Table 32

TOPIC: Fingerprinting approaches: Impact for biosimilars and innovative products

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SCOPE:

FDA defines Fingerprint-like as "Integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences." There are numerous analytical methods that can be used to establish the fingerprint of a biologic, whether as part of overall characterization, a comparability assessment, or a biosimilarity claim. Fingerprint analysis of a biologic should cover sequence and protein modification analysis, determination and characterization of higher order structures, understanding of functional bioactivity, identification of glycoforms, and impurity profiling.

BULLET POINTS FOR DISCUSSION:

1. What analytical methods are available to investigate the following
   o sequence and protein modification analysis
   o determination and characterization of higher order structures
   o understanding of functional bioactivity
   o identification of glycoforms
   o impurity profiling
2. For comparability assessments or biosimilarity claims, how are statistical and non-statistical assessments performed? What challenges might be faced in these assessments?
3. How does fingerprint analysis change throughout development into commercialization and post-approval?
4. How have the expectations changed for development programs when the product is highly characterized analytically (e.g., amount of data to support changes that are made in late stage/commercial)?

NOTES:

- What is “fingerprint-like similarity”? Table agreed that it's not well defined. FDA Guidance document is very general, with no definition.
  o Even defining a “fingerprint” is misleading. It is not complete molecular understanding, because you need to understand what is behind the peaks, etc.
  o Any one test is only a contribution to a fingerprint. For example, an NMR result alone is not a full fingerprint. A fingerprint takes into account the totality of the analytical data, using a number of methods.

1 FDA Guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product", December 2016
From the biosimilarity standpoint, it is important to identify the differences and determine whether these differences have a meaningful impact. The Sponsor needs to be able to justify why differences are not clinically meaningful.

There was a lengthy discussion on whether the term "fingerprinting" should continue to be used, in particular since there is not well-defined guidance. Instead, the Table felt that "highly similar" was the more appropriate term.

Consideration should be taken if you "zoom in" to a region of a spectrum or chromatogram. The thought was that there will always be differences if you keep looking.

Two bases for determining the "fingerprint" are strong CQA analysis, along with setting similarity ranges based on significant data set.

Fingerprint is a multidimensional assessment.

Some participants felt that there was no need to worry so much about the semantics of the term “fingerprint”, rather what information we are gathering.

Fingerprinting isn’t really anything new – this is what we’ve been doing anyway with all of the different types of analytical technologies.

While some participants felt that it was important to use the best technologies available to understand your molecule, others questioned whether advanced technologies really pay off? It is the totality of the evidence that matters. Need to understand whether they are relevant.

It was felt that it is the Sponsor’s choice as to what methods are used, but there should be a rationale why some are used and why some are not.

There was discussion around using multivariate statistical approaches such as PCA to compare large amounts of data to measure combined QAs rather than each individual attribute when there are a large number of attributes.

- You will always find differences using such an approach.
- Intention is not to show biosimilarity with PCA, but rather to identify the attributes that contribute the most to differences.
- How to eliminate bias in large dataset? Originator can have many different lots coming from the same DS, which would bias the results. Need to figure out the independent lots so that this can be accounted for in the statistical analysis. Whatever approach you take needs to be justified.
  - Can use isotope profile to identify which DP lots are from the same DS lot.

Is thinking evolving such that a high degree of similarity means you only need to do PK/PD? Depends if it is a chronic or acute indication, etc. To reduce risk, the more methods you use, the more you know about your molecule.

The idea of reference products for biologics was discussed. It was felt that this is like comparing to moving targets because there is variability in originator material. This challenge is generally mitigated by analyzing a large number of lots sourced from the
different regions for reference. You will likely need a much larger number of lots for biosimilars, as compared to typical comparability. Some attributes may need more lots due to method variability.

- The table discussed the key areas that should be addressed to demonstrate “fingerprint-like similarity”:
  - A careful CQA assessment has been performed
  - Similarity ranges are determined based on sound science
  - CQAs have been hit
  - Anything that is different needs a rational explanation
  - Need to understand MOA
- If you miss on a Tier 1 attribute according to equivalence but can justify that it is not clinically meaningful, then can you say it’s a fingerprint? There is no hard rule about how to define similarity ranges. Need to look at the whole picture, including process consistency, etc. There is room and products have been approved that were not exactly within the defined range, but has still been found to be acceptable with the justification. No examples shared where people didn’t “miss” on any attributes.
- How to evaluate HCP for biosimilars as an impurity? No need or expectation to match. Process-related impurities are not relevant for biosimilars. They need to be controlled as you would for any process. Do you need to evaluate the HCP in the originator?
  - Most biosimilar companies are providing process-specific HCP programs
- Has there been a guidance published about what is considered to be highly similar from a statistical perspective? None yet.
- Use of forced degradation is expected, but to what level?
  - But what differences are meaningful?
  - Also need to consider if methods are sensitive enough to detect differences
- For innovator products, how much fingerprinting would you do to characterize manufacturing changes during development? Impact on comparability?
  - For biosimilars, it would be something beyond what people are already doing for comparability
  - Wouldn’t normally see the depth in a comparability study as you would for a similarity study
  - Original manufacturer has the history and you have the product knowledge and know what you’re looking for, and you know what process changes you are making to inform the risk assessment
  - Can’t compare the bar for comparability vs biosimilarity