# 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

# 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


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