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Bioanalytical comparability of biotechnology products subject to changes in their manufacturing process

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BIOANALYTICAL COMPARABILITY OF BIOTECHNOLOGY PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS

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Over lifecycle, from development through all industrialization stages and then over manufacturing history across multiple sites, a biotechnology product must show very high levels of quality consistency, as that is a pre-requisite for safety and efficacy to patients (cf. ICH Q5E, 2004).

Bioanalytical similarity has acquired over the last years another meaning with the introduction of biosimilars: products that in principle cannot be identical to their reference products as processes used and other design options are not exactly identical, leading for example to minor differences in clinically inactive components. However, biosimilars must be proven to be pharmacologically identical to their reference products.

The two extremes above, in terms of bioanalytical similarity, are often confounded. The classical use of bioanalytical information is still today very limited in scope and aim. An analytical technique is often used to determine the presence of a few species (e.g., glycoforms, isoforms, high-molecular weight aggregates) and ignore information also captured in other regions of that particular analytical domain (e.g., impurity peaks and their relative distribution). Moreover, small variations of the entire fingerprint by one analytical technique over several lots of the same product go completely unnoticed and may erroneously be attributed to minor variability of method performance and not a change in the manufacturing process with a direct impact on product differences.

Recently, FDA defined different levels of similarity (Draft Guidance, May 2014, “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product”) namely the concepts of (1) “highly similar with fingerprint-like similarity” and that of (2) “residual uncertainty” in regard to similarity.

Here we present a new approach to combine whole analytical domains from different techniques used to assess similarity in biocomparability investigations that can (a) detect very small differences, (b) establish therefore high levels of similarity and (c) assess residual uncertainties. We will illustrate our approach on reference products over their lifecycle and to compare reference with putatively similar products. The outcome of assessments (a) through (c) can then be linked to the pharmacological performance or both types of biotechnology products, and support regulatory or other decisions related to managing filings.