Roundtable Session 1 – Table 2 – Vaccine Potency – Compare and Contrast Potency Tests for Different Vaccine Modalities

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Abstract:

Topic Scope: Within vaccines, potency is an important product attribute that may link product characteristics to immunogenicity and/or efficacy. The type of potency test developed can vary by vaccine modality (e.g., subunit/VLP, live virus, RNA), and the data can be interpreted and implemented differently by modality and across development phases. In this roundtable session, we will discuss similarities and differences between potency tests, including but not limited to: development challenges, regulatory strategies and links to clinical performance.

Discussion Questions:

1. How do potency measurements differ by vaccine modality?
2. Do the challenges of developing potency methods differ by vaccine modality (e.g. reagent screening, method variability, clinical relevance, etc)?
3. How are potency tests linked to clinical performance, and does it differ by vaccine modality?
4. Are all potency measurements across vaccine modalities a CQA and/or release and stability method?

Notes:

Participants discussed how potency concepts, assay expectations, and regulatory strategies differ across vaccine platforms (mRNA/LNP, viral vectors, subunit/VLP, inactivated, polysaccharide, and bacterial vaccines). Themes included assay selection, relevance to clinical performance, reagent challenges, adjuvant effects, and evolving global regulatory positions.

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1. Modality-Specific Approaches to Potency

mRNA/LNP Vaccines

- It was discussed if mRNA quantity alone is potency as in practice, developers rely on in vivo or cell-based expression assays—often semi-quantitative—to infer biological activity.
- The LNP component is a major driver of potency/efficacy, influencing both delivery efficiency and expression magnitude.
- Alignment on what constitutes *“biological potency”* remains variable across organizations.

Viral Vector Vaccines

- Potency generally measured via cell-based expression assays; assays capture lot-to-lot consistency but may show greater inherent variability than plate-based ELISA methods.
- Regulatory expectations are similar, but defining what element is truly “potent” (vector infectivity vs. transgene expression) can be modality-dependent.

Subunit, VLP, and Inactivated Vaccines

- Historically relied on in-vivo animal potency (post-WWII legacy).
- Over time, agencies—especially CBER and EMA—have accepted transitions to in-vitro ELISA-based assays, though this required extensive bridging data and often 30+ lots to establish high/low dose ranges for products that were approved using in-vivo potency. Newer vaccines typically start development with in-vitro potency only.

Bacterial Vaccines

- Considered a “different world” due to complex antigens and limited animal model relevance.
- Structure–function understanding is essential; Phase 3 typically forces mature potency methodology.
- Animal models are often unreliable (“primates lie, mice don’t tell the truth”), leaving clinical correlation as the ultimate benchmark.

Polysaccharide and Conjugate Vaccines

- Historically used old technology rate nephelometry.
- An example with 23 serotype qualification demonstrates a resource-heavy approach.
- Conjugate vaccines have transitioned more successfully to ELISA-based potency measurements.

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2. Challenges in Potency Assay Development

Reagents & Standardization

- Progress is easiest when standardized reagents exist (e.g., DTP), but many modalities lack such infrastructure.
- Some companies coordinate CMC–clinical alignment by jointly selecting critical reagents and immune markers.

Adjuvant Interference/Impact

- Aluminum salts ($AlPO_4$, AlOH) complicate antigen measurement in-vitro.

    - Desorption before ELISA may lead to non-representative antigen recovery (i.e. potency measurement does not account for immunogenicity boost from adjuvant).
    - Inhibition ELISAs may partially overcome epitope masking.
- Assessing Bound vs. Unbound Antigen
    - %-binding (or tightness of binding) may track better with in-vivo immunogenicity than total antigen content/potency, but is highly dependent on the individual antigen.
    - ELISA often insufficient; SPR or cell-based uptake assays may offer more mechanistic insight but lack regulatory precedent.

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3. Linking Potency to Clinical Performance

- For many vaccines, clinical immunogenicity correlates only indirectly with assay potency readouts.
- Sponsors bear responsibility to define clinically relevant antibodies or biomarkers, especially when no animal model exists.
- For legacy products (e.g., pertussis), historical mixtures performed well without strong structure–function clarity; increased purity can paradoxically reduce animal-measured potency without affecting ELISA readouts.

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4. Global Regulatory Considerations

- US/EU increasingly support in-vitro potency if supported by robust bridging packages (for legacy products) or justification for surrogate measurements.
- China maintains a strong preference for animal-based potency, even for globally harmonized products.

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5. Specification Setting Across Development

- In-vivo assay specs tend to be wide due to animal model lack of sensitivity; in-vitro specifications may become tighter as development progresses.
- Early clinical phases face tension during development:
    - Clinical teams want maximum doses for safety/immunogenicity.
    - CMC wants high/medium/low lots to support specification setting.
- Setting specifications before ~30 lots is challenging but often required for accelerated programs.

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6. Multivalent & Complex Vaccines

- Large multivalent vaccines (e.g., 12+ antigen combinations) present combinatorial challenges in reagent qualification, supply chains, and assay validation.
- Potency assays must account for antigen-specific behaviors within combinations.

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7. Emerging Concepts

- Universal flu vaccines have shown theoretical potency alignment but limited real-world success.
- Discussions highlight the need for potency assays that reflect biologically meaningful mechanisms, not just analytical detectability.