Roundtable Session 2 – Table 4 - Product Characterization and Role of Your Potency Assays

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Abstract

Modern biologic drugs have more and more complicated structures and mechanisms of action (MoAs). A standard strategy is to pick the most critical attributes to monitor on lot release and stability panels, and other attributes are tested with characterization assays

Discussion Topics

I. Challenges associated with in-licensed products

In-licensing a biologic product can create substantial challenges for implementing potency assays, particularly when legacy methods and critical reagents must be transferred across organizations.

1) Lot-release methods
    a. Legacy methods may rely on proprietary or non-transferable critical reagents (e.g., specific cell banks, labeled reagents) with limited traceability (documentation gaps) or limited availability, necessitating method redevelopment and subsequent validation at the receiving company.
    b. Legacy methods may exhibit a high rate of invalid runs and out-of-specification (OOS) results due to poorly characterized critical reagents, requiring assay remediation prior to commercial validation. One participant described a complex bridging strategy that aligned two legacy ELISAs and a cell-based assay to a functionally relevant assay before commercial validation.
2) Biological characterization package
    a. Incomplete biological characterization packages in the original IND (e.g., limited evaluation of Fc effector functions and/or secondary mechanisms of action [MoA]) may require additional studies by the receiving company to support IND amendments or biologics license application (BLA) submissions.

II. Approaches for characterization assays supporting clinical development

1) Fit-for-purpose assessment and implementation
    a. Most participants reported conducting a limited qualification ("mini-qualification") or “method verification” to evaluate key performance characteristics (e.g., accuracy and precision). These activities may be executed without a formal protocol or predefined acceptance criteria yet can provide sufficient confidence to interpret meaningful potency changes in forced-degradation or correlation studies.

b. Some participants indicated that they do not report relative potency values for certain characterization activities; instead, they review qualitative dose response curves to assess biological activity of toxicology and GMP lots.

c. Participants discussed leveraging prior characterization data (e.g., effector-function assessments) across molecules with similar MoAs. For example, Fc receptor binding data may be referenced for Fc-null antibodies with well-characterized amino acid substitutions. However, molecule-specific evidence of correlation between reporter readouts and functional outcomes (e.g., ADCC reporter activity vs. target-cell killing) may still be required rather than relying solely on historical correlation studies.

d. Regulatory expectations for antibody drug conjugate (ADC) bystander activity were discussed. Health authorities generally expect bystander activity to be characterized when it is claimed as a secondary MoA. Further alignment may be needed on whether bystander activity should be treated primarily as an in vivo characteristic or as a molecule attribute that warrants control within the CMC strategy.

III. Adoption of platform approaches for potency assay implementation

a. Participants broadly agreed that a predefined platform approach (e.g., binding ELISA early in development cell-based assay later) enables rapid alignment on fit-for-purpose potency methods for first-in-human (FIH) studies. This reduces prolonged assay selection debates and late method pivots that can delay IND readiness. However, given increasing molecular complexity and multi-MoA designs, most companies complement the release assay with additional characterization assays in the IND to support a more comprehensive understanding of mechanism(s) of action.

b. There was consensus on aligning CMC potency assays with preclinical discovery data to maintain continuity of biological relevance across development. Early alignment anchors the CMC potency definition to the MoA, functional endpoints, and structure-function relationships used for candidate selection and in vivo efficacy, reducing the risk of disconnects later in development. This is particularly important for Fc effector-function claims made early in development, which can be difficult to remove in later clinical phases. Overall, this continuity strengthens scientific justification, increases confidence in clinical translation, and reduces the likelihood of late-stage assay rework or regulatory questions driven by shifts in potency definition.