Roundtable Session 1 - Table 5: Potency Assays / Use of Structure Function Models: MOA / Replace Biological / Cell-based Assays/ Replacing in-vivo with in-vitro Potency Assays

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Abstract:

Potency assays play an essential role in biologics development, enhance product and process understanding, and are a regulatory requirement for product release and stability testing. New and complex biologic modalities, some with multiple mechanisms of action, may require product development teams to employ a wide array of bioassays to comprehensively characterize structure-function relationships. Knowledge gained through structure-function studies informs the selection of potency assays, facilitates determination of critical quality attributes, and underwrites the product control strategy. At this table, we will examine the regulatory expectations for potency assays, discuss strategies for structure-function studies and potency assay development, and review bioassay trends.

Questions for Discussion:

How may structure-function studies be used to increase understanding of the mechanism(s) of action (MOA)?

How may structure-function study results be used to justify selection of potency assay(s) for quality control lot release and stability testing?

What strategies are used to select lot release potency assay and the other methods used to characterize the biological activity of the product?

What technologies are emerging to support new biologic modalities with complex or multiple MOAs?

What trends are observed in the acceptance of in vitro bioassays as suitable measure of product potency vs. in vivo bioassays?

What trends are observed in the acceptance of non-cell based binding assays as suitable measure of product potency vs. cell-based bioassays?

Notes:

1. What technologies are emerging to support new biologic modalities with complex or multiple MOAs?

- The ”lab on a chip” technology that was presented yesterday would likely have great application in R&D and elucidation of MOA but is unlikely to be accepted in a GMP environment.
- What limits new technology from being adapted in the GMP environment:
    - Potential Supply chain issues
    - Assay Variability
    - Technical hurdles
    - Regulatory differences
    - Adoption of new technology is not uniform across agencies
- Suggestions to overcome some of the limitations:
    - Give it time—Flow cytometry was never in GMP environment, now it is. Some never make it
    - If there is supporting data we should accept technological advances
        - it won’t be a smooth path because we have difference across regulatory agencies
    - Early implementation of these new technologies used early in programs will allow for a worth of knowledge that will add in convincing the agencies.
    - How you tell the story effects how it is accepted by the agencies.
        - The guidelines allow you to decide what assay to use—so you must tell the appropriate story to aid the agencies in understanding the new technologies.
    - if someone is publishing papers that helps, but not enough—type meetings should be used to help with these conversations
    - Pre-meetings are super helpful for meetings about new technologies
- Some technologies are more than what is needed and it’s not always appropriate to use the latest technology.
    - For immunoassays, using SPR by Biacore to replace an ELISA or using MSD when there is no LOD issue with the standard ELISA.
    - If it’s not adding anything, why use it. Will the lab on the chip be better than a standard 96 well plate?
    - For CROs, it’s often about using the technology they already have. This can include trying novel applications for the current technology to characterize the molecule.

2. Do you need a potency assay for every step of your complicated MOA (Ex. Gene Therapy)?

- Start broad and gather information and as program progresses you can start knocking out other MOA –getting down to the MOA that shows its efficacy and safe.
- Pre-clinical/ phase 1—you want a big tool box—you may not need all of them—but will want to understand all the mechanism—characterization—hopefully you can narrow down---you don’t want to be blind later because you don’t have the big toolbox.
- new potency assay of gene therapy—if you have assay with activity and expression that will work—you don’t have to assay for everything
- Regulatory wants to see as close as possible to the end and you need justification for where you stopped.
- Suggested to ultimately find an assay that’s representative of the rest.

3. Does it make sense to still include an animal model for one MOA that can't be replicated with an in vitro assay?

- In vivo studies have an important place for POC, early RD work
- You want to avoid using animals for release tests, if possible.
    - For vaccines, the variability can depend on the animal and not the product
    - Once you have an in vivo release test, it can be very challenging to remove it.
- All MOA for Vaccines are hard to know—
- Should have well rationale potency assay that works well and are not as variable.

4. How many companies are still looking at in vivo?

- Client are still using in vivo for things like vaccine and insulin release testing
- In vivo models are used for early discover for a vaccine.
- Still has an in vivo release and stability assay for a drug in the US which requires 100 animals for each timepoint.
- We had a product that eliminate animal assay in the 80s---2022 we were able to finally remove the in vivo assay from the test panel.
- Don't register with an animal. Legacy assay—EU is quick to allow you to remove in vivo, US wants some history—other countries take a long time.

5. Discussed working with regulatory agencies.

- There is an understanding from everyone that we need to move towards a harmonized regulatory agency with consistency.
    - An example of why this is important: CMC team must perform all the release tests required by different agencies, because they do not always know where the batch of material will end up.
- Limitations:
    - Not all agencies have a way to talk to other agencies. Some agencies have interagency meetings.
    - There are so many new mod. that the agencies are trying to understand these new control strategies.
- But if there are specific issues, the sponsors can drive these meetings.
- You can ask them to talk to the other countries.