Replacing *in vivo* tests:  
A OVRR regulator’s perspective

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My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
Focus

• Product testing requirements and recommendations in general
• Replacement of approved product tests
Product quality control

• Process control
  – Process validation
  – Manufacturing consistency
    • Batch production records

• Intermediate, drug substance and drug product testing
  – Assay selection: able to detect relevant changes in critical quality attributes
  – Assay validation: method adequately precise and accurate for its intended purpose
Release testing for licensed products

• Relevant regulations
  – 21 CFR 211.160: General requirements
  – 21 CFR 211.165: Testing and release for distribution

• Guidance documents
  – Analytical Procedures and Methods Validation for Drugs and Biologics, CDER/CBER July 2015
• Each BLA must include a full description of the manufacturing process, including analytical procedures that demonstrate the manufactured product meets prescribed standards of identity, quality, safety, purity, and potency.

• Analytical procedures must “meet proper standards of accuracy, sensitivity, specificity, and reproducibility and are suitable for their intended purpose.

• When an analytical procedure is approved/licensed as part of the NDA, ANDA, or BLA, it becomes the FDA-approved analytical procedure for the approved product.
Method replacement
CDER/CBER 2015

Over the life cycle of a product, new information and risk assessments (e.g., a better understanding of product CQAs or awareness of a new impurity) may warrant the development and validation of a new or alternative analytical method.

- The new method coupled with any additional control measures is equivalent or superior to the original method for the intended purpose.
- The new analytical procedure is not more susceptible to matrix effects than the original procedure.
Typical *in vivo* tests for vaccines

- **Potency**
  - Immunize animals
  - Measure immune response or challenge animals
  - Calculate relative or absolute potency

- **Safety**
  - Dose animals
  - Measure adverse outcome
  - Compare outcomes to reference or established limit
in vivo Potency tests

Advantages

• Final drug product test
• Adjuvanticity (if relevant)
• Interaction among product components
• Complexity of epitopes
  – Does not need complete understanding of protective mechanism or epitopes
• Holistic measurement of immune response
• Demonstrated to be able to detect changes to product during licensure
**in vivo** potency tests

Disadvantages

- Relevance of animal to human protective responses
- Variability
- Expense
- Time
- Nonconformance with the 3Rs
Ideal *in vitro* potency test

- Test all active components of the final product
- Biologically relevant
  - Measures critical quality attributes that contribute to potency
  - Sensitive and specific
- Precise and accurate
- Sustainable
in vivo Safety

• Advantages
  – Holistic approach
  – Interaction among components
  – Measures multidimensional biology of adverse effects

• Disadvantages
  – Relevance of animal responses to human experience
  – Variability
  – Expense
  – Time
  – Nonconformance with the 3Rs
Concerns when replacing approved tests

• Maintenance of consistent product quality
  – Unlikely to generate additional clinical data to support change in testing

• Ability to detect relevant changes in product quality
  – Assess changes in potency
    • Antigen content (concentration)
    • Antigen structure (forced degradation)
  – Assess changes in safety
    • Impurities and contaminants in the matrix, or inherent reactogenic components
  – Assess changes over time when used in stability testing

• Ability to set appropriate product acceptance limits based on comparability of the two methods
  – Proposed test should not accept lots that would be rejected by the approved test
  – Proposed test has equivalent or better sensitivity
Comparison issues

• Comparisons of test results for lots within the normal manufacturing range may be uninformative
  – Not enough product variability to distinguish the product from the assay variability
  – Overcome using mock samples with known levels of analyte that would be out of specification

• Identification of the analytes relevant to critical quality attributes
  – All immunogenic epitopes may not be relevant to efficacy
  – Endotoxin is not the only pyrogen
Friendly advice

• Changes to product potency and safety tests for FDA licensed vaccines require approval before implementation
• Approaches to demonstrate comparability may be product and test specific
• Talk to us early, talk to us often
• Use the existing guidances as resources