

# Regulatory Issues for Maternal Immunization

Marion Gruber, Ph.D.

Director

Office of Vaccines Research & Review  
Center for Biologics Evaluation and Research  
US Food and Drug Administration

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# Overview

- Importance/benefits of maternal immunization
- Challenges
- US-specific considerations
- Maternal immunization studies
  - Data required for indication in pregnant women
  - Other considerations
- US initiatives addressing the need
- WHO efforts
- Conclusion

# Maternal Immunization: Why?

- Vaccination of pregnant women may provide important benefits to the mother and/or infant.
- May offer new approaches to prevent newborn and infant infections
  - Use of licensed vaccines, e.g., for influenza, pertussis
  - Development of new vaccines, e.g., Group B Streptococcus, respiratory syncytial virus

# Maternal Immunization: Experience

- Maternal immunization with tetanus toxoid vaccines during the 3<sup>rd</sup> trimester of pregnancy has been successful in preventing neonatal tetanus in developing countries.
- Experience serves as proof-of-concept that maternal immunization can be used to protect neonates and young infants.

# The Challenge

The implementation of maternal vaccination programs has been poor or modest in many countries.

## WHY?

- Limitations of available safety & effectiveness data in pregnant women
- Theoretical concerns about fetal risk
- Manufacturers' liability concerns
- Lack of infrastructure for storing vaccines in antenatal clinics
- Perceived regulatory obstacles

# U.S. Specific Considerations

## “What is Labeling?”

### Labeling

- Package insert (PI), package circular, prescribing information (21 CFR 201.57)
- Container label
- Package label
- Patient package insert
- Medication guide
- Instructions for use
- Risk management materials
- Promotional materials

### Prescribing Information

- Primary mechanism through which FDA and drug manufacturers communicate essential, science-based prescribing information to health care professionals
- Owned by manufacturer
- Reviewed by FDA

# US Specific Considerations: Labeling Requirements

## 21 CFR 56/57 (Labeling)

- Labeling provisions require that prescribing information must summarize essential information needed for safe & effective use.
- No implied indications or uses
- Labeling must not contain false or misleading claims.

# US Specific Considerations: Labeling Requirements (cont.)

- For biological products, indications listed must be supported by substantial evidence of effectiveness.
  - Such evidence is based on adequate and well-controlled studies to support the safety and efficacy of the product for a particular indication and use.
    - e.g., “influenza vaccine for use in pregnancy to protect mother and infant from influenza illness”
- In the absence of such data, the prescribing information will lack a statement that addresses use of the product in pregnancy.



# US FDA Regulations for Product Labeling

- Indication for use
  - Based on data from adequate and well-controlled studies with pre-specified endpoints for safety and efficacy for target population and disease target
  - Information contained in the following sections of the label:
    - “Indication & usage” - Section 1 of product labeling
    - “Adverse reactions” - Section 6 of product labeling
    - “Clinical studies” - Section 14 of product labeling

# US FDA Regulations for Product Labeling (cont.)

- Use in specific populations (Section 8 of labeling)
  - e.g., pregnancy, nursing mothers, pediatric use, geriatric use, immunocompromised individuals
  - Product specific data regarding use in pregnancy typically derived from post hoc analyses of inadvertent exposures or observational post-licensure studies

# Pregnancy Labeling: Current Status and Objectives

- In US, there are no vaccines currently licensed for use specifically during pregnancy.
- Information regarding use in pregnancy contained in pregnancy subsection (section 8.1) of labeling
  - Current regulation requires classification into 5 categories with specific language for each (limited information)
- Currently licensed vaccine are categorized B or C with some exceptions
  - Category B (no adequate and well-controlled studies in pregnant women and animal data reassuring) or
  - Category C (no adequate and well-controlled studies in pregnant women and no animal data)

# What do Pregnancy Categories B & C mean?

- Category B & C allow vaccination of pregnant women if there is a determination that the vaccine is clearly needed.
  - Determination of “clearly needed” is made by public health advisory bodies, e.g., ACIP recommended inactivated influenza vaccines because pregnant women are at risk for serious consequences from disease.
  - Data derived from post-marketing studies and/or from maternal immunization studies published in the literature usually inform recommendations about the use of the vaccine in pregnant women.

# What do Pregnancy Categories B & C mean?

## (cont.)

Example: Inactivated influenza vaccines

- US licensed inactivated influenza vaccines are not contraindicated for use in pregnant women.
- Immunization during pregnancy with inactivated influenza vaccines is not considered “off-label” use.
- Lack of pre-licensure studies in pregnant women (lack of specific statement regarding use in pregnancy in the “Indication and usage” section of labeling) does not preclude use of inactivated influenza vaccines during pregnancy.

# US Specific Considerations (PLLR, 2008 )

- FDA has proposed a rule that would revise the labeling requirement for pregnancy and lactation
  - Remove letter categories
  - Include narrative summary of risks based on available data
  - Include relevant clinical information to help health care providers advise women about the use
  - Intended to better communicate the available information

# US Specific Considerations

## Licensure of Vaccines for Use in Pregnancy

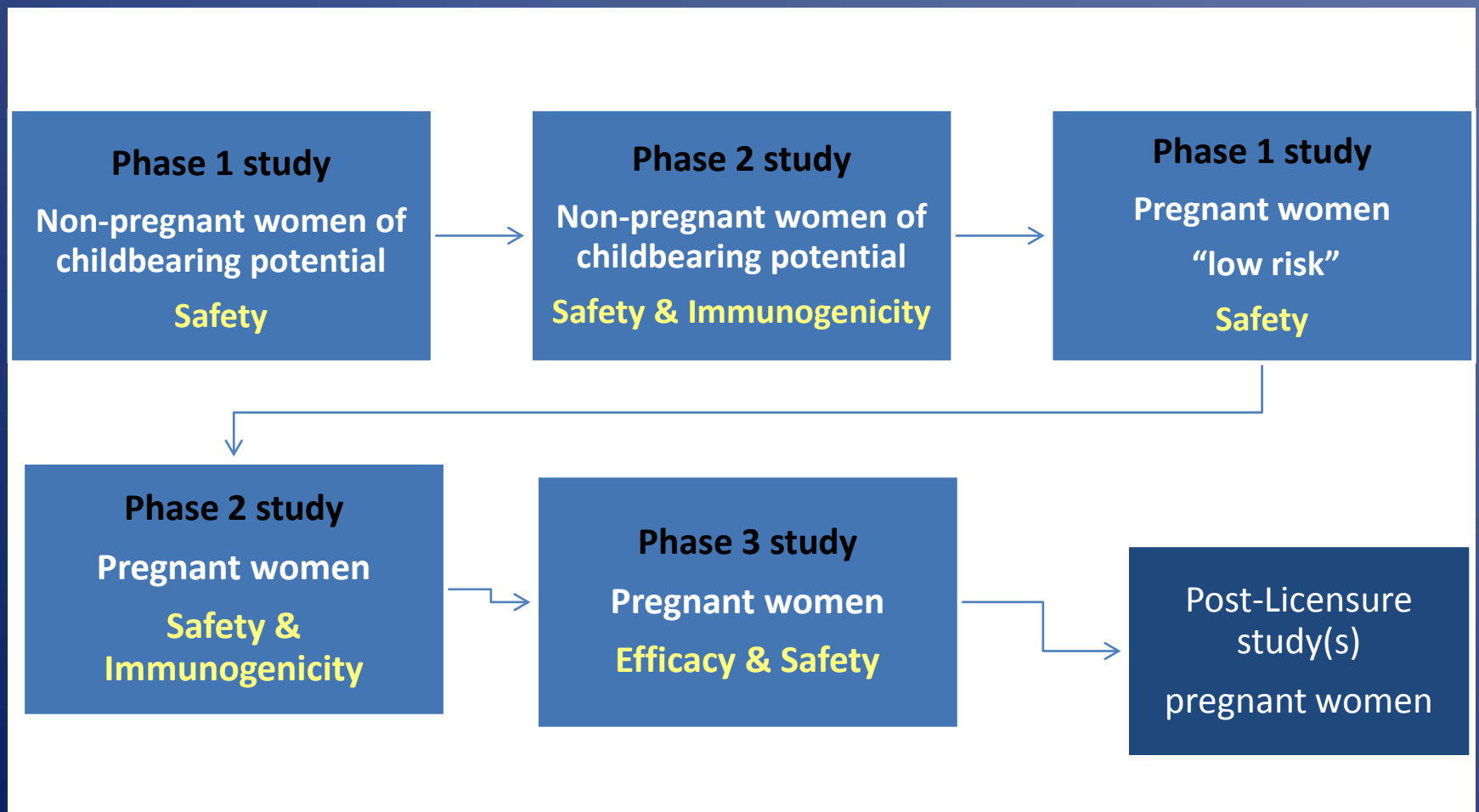
- For vaccines already licensed & approved for adults, specific FDA approval for use during pregnancy to prevent disease in the mother and/or infant may have significant impact on uptake and usage in pregnant women
- FDA approval for use of the product in pregnancy would result in labeling that would serve as a resource for practitioners
  - Facilitate safe use of the vaccine in pregnancy

# What is needed for a Pregnancy-Specific Indication?

Product specific safety and effectiveness data from well-controlled studies with pre-specified endpoints to support indication for use of vaccine in pregnancy



# Clinical Development of Preventive Vaccines for Use in Pregnancy: Pre-Licensure Studies



# Maternal Immunization Studies: Assessment of Safety

- Need to assess safety in mother and infant
  - Adverse event monitoring in mother (local/systemic)
  - Pregnancy outcomes, perinatal events
  - Postnatal events (infant growth & development)

# Maternal Immunization Studies: Assessment of Safety (cont.)

- Develop framework for defining AEs as maternal or infant & strategy for causality assessment
  - Consider current standards for obstetrics/neonatal care to define specific AEs as ‘serious’
  - Consider expected background rates for common AEs
- Specification of halting criteria
- Grading of the severity of adverse outcomes (NIH consortium)

# Maternal Immunization Studies: Assessment of Safety (cont.)

- Size of the safety data base (product dependent)
  - Assessment of common adverse events
    - e.g. spontaneous abortion, preterm birth
  - Criteria used to calculate sample size should take into account the capacity to characterize common adverse pregnancy outcomes
  - Capacity to detect rare unanticipated AES pre-licensure limited
    - pre-licensure clinical studies to detect rare AES (e.g., individual congenital anomalies) not anticipated

# Maternal Immunization Studies: Assessment of Safety (cont.)

- Post-licensure safety evaluations
  - Pharmacovigilance plan, e.g.,
    - VAERS
    - Observational studies conducted in health systems
      - Evaluation of rare adverse events
    - Specific studies to further investigate a safety signal if apparent in pre-/post-licensure data
    - Pregnancy registries

# Maternal Immunization Studies: Assessment of Efficacy

- Need to assess efficacy in mother and/or infant, depending on indication
- Ideally trials are randomized and controlled
  - Standard of care influences study design
- Endpoints/specific outcomes
  - Clinical endpoint (e.g., culture confirmed disease)
  - Immunological endpoint
  - Other clinical endpoints to infer effectiveness
- Duration of protection in mother and/or infant

# Maternal Immunization Studies: Assessment of Efficacy (cont.)

- Establishment of effectiveness when a clinical endpoint study is infeasible
  - Use of alternative endpoints when there is uncertainty as to the capacity of this endpoint to predict effectiveness
    - “reasonably likely to predict clinical benefit”
    - accelerated approval with confirmatory studies post-licensure

# Maternal Immunization Studies: Immune Response Considerations

- Persistence of immune response in the mother
- Efficiency of placental transport of antibodies
- Persistence of maternal antibody in the infant
  - Cord blood titer, correlation with maternal antibody
- Clinical immunogenicity studies in infants
  - Evaluation of immune interference



CBER is considering a VRBPAC meeting to discuss data requirements & considerations for safety and effectiveness regarding maternal immunization.

# US Initiatives Addressing the Need

- Some innovative systems for evaluating safety of licensed vaccines in pregnancy are under development:
  - CDC's Vaccine Safety Datalink project to develop pregnancy database linking birth records with maternal records
  - FDA/CBER launching project to evaluate the ability to conduct surveillance for pregnancy outcomes after vaccination in PRISM program<sup>‡</sup>
- FDA stands ready to provide regulatory guidance to manufacturers seeking indication for use of product in pregnancy.

<sup>‡</sup> *Post-licensure Rapid Immunization Safety Monitoring*

# WHO Efforts

- 2012 Global Vaccine Action Plan
  - Vision for universal access to immunization, throughout the individual's life; includes use of vaccines during pregnancy
- 2014 Global Vaccine and Immunization Research Forum (WHO a co-sponsor)
  - BMGF presented its maternal immunization platform targeting 5 diseases: influenza, RSV, pertussis, GBS, tetanus.

# Conclusion

- Progress HAS been made over the last decade for maternal immunization programs.
  - Some maternal immunization studies are completed or underway.
  - However, continued support is needed, both to gather additional data on licensed vaccines and also to develop new vaccines specifically intended for maternal immunization.
- Barriers to maternal immunization are being assessed and addressed at national and international levels.

## Conclusion (cont.)

- FDA recognizes the need for better communication of available data to help health care providers advise women on use of vaccines during pregnancy.
- Action is being taken to revise product labeling requirements for pregnancy and lactation.
- The window of opportunity to move forward with maternal vaccination programs is now.