antibodies. Every change of therapy theoretically represents a new risk for antibody formation, especially due to other accompanying substances (including formulary excipients) and other chemical residues from the manufacturing process. Thus, immunogenicity may affect the safety and probably the efficacy of the biologics.

So far, there are no studies that have investigated multiple switches of therapy from an original product to its biosimilar (and back again). To clarify this question, a systematic recording of the prescribed biologics in registries including long-term analyses of these registries is necessary.

***Due to concerns regarding the immunogenicity of biologics, multiple, medically unnecessary therapy changes should not be performed unless study data is available.***

#### **12 Interchangeability in the context of discount agreements in pharmacies (Pharmacy-led substitution)**

While the market authorisation of biosimilars is centrally regulated at the EU level through the EMA, decisions on whether biosimilars and original products can be exchanged or substituted are regulated at the individual country level.

Original products and biosimilars should not be interchangeable with each other in pharmacies, as this may lead to a lack of transparency and close monitoring of biosimilars. It is not acceptable that a patient is given a biosimilar by telling him that only the name of the product has changed. Doctors should always be involved if a biologic is exchanged for another one.

The aspect of interchangeability also applies to biosimilars which come from different development and production lines, as for them only a similarity and no equality can be assumed.

***Original products and biosimilars should not be interchangeable with each other in pharmacies. The exchange of biologics is only considered to be without problems if it is the same product in a different wrapping (so-called "bioidenticals" – see glossary).***

## Glossary:

**Bioidenticals:** These are biotechnologically produced medicinal products from a manufacturing process that runs under identical conditions. However, bioidenticals are being marketed by different license holders under different trade names. In September 2013, the EMA approved two identical biosimilars (bioidenticals) for the active ingredient infliximab: Remsima® and Inflectra®. In this case, the manufacturer produces a biosimilar and has granted distribution rights to two different companies. Remsima® and Inflectra® are interchangeable in the pharmacy.

**Biobetters or biosuperiors:** These are replicas of other biologicals (second-generation biologics) that have been structurally and / or functionally modified with the aim of improving clinical efficacy or reducing side effects. These biologics usually go through the entire development and approval cycles.

**Biomimics:** These are **Intended Copies** of already licensed biologicals that have not undergone the approval process for biosimilars that comply with EMA regulations. Biomimics are sometimes referred to as biosimilars and are approved, for example, for rheumatoid arthritis in countries in South America as well as China and comply with the local regulations of the authorities. They do not meet the EMA standards.

**DMARD:** Disease modifying anti-rheumatic drug.

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