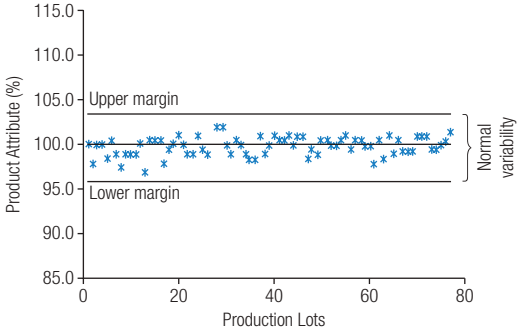
Biosimilars

Hot Topic: Biologic Comparability Testing Versus Demonstration of Biosimilarity

How Are Biologics Monitored to Ensure that Quality is Maintained From Batch-to-Batch?

- Based on time and experience with a product, manufacturers establish acceptable ranges of variation and tightly control key product attributes that are likely to impact biological function[1–3]

Normal Variability in Final Product for a Monoclonal Antibody[2]



How Are Biologics Monitored to Ensure that Quality is Maintained Following a Manufacturing Change?

- Changes to the manufacturing process for biologics often occur post-approval (for example, to improve quality, efficiency and/or reliability of manufacture)[1–3]
- These changes require rigorous risk assessments in accordance with international guidelines to confirm that product attributes remain within the pre-defined ranges of variation with no anticipated impact on quality, safety, or efficacy[1]

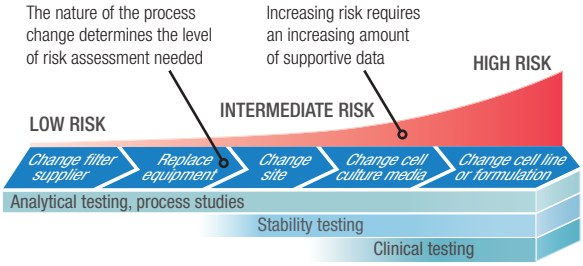


Figure adapted from Lee JF, et al. Curr Med Res Opin 2012;28:1053–1058

Comparability testing is required following manufacturing process changes for approved biologics[1]

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How Does the Development of a Biosimilar Differ From Demonstration of Comparability After a Manufacturing Process Change?

Demonstrate Biosimilarity[4–6]

Different manufacturer, new product biosimilar candidate compared with reference product

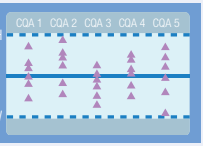
No access to reference product's history, manufacturing process, established controls or acceptance parameters

Fully characterize reference product

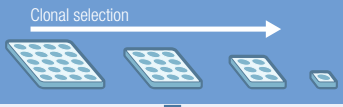
- Primary structure
- Higher order structure
- Receptor binding and immuno-chemical properties
- Stability
- Biological function
- General properties, excipients

Identify reference product critical quality attributes (CQAs) and establish acceptable ranges of variation

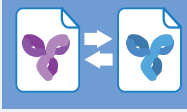
Each data point represents testing from a unique reference lot



Develop and identify cell clone that meets predefined margins, establish cell banks and manufacturing process



Establish biosimilarity



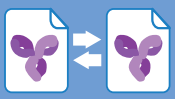
Analytical studies	✓
Non-clinical studies	✓
Comparative clinical PK/PD	✓
Clinical safety, efficacy and immunogenicity evaluation	✓

Demonstrate Comparability[1,4]

Same manufacturer, same product tested before and after change

Extensive knowledge of product history, manufacturing process, established controls and acceptance parameters

Establish comparability



Analytical studies	✓
Non-clinical studies	?*
Comparative clinical PK/PD	?*
Clinical safety, efficacy and immunogenicity evaluation	?*

*May/may not be required depending on risk of process change

Demonstration of biosimilarity is a much more complex process compared with the demonstration of comparability of a biologic before and after a manufacturing process change[3,4]

References

1. ICH. ICH Harmonised tripartite guideline: Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E. 2004. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf; 2. Ramanan S, Grampp G. BioDrugs 2014;28:363-72; 3. Declerck P, et al. Pharm Res 2016;33:261-8; 4. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry, 2015. Available at: http://www.fda.gov/downloads/drugs/ guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf; 5. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf; 6. McCamish M & Woollett G. Clin Pharmacol Ther. 2012;91:405-17. All links accessed November 2017

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