

## Biological medicines: what you need to know about manufacturing?

All biological medicines are complex and sensitive to their manufacturing process in ways that chemically synthesized, small molecule medicines are not. This paper will help you to understand the terminologies of batch to batch variation, manufacturing change and biosimilarity.

The production of biological medicines,<sup>1</sup> including biosimilar medicines, is a complex process which requires a very high level of technical expertise. Typically about 250 tests are done throughout the production process compared to about 50 tests for a chemically-manufactured small molecule medicine. Each manufacturer develops their own proprietary manufacturing processes, including the use of specific living cells (called the cell line).

Due to their large size, complex structures, and the fact they are derived from living organisms e.g. cell lines, biologics are intrinsically sensitive to their manufacturing processes. This sensitivity can result in **intrinsic variation** from one batch to another, and as **differences introduced by changes** to existing manufacturing processes or by creating a new process like when developing a biosimilar medicine. Whilst terms like batch to batch variability, manufacturing change and biosimilar development have overlapping scientific principles, their context and management are distinct and require different considerations by the manufacturer, the regulator and the healthcare system. Applying the correct term and context will help to avoid misunderstanding and facilitate a better understanding of all biological medicines.

- **Batch to Batch Variability:** Applicable to all biological medicines, including biosimilars, due to complexity of their manufacturing processes. This intrinsic variation (batch to batch variability) must be controlled within defined ranges or limits that are proposed and monitored by the manufacturer and agreed by the regulator.
- **Manufacturing Change:** During the commercial lifecycle of biological medicines, planned changes occur to the manufacturing process. These are generally minor but occasionally may be considered significant. The manufacturer must ensure the process is still controlled and the intrinsic variability (batch to batch variability) remains within release specifications approved by the regulatory authority. The manufacturer has to demonstrate that the proposed change does not impact on the quality, safety or efficacy of the medicine via a **comparability exercise**<sup>2</sup>. This assessment is informed by the historical manufacturing, non-clinical and clinical data available to the manufacturer. Depending on the type and number of proposed changes and the potential impact they may have on the product, the regulator may ask for the historical data around the product and process, additional analytical data, nonclinical and clinical data. However, the primary aim is to request only the data that is needed to make a robust assessment. Substantial manufacturing changes are undertaken less commonly and can result in a new version of the product. Such changes would require a full range of comparability data (including clinical evidence) to support the change. Impact to patients is also managed because the supply of pre- and post-change product is generally controlled by the manufacturer to provide a

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<sup>1</sup> A medicine that contains one or more active substances made by or derived from a biological source. Some of them may be present in the human body and examples include proteins such as insulin and growth hormone. Active substances in biological medicines are larger and more complex than those of non-biological medicines. (NHS England, ['What is a biosimilar medicine?'](#) September 2015.)

<sup>2</sup> "The goal of the comparability exercise is to ensure the quality, safety and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes. The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product." *European Medicines Agency, ICH Topic Q 5 E Comparability of Biotechnological/Biological Products, June 2005 CPMP/ICH/572 1/03.*

transition of product version in use. The scientific principles underpinning the comparability exercise to support a manufacturing change also serve as the basis for developing a biosimilar medicine.

- **Biosimilar Development:** A biosimilar medicine is developed to be highly similar in structure and clinically equivalent to an existing biological medicine. A biosimilar medicine is developed without access to the proprietary manufacturing data and materials used for the existing biological medicine. Consequently, the biosimilar manufacturer must reverse engineer their molecule and develop their own proprietary manufacturing process, using data derived from testing batches of the existing biological medicinal product as the reference (hence 'reference product'), using state of the art analytical techniques. Once the biosimilar manufacturer has developed their own manufacturing process, they must test and compare their molecule with multiple batches of the reference product. The requirement is that it should be highly similar in terms of structure, function and clinical outcome; usually based on data from analytical studies, animal studies and a clinical study or clinical studies. Biosimilar medicines do not have to be identical to the reference product but they must be highly similar with respect to attributes that are important to how the medicine functions; and any minor differences must be shown to have no clinically meaningful impact on the safety and efficacy of the medicine. To achieve this, biosimilar manufacturers apply a more comprehensive version of the comparability exercise used by originators to manage post-approval manufacturing changes.

Throughout the lifecycle of all biological medicines, including biosimilars, manufacturers work closely with the regulatory authorities, who must be notified and review and approve all changes to a biological medicine; providing assurance to patients their medicine is consistent.