In Utero Exposure to Drug and Biologic Products: Regulatory Considerations

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July 11, 2024

Disclosures and Disclaimers

- We have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent our opinions and do not necessarily represent the views of FDA

Outline of Presentation

- Background
- Current regulatory framework
- Examples of immunosuppressive effects after in utero exposure
- Knowledge gaps
- Workshop sessions

Background:
In utero Exposure to Drug and Biologic Products

Pregnant individuals report taking an average of 2.6 medications at any time during pregnancy

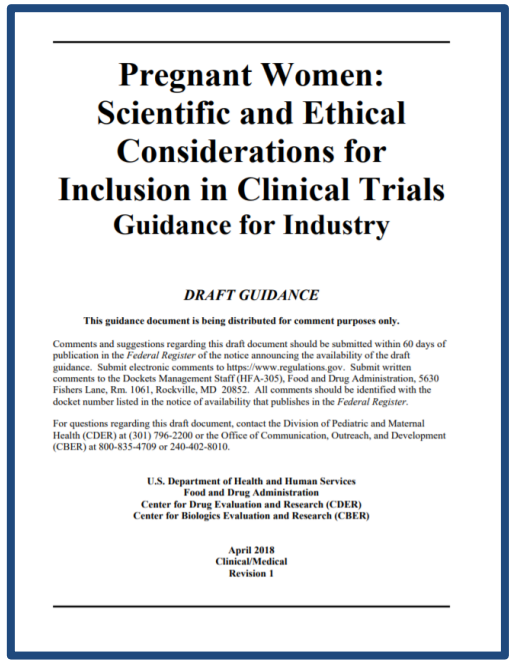
Medication use may expose the fetus and infant to the medication through placental transfer

Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernández-Díaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol*. Jul 2011;205(1):51.e1-8. doi:10.1016/j.ajog.2011.02.029

Current Regulatory Framework

Regulatory Framework: Inclusion of Pregnant Individuals in Drug Development Trials

- Historical landscape
  - Exclusion *from* research
  - Consequently, there are limited to no human safety data at the time of drug approval
- Current landscape
  - Inclusion to protect *through* research
  - Ethical considerations
  - Exclusion should be justified
  - Requirement to conduct nonclinical studies
- Efforts to advance inclusion of pregnant individuals
  - PRGLAC
  - NASEM
  - ICH



Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Division of Pediatric and Maternal Health (CDER) at (301) 796-2200 or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical
Revision 1

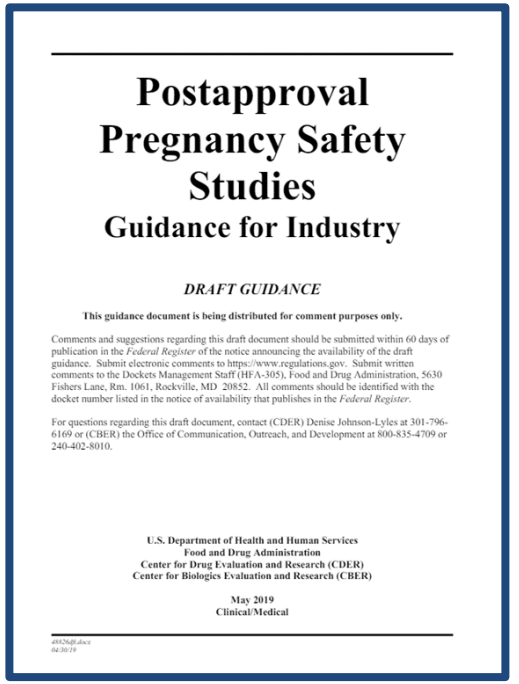
TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN (PRGLAC)

ICH harmonisation for better health

Regulatory Framework: Collection of Pregnancy Safety, PK and In Utero Exposure Data

- PMRs for Pregnancy Safety Studies
  - Pregnancy exposure registries
  - Complementary studies
  - Descriptive pregnancy safety studies
- Information that could be obtained from these studies
  - Pregnancy outcomes
  - Congenital malformations
  - Infant outcomes
  - Pharmacokinetics (PK) to inform dosing in pregnancy
  - Abnormalities of immune system development in offspring of exposed mothers

➢ Challenge: Identifying measures to evaluate PK and abnormalities of immune system development in neonates and infants



Postapproval Pregnancy Safety Studies

Guidance for Industry

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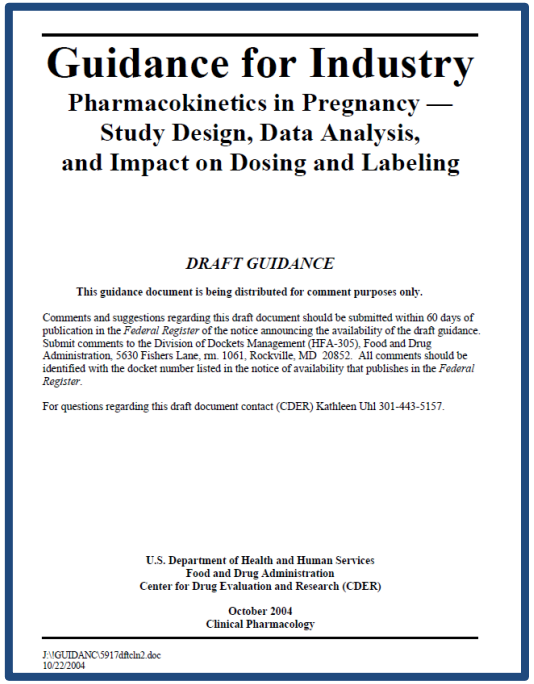
For questions regarding this draft document, contact (CDER) Denise Johnson-Lyles at 301-796-6169 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical



Guidance for Industry

Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling

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For questions regarding this draft document contact (CDER) Kathleen Uhl 301-443-5157.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2004
Clinical Pharmacology

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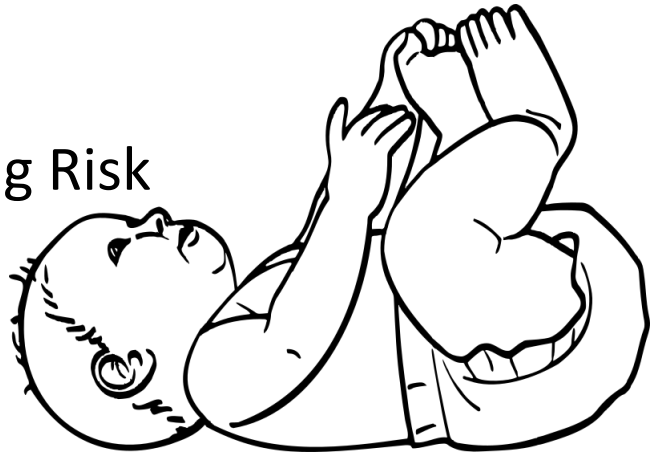
10/22/2004

Regulatory Framework: Labeling

- 8.1 Pregnancy:
  - Risk Summary
    - Relevant Data: human, animal, pharmacologic
    - Risk of Adverse Developmental Outcomes
  - Clinical Considerations
    - Relevant Information on Fetal/Neonatal Adverse Reactions
    - Intervention for Monitoring or Mitigating Risk



21 CFR 201.56 Requirements of content and format of labeling for human prescription drug and biologic products
21 CFR 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

Examples of Drug and Biologic Products with Immunosuppressive Effects in Offspring After In Utero Exposure

Drug: Baricitinib

MOA*	Janus kinase (JAK) inhibitor
Indication	For the treatment of active rheumatoid arthritis, severe covid-10, severe alopecia areata
Source of Data	Pre-market nonclinical study pre- and post-natal development (PPND) study
Safety Signal	Decreased cytotoxic T cells in rat offspring exposed in utero

8.1 Pregnancy

Risk Summary

In animal embryo-fetal development studies, oral baricitinib administration to pregnant rats and rabbits at exposures equal to and greater than approximately 11 and 46 times the maximum recommended human dose (MRHD) of 4 mg/day, respectively, resulted in reduced fetal body weights, increased embryolethality (rabbits only), and dose-related increases in skeletal malformations. No developmental toxicity was observed in pregnant rats and rabbits treated with oral baricitinib during organogenesis at approximately 2 and 7 times the exposure at the MRHD, respectively. In a pre- and post-natal development study in pregnant female rats, oral baricitinib administration at exposures approximately 24 times the MRHD resulted in reduction in pup viability (increased incidence of stillborn pups and early neonatal deaths), decreased fetal birth weight, reduced fetal body weight gain, decreased cytotoxic T cells on post-natal day (PND) 35 with evidence of recovery by PND 65, and developmental delays that might be attributable to decreased body weight gain. No developmental toxicity was observed at an exposure approximately 5 times the exposure at the MRHD *(see Data)*.

*MOA = Mechanism of Action

Biologic: Alirocumab

MOA	Monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9)
Indication	For the treatment of cardiovascular disease & hypercholesterolemia
Source of Data	PPND study
Safety Signal	Suppression of humoral immune response in infant monkeys exposed in utero

8.1 Pregnancy

Risk Summary

Available data from clinical trials and postmarketing reports on PRALUENT use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In animal reproduction studies, there were no effects on embryo-fetal development when rats were subcutaneously administered alirocumab during organogenesis at dose exposures up to 12-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. In monkeys, suppression of the humoral immune response was observed in infant monkeys when alirocumab was dosed during organogenesis to parturition at dose exposures 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks. No additional effects on pregnancy or neonatal/infant development were observed at dose exposures up to 81-fold the maximum recommended human dose of 150 mg every two weeks. Measurable alirocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that alirocumab, like other IgG antibodies, crosses the placental barrier. Monoclonal antibodies are transported across the placenta in increasing amounts especially near term; therefore, alirocumab has the potential to be transmitted from the mother to the developing fetus.

Biologic: Infliximab

MOA	IgG1κ monoclonal antibody specific for human tumor necrosis factor alpha (TNF-α)
Indication	For the treatment of IBD, RA, PsA, Pso, AS*
Source of Data	Case reports Pharmacovigilance
Safety Signal	• Detectable drug levels months after birth in human infants exposed in utero • Death from sepsis & disseminated Bacille Calmette-Guérin (BCG) in human infants exposed in utero

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that there is an increased risk of adverse pregnancy outcomes in women with inflammatory bowel disease or rheumatoid arthritis associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2.5 kg) and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants *[see Warnings and Precautions (5.13)]*. Cases of agranulocytosis in infants exposed *in utero* have also been reported *[see Adverse Reactions (6.3)]*.

*IBD = Inflammatory Bowel Disease; RA = Rheumatoid Arthritis; PsA = psoriatic arthritis; Pso = plaque psoriasis; AS =ankylosing spondylitis

Knowledge Gaps

- Fetal immune system development
- Infant immune system function
- Other Potential Impacts

Workshop Overview

Day 1

- ***Background Session:*** Background and Current Landscape
- ***Session 1:*** Current Clinical and Safety Considerations
- ***Session 2:*** Nonclinical Evaluation of Placental Transfer and Immunotoxic Potential
- ***Session 3:*** Framing Concerns for In Utero Exposed Infants Based on Available Data

Day 2

- ***Session 4:*** Clinical Study Design Considerations
- ***Session 5:*** Synthesis, Future Directions, and Next Steps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