Biosimilarity and Comparability after Manufacturing changes: Can a biologic become a biosimilar of itself?

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Executive Summary

Biological medicines are derived from living organisms. Manufacturing changes can therefore have an impact on the properties of the biological medicine. This has led to questions whether a biological medicine that has undergone manufacturing changes was still the same product as the one used in the original clinical trials – or in other words: whether the respective medicine would have become a biosimilar to itself. The regulatory basis for the assessment of a post-approval manufacturing change and for demonstration of biosimilarity is different; for the former the process is well known and extensive data is available, whereas a manufacturer of a biosimilar product will not have knowledge of the manufacturing process of the reference product hence not be able to refer to as much historical data, particularly clinical . Therefore, calling a biological medicine 'a biosimilar of itself' confuses the concepts of manufacturing change and biosimilarity and bears the risk to undermine trust in biological medicines and their use.

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1. Issue

The statement that a "biological product could become a biosimilar of itself" alludes to the fact of so-called "variability over time", "intra-product variability" or "batch-to-batch variability". This is a characteristic of all biologics, originators and biosimilars, and is "kept within pre-specified limits".[1] Schneider pointed this out a few years ago: "One would have to add that also no batch of any reference product is 'identical' to the previous one – 'non-identicality' is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability)."[2] The inherent variability of biological medicines is because they are derived from living organisms e.g. cells which are susceptible to many external influences including manufacturing changes.

Due to inherent variability it has sometimes led to questions whether a biological medicine that has been on the market for some years is still the same as the one used in the original clinical trials used to support approval.[3] From a legal and a regulatory perspective the claim of "a biosimilar of itself" is not correct and is misleading: "Biosimilarity" is the regulatory term used in the European Union to denote the comparability between a biosimilar and its reference medicinal product at a given time point.[4] Biosimilars are new products[5] and have a specific, pre-defined regulatory pathway and undergo an "extensive comparability exercise" to gain marketing authorization.

The demonstration of biosimilarity is different from a comparability exercise undertaken after a manufacturing change. The former assesses "*inter*-product" differences while the latter does so with regard to "*intra*-product" differences.[6] Both, originator biologics and biosimilar medicines have "intra-product" variability which must be monitored and controlled. Biological medicines have many quality attributes and because they are derived from living organisms, e.g. animal-derived cell lines, and purified by complex manufacturing processes, there will inevitably be some inherent variability. However, the combined variability of the product and the process is controlled within approved ranges. The "inter-product" comparison however, applies only to two different products, i.e. products that are developed as intended versions of the reference product, which after approval are termed "biosimilars". This EBE statement wants to shed light on the different concepts important in this context such as "manufacturing change", "comparability" and "biosimilarity".

2. Considerations

What are manufacturing changes?

Different degrees of changes. Any modifications to any biological product – the originator or the biosimilar – based on manufacturing changes are subject to tight regulatory controls and limits. Some

[1] Kurki P, Ekman N (2015), Biosimilar regulation in the EU; Expert Rev Clin Pharmacol 8(5):649-659. Because biological medicines, including biosimilars, are derived from living organisms and produced using complex manufacturing processes, there is intrinsic variability from batch to batch. This variation is kept within strict, acceptable limits, which are monitored by the manufacturer and reported to the regulator, known as "release specifications".
[2] Schneider CK (2013), Biosimilars in rheumatology: the wind of change; Ann Rheum Dis 2013 72: 315-318
[3] National Health Service (NHS) (2015), Answers to commonly asked questions about biosimilar versions of infliximab; http://www.medicinesresources.nhs.uk/en/Communities/NHS/SPS-E-and-SE-England/LNDG/London-Wide-Reviews/Answers-to-commonly-asked-questions-about-biosimilar-versions-of-infliximab/ (accessed: 04/08/2015)
[4] European Commission (2013), What you need to know about Biosimilar Medicinal Products; http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native (accessed: 18/08/2015)
[5] EMA (2014), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1); 22 May 2014; CHMP/BWP/247713/2012, p. 3: "As outlined in the Guideline on similar biological medicinal products, a company may choose to develop a new biological medicinal product claimed to be similar (similar biological medicinal product) in terms of Quality, Safety and Efficacy to a reference medicinal product, which has been granted a marketing authorisation on the basis of a complete dossier in the Community."
[6] Kurki P, Ekman N (2015), Biosimilar regulation in the EU; Expert Rev Clin Pharmacol 8(5):649-659.

products have undergone more than 30 manufacturing changes.[7] However, as pointed out in the literature such changes in manufacturing can be seemingly small and range to major ones. Because of the very nature of biological medicines "even small changes can have a large impact. But this would certainly be picked up in the comparability exercise and regulatory assessment, and via implementation of correct regulatory measures for post-approval surveillance."[8]

The different degrees of manufacturing changes lead also to different degrees of the requirements of the comparability exercise. It is informed by a "comprehensive risk assessment that considers knowledge of the existing product, scope of the process change, potential impact of the process change, and limitations of analytical methods to detect potentially relevant changes in the product."[9]

Manufacturing changes are sometimes a requirement. Most manufacturing changes made to biological medicines are smaller types of changes which require only analytical data and process studies accordingly. In addition, in order to comply with current Good Manufacturing Practices (GMP), manufacturers are expected to make refinements and improvements to manufacturing processes to adapt to technical progress. This will apply to manufacturers of approved biosimilars just as it does for manufacturers of reference medicines. Such changes do not constitute changes to the molecule that have an impact on safety and efficacy.

Establishing Biosimilarity

While the scientific principles are the same, biosimilar development is more complex than a manufacturing change: The scientific methods and principles supporting the comparability exercise required for changes in the manufacturing process of a given biological medicinal product and for development of a biosimilar medicinal product are the same.[10] "Biosimilarity" is the regulatory term used in the European Union to denote the comparability between two different products, a biosimilar and its reference medicinal product.[11] The statement that biosimilarity is different from a manufacturing change is further underlined by the fact that such a pathway is also open to originator products after a manufacturing change.[12]

In contrast to manufacturing process changes and establishing comparability, developing a biosimilar medicine is more complex and data requirements are higher.13 For comparability the focus is on a specific change and the respective potential impact on the product. Showing biosimilarity, however, is designed from the beginning with a much broader scope: Testing is generally required in all three disciplines (CMC/ analytical, preclinical, clinical), and is designed to find and interpret any differences. Since a biosimilar manufacturer usually has significantly less manufacturing data and limited non-clinical and clinical data, more extended testing and justifications are required to satisfy the criteria for biosimilarity.

The overarching EMA Guideline clearly states that the "standard generic approach"14 is not sufficient to

[7] Schneider CK (2013), Biosimilars in rheumatology: the wind of change; Ann Rheum Dis 2013 72: 315-318
[8] Schneider CK (2013), Biosimilars in rheumatology: the wind of change; Ann Rheum Dis 2013 72: 315-318
[9] Lee JF, Litten JB, Grampp G (2012), Brief review. Comparability and biosimilarity: considerations for the healthcare provider; Curr Med Res & Opinion 28(6):1053-1058
[10] European Commission (2013), What you need to know about Biosimilar Medicinal Products; http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native (accessed: 18/08/2015)
[11] European Commission (2013), What you need to know about Biosimilar Medicinal Products; http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native (accessed: 18/08/2015)
[12] In some exceptional cases, such as for a product where an exchange of a chemical-synthetic with a recombinant cell-based manufacturing process takes place, the manufacturer may consider applying for a biosimilar marketing authorisation instead of an application as a new medicinal product since such a change is out of the scope of the ICH Q5E Guideline.
[13] National Health Service (NHS) (2015), Answers to commonly asked questions about biosimilar versions of infliximab; http://www.medicinesresources.nhs.uk/en/Communities/NHS/SPS-E-and-SE-England/LNDG/London-Wide-Reviews/Answers-to-commonly-asked-questions-about-biosimilar-versions-of-infliximab/ (accessed: 04/08/2015)
[14] EMA (2014), Guideline on similar biological medicinal products; 23 October 2014; CHMP/437/04 Rev 1

gain marketing authorization for a biosimilar. Rather, "the success of developing a biosimilar will depend on the ability to produce a medicinal product which is similar to the reference medicinal product, and to convincingly demonstrate the similar nature of the concerned product. This includes comprehensive physicochemical and biological characterization and comparison and requires knowledge on how to interpret any differences between a biosimilar and its reference medicinal product."15 According to Weise et al., this means that data requirements for gaining marketing authorization, i.e. for establishing "biosimilarity", are higher than for approval of a manufacturing change.16

The reasons for the higher requirements lie in the nature of manufacturing biological medicines. Each manufacturer has its own unique cell lines and develops its own proprietary (unique) manufacturing processes.17 The biosimilar developer does not have access to the manufacturing process of the reference product and therefore has to engineer its own manufacturing process and corresponding analytical tools, capable of manufacturing a product as similar as possible to the reference product.18 The owner of the reference product, on the other hand, does not only establish comparability but has also the full understanding of his own manufacturing process and the respective manufacturing change(s).

Summary comparison of manufacturing change and biosimilar development

	Manufacturing change	**Biosimilar development**
Objective	Optimising an approved process for a product that has previously undergone significant R&D, with a full preclinical program and extensive clinical trial data in each approved indication and regimen	Attempting to reverse engineer, or create a version of the innovator product starting from published information and the product on the market
Scientific principles of assessing comparability	Same	Same
Purpose of the assessment	Impact of a manufacturing change on an existing product, i.e. comparability between pre- and post-change product	Marketing authorisation of a new product, i.e. comparability between two individual products in order to show similarity
Requirements for approval	Risk-based approach, i.e. level of assessment and data required depends on the level of change (e.g. see ICH Q5E)	Comprehensive, comparative analytical and functional testing followed by tailored clinical development, the extent of which is defined in over-arching clinical or product specific guidelines[19]
Manufacturing process knowledge	Available with regard to the pre- and post-change product	Not available for the product with which the biosimilar is compared. Must be developed without knowledge of reference product manufacturing processes or control strategies

3. Conclusion

The scientific principles of assessing manufacturing changes and biosimilarity are the same; however, the regulatory basis for each is different. In case of a manufacturing change the manufacturer knows his

[15] EMA (2014), Guideline on similar biological medicinal products; 23 October 2014; CHMP/437/04 Rev 1
[16] Weise M et al. (2011), Biosimilars – why terminology matters; Nature biotechnology 29;8: 690-693
[17] European Commission (2013), What you need to know about Biosimilar Medicinal Products; http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native (accessed: 18/08/2015)
[18] Weise M et al. (2011), Biosimilars – why terminology matters; Nature biotechnology 29;8: 690-693
[19] EMA (2014), Guideline on similar biological medicinal products; 23 October 2014; CHMP/437/04 Rev 1: "Whether the biosimilar approach would be applicable for a certain biological medicinal product depends on the state of the art of analytical methods, the manufacturing processes employed, as well as the availability of clinical models to evaluate comparability."

own manufacturing process, whereas a biosimilar manufacturer does normally not possess the knowledge about the manufacturing of the reference product. This is also reflected in the fact that there are two different regulatory approval processes in place. Calling a biological medicine 'a biosimilar of itself' confuses the concepts of manufacturing change and biosimilarity and bears the risk to undermine trust in biological medicines and their use.