

## Biosimilars- Frequently Asked Questions

### 1. What is a biologic?

A biological medicine (commonly referred to as a “biologic” or “biopharmaceutical”) is a medicinal product made by or from living organisms, tissues, or cells and contains a biological active substance.<sup>1</sup> Most biological medicines in clinical use contain active substances made of proteins, they are often large, complex molecules. Common biologics, such as monoclonal antibodies, are typically 1000 times heavier than a small molecule such as ibuprofen<sup>2</sup>. Because of this complexity, their manufacture can only be done in living cells, not through chemical synthesis like most small molecules. Accordingly, they are difficult to make, and difficult to copy with EU legislation stipulating strict manufacturing requirements.

### 2. What is a biosimilar?

Medicines in Europe are regulated and approved by the European Medicines Agency (EMA). “Biosimilar” is a term that the EMA uses to designate that a medicine has been certified for use by a particular approval route. The correct use of this term is only with reference to biologics that have been approved in highly regulated markets, such as Europe, the United States, Australia, Canada or Japan, and that meet strict criteria of quality and comparability to their respective reference biologics.<sup>3-14</sup>

A biosimilar is a medicine highly similar to another biological medicine already marketed in the EU (the so-called ‘reference medicine’). Approved biosimilar medicines can only be marketed once the period of market protection (patent) of the reference medicine expires.

To be approved by this route the EMA defines a biosimilar as “a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)”.<sup>3</sup> The EMA lists the following specific features of a biosimilar medicine<sup>15</sup>

- **Highly similar to the reference medicine**

The biosimilar has physical, chemical and biological properties very similar to the reference medicine. There may be minor differences from the reference medicine which are not clinically meaningful in terms of safety or efficacy. A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise.

- **No clinically meaningful differences compared with the reference medicine**

No differences are expected in clinical performance. Clinical studies that support the approval of a biosimilar confirm that any difference will not have an effect on safety and efficacy.

- **Variability of biosimilar and reference medicine kept within strict limits**

Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as allowed between batches of the reference medicine. This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.<sup>16, 17, 18, 19</sup>

- **Same strict standards of quality, safety and efficacy**

Biosimilars are approved according to the same strict standards of quality, safety and efficacy as for any other medicine. By definition, biosimilars are required to have an identical amino acid sequence, the same route of administration and strength as the reference medicine.

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The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability.

### 3. What is a biomimic?

Biomimics, also called “non-comparable biologics”, “biocopies”, “intended copies”, or “non-regulated copies”, are copies of biological reference medicines that do not meet the strict regulatory requirements for biosimilar approval, such as those set up by the WHO, EMA or FDA, but are being marketed in some countries. These compounds do not fulfil the definition of a biosimilar.<sup>3-7</sup>

### 4. How are biosimilars developed?

The development of biosimilars is a systematic process with two key stages. The first stage consists of the thorough characterisation and understanding of the reference medicine (the “target”) which forms the basis of the target-directed development of a biosimilar. The second stage establishes biosimilarity between the proposed biosimilar and the reference medicine in a stepwise approach, the so-called comparability exercise.

### 5. Why isn't a biosimilar a generic medicine?

A biosimilar is not regarded as a generic of a biological medicine because the natural variability and more complex manufacturing of biologics do not allow an exact replication of the molecule. More studies are required for a biosimilar to be approved than for a generic medicine. For example; quality studies comparing the structure and biological activity of the biosimilar with the reference medicine, demonstration of biosimilarity using comprehensive comparability studies and clinical data in a sensitive indication. Owing to their complexity and rigorous scientific evaluation, biosimilars are much more costly and take longer to develop than traditional generic medicines – taking up to 8 years and upwards of \$300million vs. \$3million in investment to develop<sup>20</sup>.

### 6. How are biosimilars approved?

The EMA will approve a proposed biosimilar only if they are convinced that the presented “totality of evidence” is both substantial and sensitive enough to demonstrate that the biosimilar matches the reference medicine and that there are no clinically meaningful differences in terms of purity/quality, efficacy/potency and safety<sup>3,4</sup> “Totality of evidence” is a term used to describe the results of the entire development program for a biosimilar and involved data from analytical, preclinical and clinical studies. The non-clinical and clinical data needed to approve a biosimilar are different from those needed for a biological medicine with a new active substance. The biosimilar relies on the safety and efficacy experience gained with the reference medicine.

This is achieved with comprehensive comparability studies and pharmaceutical quality data. Comparability is a well-established scientific principle of regulatory science used after manufacturing changes to biologic medicines during their commercial life. Comparative trials are designed to confirm biosimilarity and clinical performance; they do not need to repeat all the pivotal studies to the reference medicine to prove safety and efficacy in humans but are designed to rule out clinically relevant differences in safety or efficacy between the biosimilar and the reference medicine and to confirm biosimilarity.

### 7. What is extrapolation?

Extrapolation is the scientific and regulatory process of granting a clinical indication to a medicine without conducting a clinical efficacy and safety study to support that indication.<sup>9</sup> Extrapolation is a well-established principle that is applied to all biologic medicines, reference or biosimilar, if they undergo a major change in their manufacturing or a change in formulation. To confirm the biologic remains as safe and effective after the change, clinical data may be required by the regulatory authority. These are

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typically generated in one indication and then, taking into account the overall information gained from the comparability exercise, extrapolated to the other indications.<sup>9</sup>

This process is also applied to biosimilars in their licensing. After a full characterisation of the molecule in both *in vitro* and pre-clinical settings, where it must be proven to be equivalent to the reference medicine, clinical trials are conducted to confirm the analytical work already completed. The clinical trial populations are carefully chosen and confirmed with the regulatory agencies in order to demonstrate the critical attributes of the biosimilar molecule are equivalent to the reference medicine. Since the aim of these studies is to confirm comparability of the molecules and not to prove that the biosimilar works in every disease state, as this has already been demonstrated by the reference medicine, the number of studies that are required is less and the data can be extrapolated to indications not studied.

## 8. Can biosimilars be used with the same confidence as the reference medicine?

Yes. Authorised biosimilars are as safe, and efficacious as their reference medicines.<sup>11</sup> Safety monitoring of biosimilars follows the same requirements that apply to all biological medicines<sup>21</sup> for example collecting spontaneous ADRs and submitting PSURs and as with all new biological medicines additional monitoring is in place indicated by the black triangle.

The European commission (EC) has expressed its confidence in the quality of biosimilars. Their 2013 consensus document “What you need to know about biosimilars” states that “biosimilar medicinal products have been used safely in clinical practice in the European Union since 2006”.<sup>18</sup> Over the last 10 years the EU monitoring system for safety concerns has not identified any relevant differences in the nature, severity or frequency of adverse effects between biosimilar medicines and the reference medicines over 400 million patient days of experience<sup>22</sup>.

## 9. Why aren't biosimilars 100% identical with their reference medicine?

All biologics, be it the biologic reference medicine or the biosimilar, are made by living organisms which are naturally variable and so have a certain inherent degree of minor variability of the biologic system (“microheterogeneity”). This minor variability must fall within the acceptable range to ensure safety and efficacy during the manufacturing process.

Because of microheterogeneity, two biologics produced in isolation of one another cannot be identical, not even two batches of any biologic - reference medicine or biosimilar - are formally 100% identical.<sup>15,16</sup> This may happen because the manufacturing processes are modified during the commercial life of the biologic medicines but importantly, this inherent variability can be detected using sensitive analytical tools and is tightly controlled during the manufacturing process, with limits and specifications agreed with the regulatory authorities to ensure the consistent safety and efficacy of the biologic and the biosimilar.

## 10. Is the immunogenicity of biosimilars different from the reference medicine?

No. Immunogenicity, the ability of particular substance to provoke an immune response, must be equivalent.<sup>23</sup> A biosimilar will not be approved if there are any doubts that the immunogenicity is not comparable to the reference medicine, as a biosimilar must be equivalent in terms of safety.<sup>4, 10, 24, 25</sup>

Many biological medicines are intended for long term management of chronic conditions and difference biologicals with slight differences may be used over time. A harmful immune response is unlikely after a manufacturing process change because comparability studies prove that the batch from the new process is of the same quality and free of impurities or aggregates that can trigger immunogenicity. Similarly, harmful immunogenicity is unlikely after switching between biologicals<sup>26</sup>

## 11. Are biosimilars less effective because they are cheaper?

No, biosimilars must be just as effective as their respective reference medicines.<sup>11</sup> They are less expensive than the reference biological because they benefit from a tailored clinical development and the option for extrapolation of indications. Therefore, biosimilars have a less cost-intensive overall development programme.<sup>17</sup> This is the main reason they can be marketed at a lower price.

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## 12. Why are biosimilars prescribed by brand name?

It is important for traceability that all biological medicines, including biosimilars, can be identified by trade name (brand name) and batch number. This is particularly important in cases where more than one medicine exists on the market with the same INN. In line with EU requirements for ADR reporting, this ensures that any biological medicine can be identified, if any product specific safety concern arises.

## 13. What is switching?

Switching is the decision of the treating physician to exchange one medicine for another medicine, with the same therapeutic intent, in patients who are undergoing treatment.<sup>18</sup> For example, transitioning the patient from the reference medicine to the biosimilar.

Switching is a vernacular term that is not defined in law or regulations. In the UK any decision to transition a patient from one biological medicine to another, including a biosimilar (or vice versa) should involve the prescriber in consultation with the patient.

## 14. Is switching of patients who are treated with a reference medicine to a biosimilar medicine (and vice versa) safe?

No medicine can be considered as safe. Biosimilars are developed to be highly similar to their respective reference products and are approved only if they are proven to be as safe and as effective as the reference molecule. They must have no clinically meaningful differences in terms of safety, efficacy or quality. Under guidance of a physician; a treating physician is the best suited individual to make this decision, patients treated with a reference product can be safely transitioned to a biosimilar. Based on the currently available data, switching between a biosimilar and its reference biologic does not appear to impact efficacy/safety, immunogenicity or traceability in case of an adverse event. Traceability pertains to whether the adverse event has been caused by the reference medicine or the biosimilar.<sup>27-40</sup> Transitioning patients should involve the prescriber in consultation with the patient.

## 15. What is interchangeability?

From a regulatory perspective, different definitions and requirements for interchangeability apply across geographies. In the EU, interchangeability describes the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.<sup>18</sup> In the EU, the regulation of interchangeability is governed by the individual EU Member States.

## 16. What is substitution?

For any medicine, including biosimilars, there are two different types of substitution that can occur: automatic substitution and substitution. Automatic substitution is the practice of dispensing one medicine, instead of another equivalent and interchangeable medicine, at the pharmacy level without consulting the prescriber.<sup>41</sup> Substitution is the practice of dispensing one medicine, instead of another equivalent and interchangeable, with consultation of the prescriber. In Europe, the EMA has left the decision of automatic substitution and substitution to the decision of individual member states. In the UK automatic substitution of biological medicines, including biosimilars, is not permitted. Prescribing by brand name reduces the risk of one biologic brand being automatically substituted by the pharmacy for another, without a review and due consideration by the prescribing clinician.

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