Table 9: HOS in Relation to Comparability Studies

FACILITATOR: Marc Neglia, *Applied Photophysics*
SCRIBE: Galahad Deperalta, *Genentech, a Member of the Roche Group*

SCOPE:
Process changes in manufacturing of a drug product are required to respond to regulatory demands, increase scale, improve product quality and stability, comparability studies must ensure the absence of adverse effects by those changes on the quality, safety or efficacy of the bio-pharmaceutical product. Though established as an essential part of comparability studies, Higher Order Structure comparisons of protein therapeutics and biologics cause ongoing challenges throughout product development. This roundtable will aim at identifying, collecting and prioritizing the challenges accompanying HOS comparisons in comparability studies. We will focus on technical limitations, heterogeneity of approaches and impact of regulatory requirements. Strategies to meet these challenges will be addressed to explore how both experimental procedures and data analysis might be harmonized across the industry, how orthogonal techniques can be selected and used effectively to allow for correlations, how to fulfill general and individual requirements with limited resources, and how best practice of HOS comparisons can be established.

QUESTIONS FOR DISCUSSION:
1. What is the need and value for harmonization of approaches for HOS comparability and establishing best practice in the analysis of HOS comparisons across the industry? How do we establish this, is it industry led or regulator?
2. Biosimilar and Innovators carry out HOS comparability studies for different but related purposes. Does the approach used need to be tailored for biosimilars or innovator, or can the same approaches be used?
3. How to establish acceptance criteria systematically, is the same criterion always adequate for all products, or if not, how to objectively establish this?
4. Most HOS comparability techniques don’t provide molecular details about HOS changes observed, one would like to know the molecular level details of any changes in HOS observed, but how important is it in reality?
5. How to correlate results from multiple methods and orthogonal techniques?

DISCUSSION NOTES:
- Question: Is there a need to harmonize HOS strategy for comparability studies across the industry?
- Most felt that companies we're doing similar strategies already, in that HOS methods tend to supplement the foundation of characterization/release assays + stability data + bioassay data (or be included as part of the extended characterization package).
- Most agreed that what is needed in the comparability package is more important that which methods.
- Discussion point: Need sensitive bioassay to match the sensitivity of newer HOS methods. Bioassays tend to have wide specs (e.g. 60-120% or 80-120%), which would not align with (or would supersede) very small structural changes that something like NMR could detect.

- Discussion point: Perhaps new modalities (as opposed to standard mAbs) are more appropriate applications for these new HOS methods (e.g. NMR, HDX, etc). In these cases, there is less product knowledge and a better case could be made to use new HOS methods to gather potentially relevant structural data.
- Standard mAbs, on the other hand, are better understood, and perhaps more tolerant of "abuse," i.e. they can be degraded or structurally compromised and still show efficacy or still not be a safety risk.
- Most agreed that aggregates/oligomers were the most important HOS characteristic to monitor, and these can be monitored by more standard chromatography assays.
- Burden is on submitters to decide elements of comparability package and which methods are suitable to support the filing claims.
- Difficult for companies to jump into new HOS technologies (and include them in filings) for risk of not knowing how to interpret the clinical impact of the data. If you see a difference in HOS between batches, what does that mean with regards to safety and efficacy?
- For new modalities (e.g. fusion proteins, bispecifics, etc), methods like CD or FTIR may be more important in detecting clinically meaningful structural differences.
- HOS methods for comparability packages/filings: Must have or nice to have?
- Split answers, some said must have, some said nice to have. For those who supported must have, they argue that what other methods besides CD or FTIR, for example, can give information on secondary structure comparability. The opposing view, though, is what is the safety/efficacy risk or impact of a minor change or difference in secondary structure between batches (assuming characterization/release assays + stability data + bioassay data are all comparable otherwise)?
- Where is the use-case study of CD/FTIR/NMR/HDX detecting a safety/efficacy risk that a "standard" characterization/release assays + stability data + bioassay data set was unable to detect or make clear?