Table 10: Regulatory Expectations and Filing Strategy

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SCOPE:
The possible impact of the biophysical attributes of a biomolecule on the efficacy, time action, and immunogenicity have been widely reported. As a result, the ability to measure and understand changes in higher order structure has taken increasing role in regulatory submissions and filling strategies. This has placed challenging demands on the analytical strategies and methods used to measure these attributes. This roundtable will focus specifically on the regulatory strategies and methods used to control these biophysical attributes. These strategies include those used to support biosimilars, phase I IND submissions, and later phase submissions. It can cover the characterization across a large molecular weight range from insulin related molecules to viral vectors. It covers the role of formulation and process development on higher order structure. It also covers the requirements for the instruments and methods used for biophysical characterization in regulatory submissions.

QUESTIONS FOR DISCUSSION:
1. What are the regulatory expectations for the biophysical characterization of biomolecules? How do these expectations change based on:
    a. Phase of development (e.g. IND vs. BLA/MAA)
    b. Type of therapeutic modality (e.g. monoclonal antibody vs. novel fusion protein)
    c. Indication / patient population (e.g. oncology vs. autoimmune)
    d. Innovator vs. biosimilar
    e. Other considerations?
2. Under what circumstances would higher order structure testing become part of release testing?
3. What are the regulatory expectations for test methods and instrumentation used for biophysical characterization?
    a. Must test methods be ICH validated?
    b. What standards must instruments meet?
4. What characterization tool and approaches have been most effective? What are the strengths and weakness of different characterization approaches?
5. What biophysical tools are most informative for stability studies?

DISCUSSION NOTES:
- HOS methods such as AUC are moving into QC environment as the connection between the HOS and patient safety and efficacy of both proteins and new modalities grows.
- Question about how does one find out what the regulatory expectations are. Sponsors are encouraged to reach out to health authorities to get feedback on their plans prior to the initiation of definitive toxicology and clinical trials. Decisions about what is required are made on a case-by-case basis, with a 'totality of evidence' approach.
- Comment that we are so reliant on bioassay because we do not completely understand the structure-function relationship; if we did, we wouldn't need bioassay as much

- Comment that regulators are not subject matter experts in every aspect of the filing and that sponsors should completely explain their methodology, interpretation of results – tell a story with the data. Scientists may think things are obvious when in fact that may not be.