Developmental Toxicity Study Designs for Preventive Vaccines: Issues and Challenges

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Objectives

• Reproduction toxicity assessment of vaccines: past & present
  • Regulatory Considerations
• Current approach to developmental toxicity studies for preventive vaccines
• Experience derived from developmental toxicity studies for preventive vaccines
• Issues and Challenges
• Next steps
Background

• The need for evaluating the reproductive toxicity potential of drugs was precipitated in the 1960s following the Thalidomide incident

• Reproduction toxicity studies for vaccines were not conducted
  • Vaccines containing life attenuated bacterial or viral antigens not recommended for use in pregnancy
  • Vaccines considered “safe”

• Mid 90s: change in perspective
  • More women of childbearing potential participate in clinical trials
  • More products indicated for use in women of childbearing potential
    • e.g., HIV, HPV, HSV, meningococcal conjugate vaccines
  • More products recommended and/or in development for use in pregnant women
    • e.g., Flu, Td, Hep A & B, GBS, RSV
Vaccines for use in Pregnancy: Labeling

• Adequate & well controlled pre-licensure studies (21 CFR 314.126) to establish safety & effectiveness of influenza vaccines in pregnant women not conducted
  • Pregnant women excluded from pre-licensure clinical trials
  • Data from published literature frequently do not meet the bar of adequate & well controlled studies
• Currently licensed vaccines not indicated for use in pregnancy (no specific labeling claim for immunization of pregnant women)
Pregnancy Subsection of Product Labeling

- Most US licensed vaccines carry either Category B or C (21 CFR 201.57(c)(9)(i))
- Allows vaccination of pregnant women if the benefits from the use of the vaccine in pregnant women may be acceptable despite its potential risk & there is determination that the vaccine is clearly needed
  - Live vaccines not recommended or contraindicated for use in pregnancy
- Conclusions regarding developmental risk at the time of licensure frequently based solely on animal data for most products
Why Developmental Toxicity Studies for Preventive Vaccines?

• Concern for the unintentional exposure of an embryo/fetus before information is available regarding the potential risk versus benefit of the vaccine

• Balance health benefits against safety concerns for the fetus and mother
  • Clinicians frequently confronted with situations where treatment of pregnant women may be indicated
Available Guidelines

- ICH S5a: Detection of Toxicity to Reproduction for Medicinal Products (1994)
  - Allows flexible framework
  - Design product specific and indication based

  - Considered if target population includes females of child bearing potential or pregnant women
  - 21 CFR 201.57 – Specific label requirements
  - Need and strategies for developmental toxicity study will depend on the product
  - Study design discussed at FDA/SOT nonclinical workshop (2002)
Aim of Reproductive Toxicity Studies:

• “...to reveal any effect of one or more active substances on mammalian reproduction...”

(ICH S5a: Detection of Toxicity to Reproduction for Medicinal Products (1994))
Potential Toxicities for Vaccines

- Vaccine components
  - Product, formulations, adjuvants, ROA
- Immune response
  - Long direct and indirect duration of action
  - Potential adverse events on
    - Embryonic/fetal development/fetal immune system
    - Immune modulation in the mother adversely influence pregnancy outcome
Reproductive and Developmental Endpoints

- Senescence
- Mating/Fertility
- Premature Sexual Maturity
- Conception
- Zygote
- Implantation
- Embryo
- Palate Closure
- Fetus
- Birth
- Infant
- Weaning
- Juvenile
- Adolescence/Puberty

A B C D E F
Study design: Overview

Mating
- Pre-mating vaccine administration
- Gestation vaccine administration

Parturition
- Evaluation
- Antibody assay

Weaning
- Evaluation
Animal Models

- Current paradigm
  - An animal species susceptible & responsive to the test article activity, e.g., development of an immune response after vaccination
    - Timing and rate of antibody transfer may differ from human

- Practicability/feasibility
  - Pros & cons (primates?, rat?, mouse?, rabbit?)
  - Fetal examinations/post-natal tests

- Availability of historical control data

- One relevant animal species in general sufficient
  - Exceptions on a case-by-case
  - Non-human primates not generally necessary
  - Group size dependent on the animal model
Study Design

• Prior to pivotal study conduct pilot studies to evaluate response to vaccine
  • Induction of immune response
  • Placental passage of antibody

• Pivotal study:
  • ROA (usually IM, mimic clinical route)
  • Maximal dose response (1 x human dose)
    • Depends on volume, multiple injection sites possible
  • Pre-mating treatment, postnatal follow-up
  • Perform in compliance with GLP
Study Design (cont.)

Timing of dosing

• Maximum exposure to test article during gestation
• Maximum exposure to immune response should be present during gestation
• Need to initiate treatment prior to mating and boost at appropriate times during gestation
  • Prime before conception
  • Effects of additional injections
Study Design (cont.)

Number of doses

• Depends on response onset and duration
  • Maximize exposure during period of organogenesis
  • Episodic dosing
  • Sometimes dosing of subgroups at different times during organogenesis

• Difficult to adjust vaccine administrations to developmental time lines
  • “Peak response” often unknown
Study Design (cont.)

Endpoints

• Maternal toxicity (body weight gain, etc.)

• Developmental toxicity endpoints including evaluation of F1 generation through weaning
  • e.g., viability, resorptions, abortions, fetal body weight, morphology, pup weight gain, nursing activity, maternal effects
    • *ICH S5a: Detection of Toxicity to Reproduction for Medicinal Products (1994)*

• Divide study groups into subgroups
  • Caesarean sectioning
  • Weaning
Study Design (cont.)

Endpoints

• Antibody evaluations in dam, fetus, newborn
• Antibody evaluations not as measure of toxicity but to verify exposure
  • Justification of the animal model
  • Fetal antibody assessments for “proof of concept”
Study Design: 2 Tiered Approach

• Tier 1: Species selection & developmental toxicity study

  if toxicity observed, then

• Tier 2: Further studies that may include
  • Broader immunological assessments
  • Post-weaning development
  • Fertility studies
Timing of Developmental Toxicology Studies

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Discovery → Preclinical Evaluation → Clinical Development → BLA Summary → Product Labeling

ICH Documents  
FDA Guidances  
21 CFR

Phase IV
Ex. of Licensed Vaccines with Developmental Toxicity Studies

- Human Papillomavirus Vaccine
  - Vaccination of females 9-26 years of age
- Tetanus Toxoid Reduced, Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed vaccines
  - Active booster immunization in persons 11-64 years of age
  - Active immunization of adolescents and adults 11-55 years of age
- Influenza vaccines
  - Active immunization of individuals 18-64 years of age
Results: Developmental Toxicity Studies

- No vaccine-related AEs in pregnancy, parturition, lactation, embryo-fetal or pre- and post-weaning development
- No vaccine related fetal malformations or other evidence of teratogenesis
- No treatment related effects on developmental signs and behavior
- In most cases, immune response observed in test species
- Transfer of antibodies to offspring noted
Challenges

• Animal models predictive of human pregnancy?
Challenges: Animal Models

Cross-Species Interpretation

• Ideal species, *theoretically*
  • species with best response and immune system development most like humans
  • Sensitive to pathogen
• Rat? Rabbit? Mouse? Non-human primate?

• Placental Differences
  • Exposure of conceptus may not be the same as in humans

• Timing differences
  • Development of immune system
Challenges: Animal Models (cont.)

- Species-specificity of the immune response
- Species specificity of the antigen/adjuvant
  - Use of species specific homologues?
- Species may not be sensitive to pathogen
- Refinement, replacement, reduction!
Challenges: Dosing

- How to define “maximum response” to the vaccine antigen(s)?
  - Max. level of antibody production?
  - Depends on vaccine antigen
- Concerns: induction of malformations vs. (subtle) functional deficiencies
  - Neurological assessments of pups, reflexes, body weight?
- Immune function?
  - Immune assessments challenging
  - Lack of assays, species specificity of immune responses, relevance to effector functions
Challenges: Endpoints

• Endpoints chosen include those traditionally used to evaluate the potential for teratogenic effects
  • Studies conducted with investigational and licensed bacterial and viral vaccine antigens not suggestive of teratogenicity
• Adequacy of these endpoints to evaluate the potential of vaccines to adversely affect fetal development
  • Physiology, immune system, development
  • Appropriate immune endpoints for vaccine exposure during pregnancy?
• Lack of validated alternate endpoints
  • Follow-up time, validated assays
Developmental Toxicity Studies for Vaccines for Maternal Immunization

• When the goal is to protect the young infant
  • Clinical administration of the vaccine during the 3\textsuperscript{rd} trimester

• Should developmental toxicity studies for vaccines include a postweaning assessment?

• Should timing of vaccine administration mimic human time points?
Vaccines Formulated with Adjuvant

• Several companies implement toxicity assessment for adjuvants only
  • E.g. developmental toxicity studies conducted with the adjuvant only
  • In addition, developmental toxicity studies are conducted with the vaccine/antigen combination

• Comparability of animal/human immune systems?
  • Toll like receptor, etc.

• Comparability of human/animal placenta?
DIA International Workshop on Non-clinical testing of Vaccines (2007)

• Re-evaluated approaches to preclinical evaluation of vaccines & reexamined published regulatory guidance
  
  • Vaccine developmental toxicology
  • Adjuvants
  • Therapeutic vaccines
  • DNA vaccines

• Recommendation: Approaches to reproductive testing of vaccines may be revised to better address potential vaccine-specific adverse outcomes with regard to fetal development
Next Steps?

• Maintain status quo?
  • Purpose of reproduction toxicity studies: “…to reveal any effect of one or more active substances on mammalian reproduction…”

• Revise current recommendation to
  • Change/add additional endpoints?
  • Revisit choice of animal models?
  • For certain products/indications revise study designs to incorporate a postweaning evaluation of the F1 generation?

• Is it necessary to establish a working group to address these issues?
  • National/international?
Summary

• Need for developmental toxicity studies based on the vaccine’s intended clinical use
• Purpose is to provide information to be included into the pregnancy subsection of product labeling
• Unique testing approaches needed for preventive vaccines
  • Consensus reached at SOT/CBER meeting in 2002
  • CBER specific guidance 2006
• Up-to-date experience with preventive vaccines suggests no adverse outcome regarding evaluation of traditional endpoints
• Challenges remain
  • Animal models
  • Endpoints & outcomes evaluated