Table 21: Vaccines: Potency Assays – What's Love Got to Do with It?

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SCOPE:

Ideally potency tests predict and correlates clinical efficacy but in reality, it cannot show the absolute clinical relevance of a particular potency test because we do not put sub-potent vaccines into the clinic intentionally to demonstrate sub/super-potency and therefore cannot demonstrate a lot that fails potency is clinically less effective. Instead we look at the product and its attributes in a scientifically rigorous way using a consistency approach with the goal of that the product made post-licensure is just as efficacious as the lot(s) that was tested in the clinic.

Potency tests are required in all phases of clinical development through licensure, however due to the complexity of biologic products, especially vaccines, and their matrices, the in vivo format has traditionally been used. Prompted by humane considerations, efforts are underway to replace animal-based testing therefore most vaccine programs are involved in developing in vitro assays for use with new products from early development through replacement for licensed products. In vivo potency assays tend to involve an antibody-based component; therefore, antigenicity seems to be the major player in the push towards the in vitro realm. Antibody selection will therefore require thoughtful consideration about the mechanism of action and critical attributes.

QUESTIONS FOR DISCUSSION:

1. What kind of difficulties have arisen from trying to replace in vivo with in vitro assays? Has there been any harmonized agreement from regulatory agencies about replacing in vivo with in vitro late stage?
2. What level of characterization is needed for antibodies used in the in vitro assay? What are the expectations for the antibodies (functional/stability indicating)?
3. What are the rationales for having an in vivo assay when an in vitro assay exists? How much data is needed to correlate/bridge the assays?

DISCUSSION NOTES:

- Potency assays are in all phases of the product through licensure with different levels at each phase (need well developed by Phase 3). FDA now getting involved earlier in the process to give help so there's not as much time spent in the end.
- Adjuvant vaccines are more difficult to move away from animal testing since in vitro usually can't support the entire adjuvanted vaccine. But there are instances where carefully designed studies have addressed this issue
    - Control for the adjuvant in the ELISA
    - Assay work on desorption
- If you don't want to put the adjuvant in an assay, there is a need for very good characterization and consistency of manufacturing.
    - For legacy vaccines, the history of adjuvant manufacturing consistency could be very important to removing the in vivo assay

    - Use animal assays in development only and establish manufacturing consistency, then maybe get rid of the in vivo
- Agencies are willing to entertain the idea of using surrogate DS batches in leu of DP potency assays as long as there is consistency
    - New INDs- agencies looking at characterization work and need animal assays, control of all the pieces.
- Clinical wants to see if the adjuvant really makes a difference and the only way to do that is with animals. But could make a case for routinely not doing it
- Any antigen interactions with adjuvant (de- or stabilized) are usually predictable and can control for in stability, etc. Looking at the predictable degradations outside of an animal is better.
- There is a Vac 2 Vac program that pools resources together
- Antibodies can be a major roadblock to switching to invitro. Come to agencies early to get advice.
    - Epitopes for antibodies can be stability indicating or not and show a different story from the invivo. Can use a panel of antibodies/epitopes to show sensitivity to define control strategy.
    - Stability indicating invitro can predict degradation better than animals
    - Do some relevant forced deg work to show the in vitro and animal would fail the same lot. This can take some time though and difficult for stable products. Want demonstration of OOS lots without going out of biologically relevant temps for deg. Need deg relevant to manufacturing process as well
    - If you have a really stable protein, regulators shouldn't worry about seeing degradation but company should use orthogonal testing to show stability and identity. Regulatory bodies are willing to listen to arguments for improving assays and guidances.
- There are cases of global markets switching to in vitro. Took 5 to 15 years
- Since all countries are doing their own release testing, do companies need to do release for vaccines with validated assays, qualified people and overseen by QA and regulatory authorities?
    - If companies have a good track record with agencies for inspections, etc, there is a surveillance program at the FDA where companies can send in material for testing maybe once a quarter at most. But it's not understood by many and not utilized
    - Batch release from FDA holds merit around the world. But list from FDA can take that place if used correctly. FDA to talk internally if this isn't working for ROW filings.
    - At some point only results can be submitted to the agency
- For adjuvanted vaccines, try competitive ELISA, fluorescent tags
- Should use end of shelf life vaccine in clinical
    - Other company had old and new material in clinic. The data set was extremely helpful in showing differences and safety. Specs can be set using this kind of data
- For multi dose vaccines, show comparability between lots that might be used for different boosters, then it doesn't matter which lot or what stage or expiry each one is at.
- For legacy products, established a correlate of protection that was backed with animal assays
    - To get away from this, mass measurements can be correlated back to the clinic
    - Goes back to understanding what you are seeing out of your animal assay with giant assay ranges.
- Use clinical or patient samples to reverse engineer a potency assay?
    - Have to use early work and have an idea of what antigen is causing the disease. If it's very well understood and characterized then could use frozen serum