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European Medicines Agency

Q&A on the Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU

Following the publication of the joint EMA-HMA statement on interchangeability of biosimilar medicinal products approved in the EU, both EMA and National Competent Authorities (NCAs) have received questions for clarification from healthcare professionals and other members of the public. This questions and answers (Q&A) document addresses follow-up questions received after publication of the statement.

Question 1. *Does the interchangeability of biosimilars also cover situations where multiple switches are taking place – independent of frequency of switches and number of products involved?*

Answer 1. Yes, if all switches are taking place within the group of products that have the same reference product, including switches between the reference product and its biosimilars. The comprehensive comparability exercise required for establishing biosimilarity makes differences in efficacy and safety highly unlikely. The practice of using biosimilars interchangeably is already taking place in many EU Member States without any signs of differences in efficacy or safety for the patients. For instance, hospital use of a biological product may depend on which product is the winner of a tender process which typically lasts for specific period (e.g., one year), thus a biological product can change from time to time (e.g. annually).

The interchangeability statement relates to the active substance and does not cover potential issues related to the handling of different administration devices (e.g. the need for patient training when using a new device).

As for any biological medicinal product, traceability should also be ensured for biosimilars to allow for proper root cause analyses in case adverse drug reactions (ADRs) occur.

Question 2*. Does interchangeability – including the possibility for multiple switches, as discussed in Question 1 – apply to all biosimilars, e.g. also those with a more complex molecular structure?*

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Answer 2. Yes, the EU regulatory and scientific requirements for establishing biosimilarity are tailored to meet the challenges posed by differences in molecular complexities, thereby allowing for interchangeability of all EU-approved biosimilars.

Question 3. *Does the joint EMA-HMA statement on interchangeability of biosimilars mean that switching to or between biosimilars is allowed in my country?*

Answer 3. No, EMA does not regulate prescribing practices or issue clinical guidance; these matters fall under the remit of, and are issued by, the relevant bodies in each Member State. The statement on interchangeability of biosimilars is a general statement on the scientific principle highlighting that biosimilars can be used interchangeably and detailing the scientific references supporting this position. The statement is meant to support Member States that want to allow for biosimilar prescribing, including any national decision on switching done by the prescriber and/or (automatic) substitution at pharmacy level without consulting the prescriber. However, each Member State will decide on how this is applied in their territory, e.g. which biological medicines are available for prescribing in their country and whether automatic substitution with biosimilars is allowed at pharmacy level.

Question 4. *Does the statement of interchangeability apply to biosimilars that do not have all the indications of the reference or another biosimilar medicine?*

Answer 4. Yes, provided each medicine is used according to its approved conditions of use, as reflected in the EU product information. Any use of a medicine beyond its authorised indication and conditions of use is not regulated by medicine licensing authorities including EMA, and such use remains a matter of clinical judgment and expertise of the prescriber.
The reverse situation is also possible, i.e., that biosimilars are developed for new indications that have not been approved for the reference product. In this case, it is also important to follow the recommendations of use reflected in the EU product information.

Question 5. *Does the statement of interchangeability apply even if the biosimilar does not have exactly the same conditions of use as the reference or another biosimilar medicine with the same therapeutic intent?*

Answer 5. Yes, provided each medicine is still used according to its approved conditions of use, as reflected in the EU product information. There may be differences between the biosimilar and the reference medicine (e.g., differences in excipients) and these may lead to different conditions of use (such as differences in contraindications or precautions for use). Any use of a medicine beyond its authorised indication and conditions of use is not regulated by medicine licensing authorities including EMA, and such use remains a matter of clinical judgment and expertise of the prescriber.

Question 6. *How can we be sure that medicines are still interchangeable after changes in the marketing authorisation, such as manufacturing changes, have taken place?*

Answer 6. Post-authorisation changes in the manufacturing process may occur for both reference products and biosimilars. These changes need to be authorised by the authorities and are rigorously assessed. To obtain approval of such change, the developers of biological medicines are required to demonstrate through comprehensive comparability studies that manufacturing changes for any biological product (both reference biologics and biosimilars) are made in line with the EU pharmaceutical legislation and according to the recommendations reflected in the ICH Q5E guideline. This ensures manufacturing consistency and is a safeguard against changes in efficacy and safety.