Developmental Toxicity Study Designs for Preventive Vaccines: Issues and Challenges

Marion F. Gruber, Ph.D.

Office of Vaccines Research and Review
CBER/FDA

HESI Annual Meeting

June 8, 2011

Alexandria, VA

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
- CBER Guidance for Industry: “Considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications,” (2006)
  - 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:

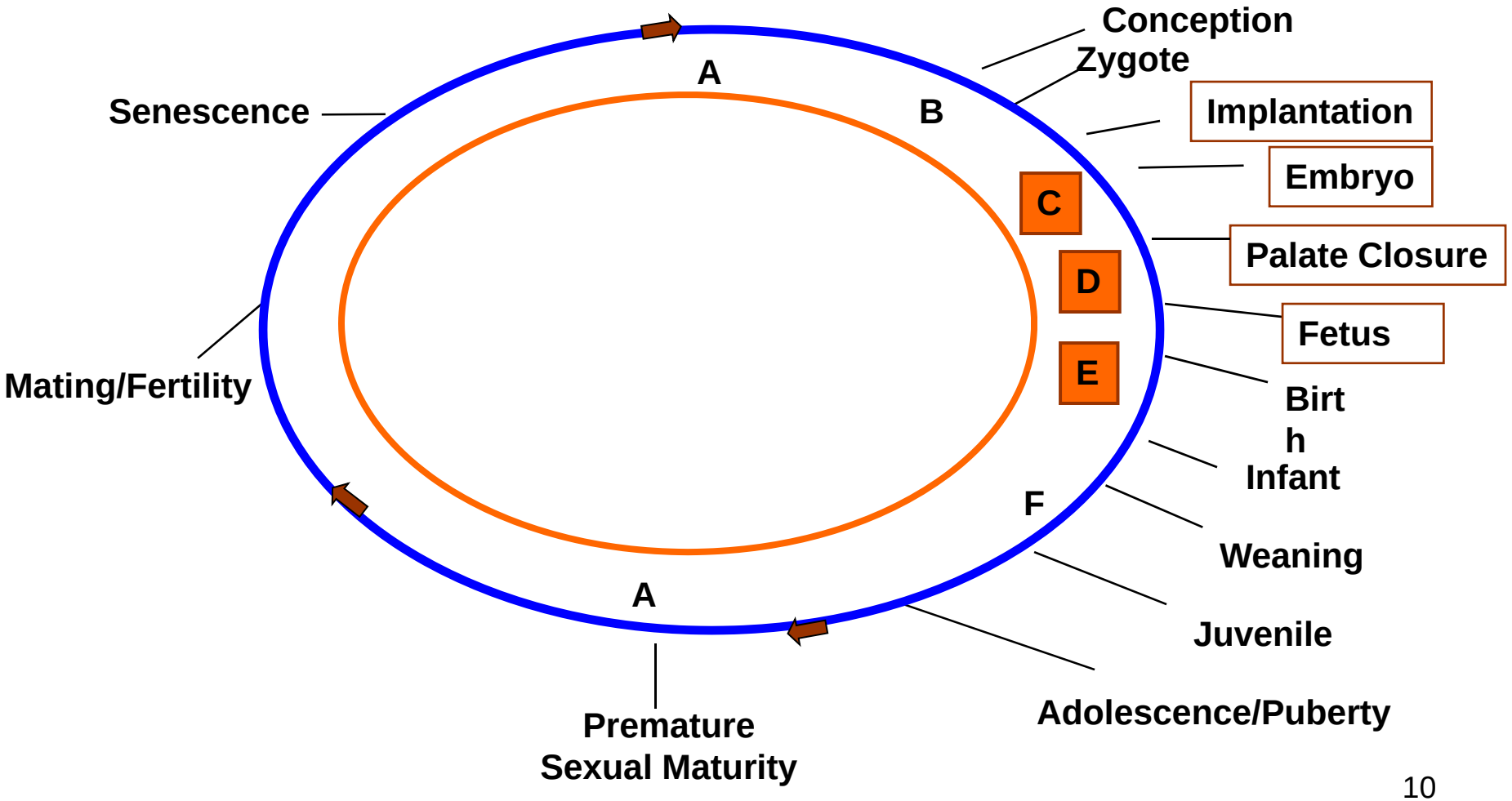
- "**…**to reveal any effect of one or more active substances on mammalian reproduction…"

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

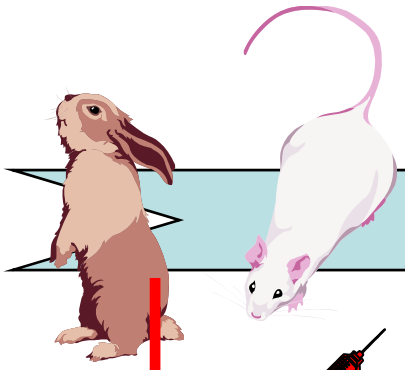
Potential Toxicities for Vaccines

- 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



Study design: Overview



Mating

Parturition

Weaning

Pregnancy

Postnatal development

Pre-mating vaccine administration

Gestation vaccine administration

Evaluation

Evaluation

Evaluation

Antibody assay

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”

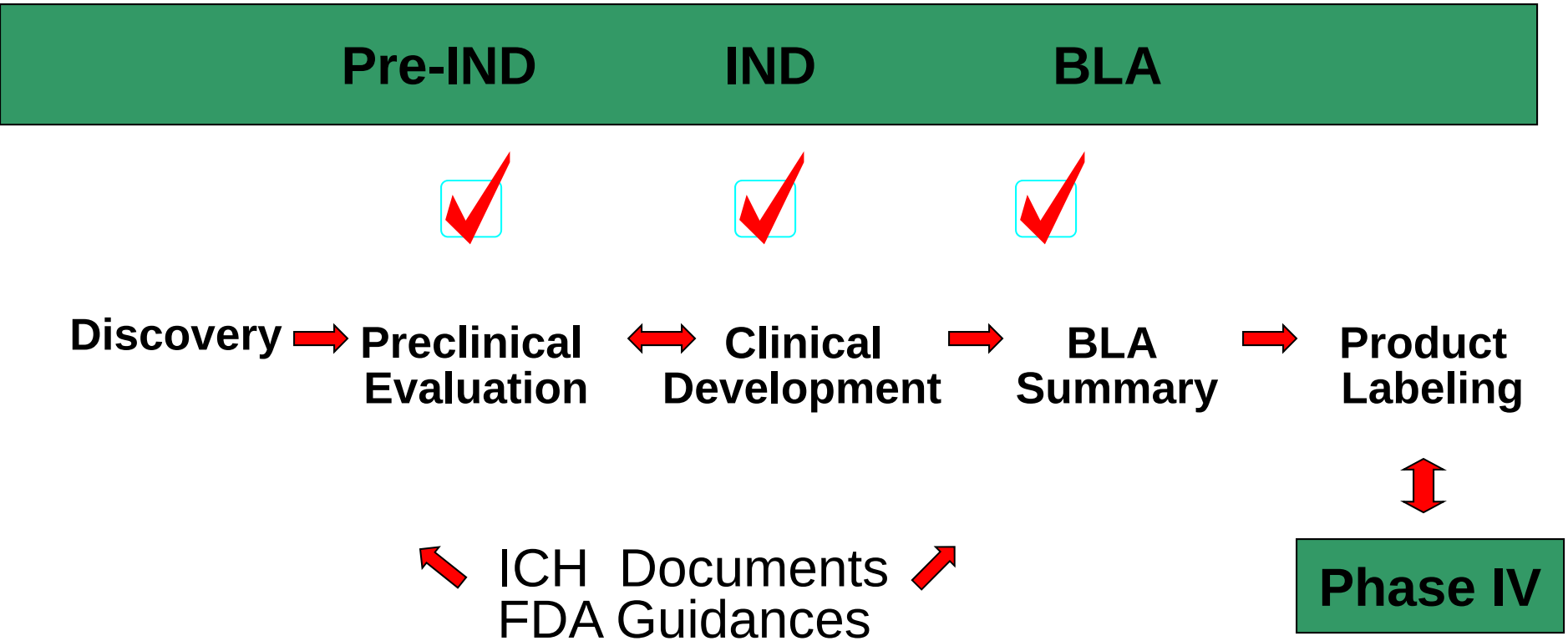
Study Design: 2 Tiered Approach

- 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



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
- Meningococal Polysaccharide [serogroups A, C, Y, and W-135] DiphtheriaToxoid Conjugate Vaccine
  - 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 3rd 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