FDA Perspective on Pregnancy-Fetal Physiologically Based Pharmacokinetic Modeling

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Disclaimer

- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and not the official position of the FDA

Current Challenges

- Pregnant and lactating individuals are underrepresented in research
  - No regulatory requirement to include in drug development
  - Need for shift in paradigm from automatic exclusion to presumed eligibility and thoughtful inclusion
  - Move from “protect from research” to “protect through research”
  - Industry concerns re: liability, lack of incentives, etc.

FDA Perspective

- Committed to advancing research in pregnant and lactating individuals
  - Lack of data in pregnant and lactating individuals is a public health issue
  - Data needed to inform benefit-risk considerations
  - FDA supports innovative approaches to advance the science
- FDA has published several guidances
  - To advance data collection in pregnant and lactating individuals

- Participant in Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)

- Required under the 21st Century Cures Act of 2016
- Objectives: Identify and address gaps in knowledge and research regarding safe and effective therapies for pregnant women and lactating women
- Prepare a report and recommendations to the Secretary of the Department of Health and Human Services (first report completed September 2018; Implementation Report published October 2020)

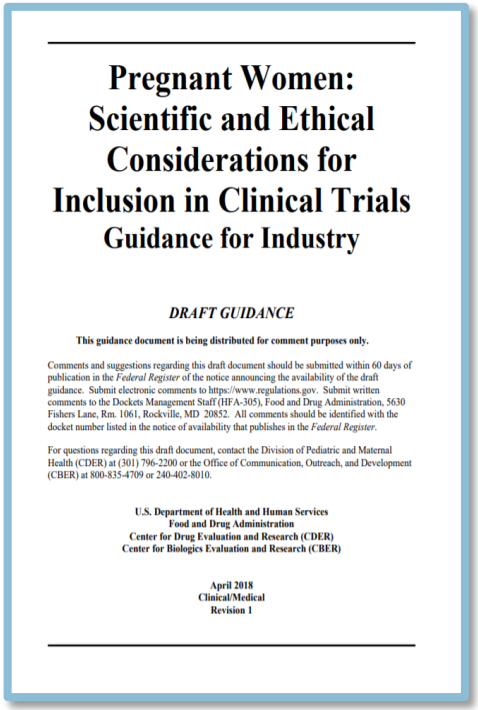
https://www.nichd.nih.gov/about/advisory/PRGLAC

PRGLAC Reports Take-Aways

- Include and integrate pregnant/lactating individuals in the clinical research agenda
- Address barriers to research (ethical considerations, liability concerns, and potential incentives)
- Need to develop research tools and strategies
  - *Physiologically Based Pharmacokinetic (PBPK) Modeling*
- Fostering education and awareness
- Creating partnerships

FDA Efforts to Advance Drug Development and Data Collection in Pregnant and Lactating Individuals: Guidances

Pregnancy and Lactation Guidances



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

DRAFT GUIDANCE

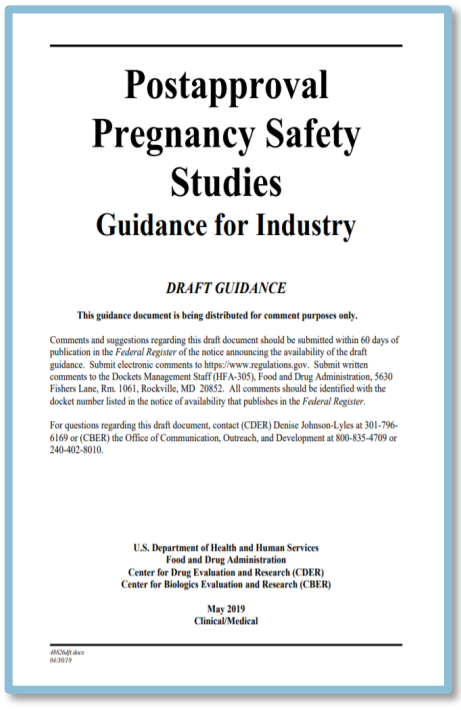
This guidance document is being distributed for comment purposes only.

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



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

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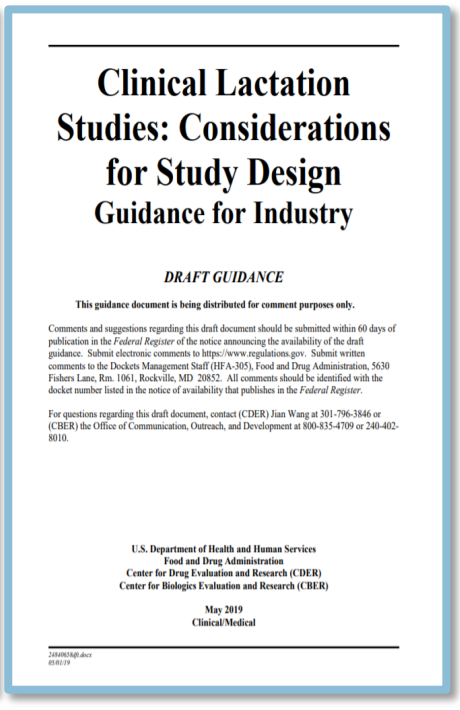
04/30/19



Clinical Lactation Studies: Considerations for Study Design
Guidance for Industry

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For questions regarding this draft document, contact (CDER) Jian Wang at 301-796-3846 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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May 2019
Clinical/Medical

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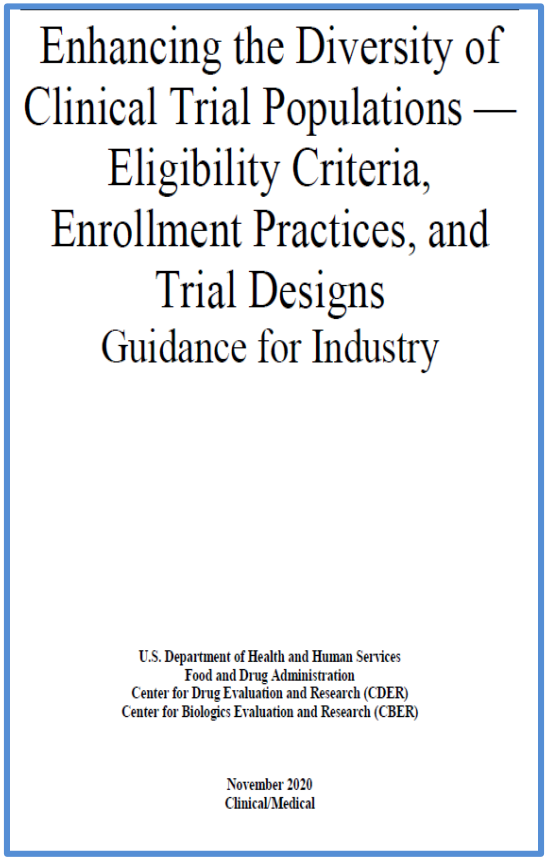
05/01/19

Guidances that Discuss Pregnancy PK Data Collection

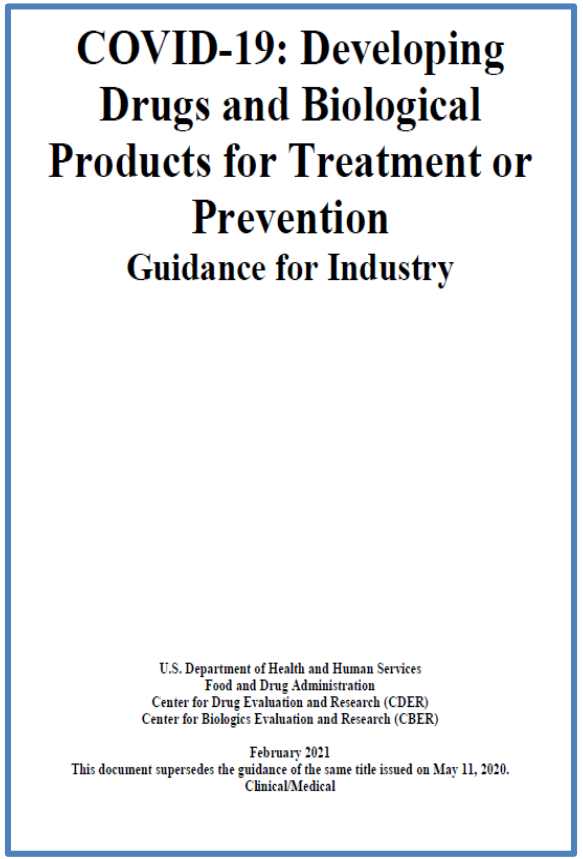


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

Guidance for Industry

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)

November 2020
Clinical/Medical

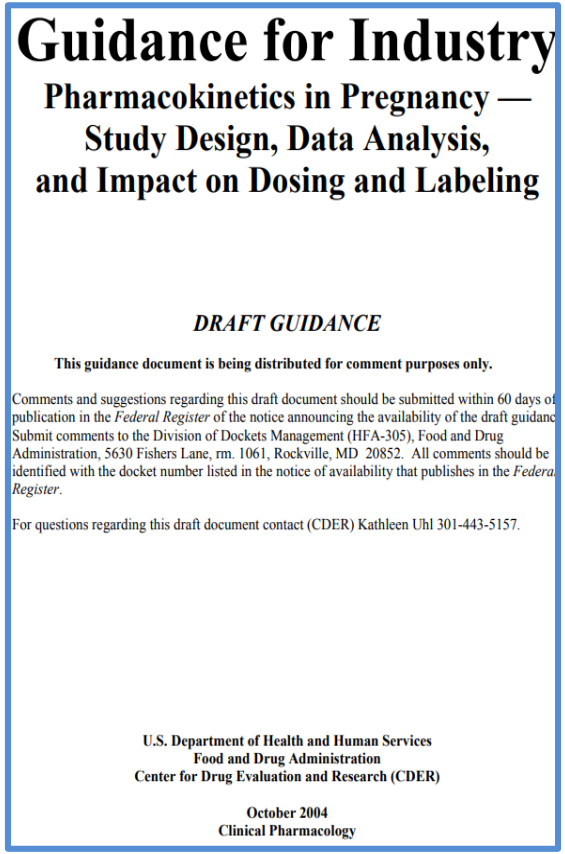


COVID-19: Developing Drugs and Biological Products for Treatment or Prevention

Guidance for Industry

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)

February 2021
This document supersedes the guidance of the same title issued on May 11, 2020.
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

Guidances to Advance Drug Development and Data Collection in Pregnant and Lactating Individuals

- Pregnant and lactating individuals are an important segment of the population that need to be studied
- Early and thoughtful consideration are needed to avoid delays
- Safety, and dosing data are key
- Innovative research strategies are needed

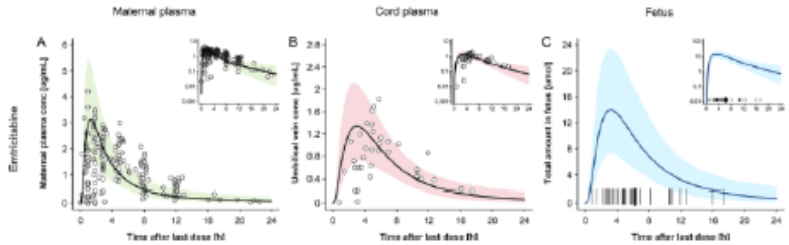
Pregnancy-Fetal PB PK Modeling

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-020-00977-w

ORIGINAL RESEARCH ARTICLE

Physiologically Based Pharmacokinetic Modeling Framework to Predict Neonatal Pharmacokinetics of Transplacentally Acquired Emtricitabine, Dolutegravir, and Raltegravir

Xiaomei I. Liu[1,2] · Jeremiah D. Momper[3,4] · Natella Y. Rakhmanina[2,5] · Dionna J. Green[6] · Gilbert J. Burckart[7] · Tim R. Cressey[8,9] · Mark Mirochnick[10] · Brookie M. Best[3,4] · John N. van den Anker[1,11] · André Dallmann[12]



The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Physiologically Based Pharmacokinetic Modeling

Physiologically Based Pharmacokinetic Models to Predict Maternal Pharmacokinetics and Fetal Exposure to Emtricitabi and Acyclovir

Xiaomei I. Liu PharmD, Jeremiah D. Momper PharmD, PhD, Natella Rakhmanina MD, PhD, John N. va Anker MD, PhD, FCP, Dionna J. Green MD, Gilbert J. Burckart PharmD, FCP ... See all authors

First published: 06 September 2019 | https://doi.org/10.1002/jcph.1515 | Citations: 16

Clinical Pharmacology & Therapeutics

White Paper | Open Access

Optimizing Pharmacology Studies in Pregnant and Lactating Women Using Lessons From HIV: A Consensus Statement

Ahizechukwu C. Eke, Adeniyi Olagunju, Jeremiah Momper, Martina Penazzato, Elaine J. Abrams, Brookie M. Best, Edmund V. Capparelli, Adrie Bekker, Yodit Belew, Jennifer J. Kiser, Kimberly Struble, Graham Taylor, Catriona Waitt, Mark Mirochnick, Tim R. Cressey, Angela Colbers on behalf of the participants of the WHO-IMPAACT workshop on "Approaches to Optimize and Accelerate Pharmacokinetic Studies in Pregnant and Lactating Women", ... See fewer authors

First published: 15 September 2020 | https://doi.org/10.1002/cpt.2048 | Citations: 4

New CDER Impact Story on Physiologically Based Pharmacokinetic Modeling of Sertraline Dosing in Pregnancy - Drug Information Update

U.S. Food and Drug Administration sent this bulletin at 08/31/2021 03:45 PM EDT

If your email program has trouble displaying this email, view it as a web page.

Physiologically Based Pharmacokinetic Modeling of Sertraline Dosing in Pregnancy

Pregnant women are a special and vulnerable population with respect to drug therapy but have often been excluded from clinical trials. CDER researchers and NCTR collaborators are working to develop quantitative predictive modeling tools to ensure that drug treatment during pregnancy maximizes maternal therapeutic benefit while minimizing fetal risk.

Pregnancy-Fetal PB PK Modeling Potential Uses

- Simulate exposure in pregnancy to inform the design and conduct of PK studies
- Support decision making about dose selection and PK sampling times when clinical data are sparse (need for fewer patients is an advantage)
- Support dosing in pregnancy
- Inform fetal exposure and toxicity
- Inform neonatal drug concentrations

Pregnancy-Fetal PB PK Modeling Considerations

- Are the clearance pathway(s) of the drug well verified
- Can the drug model predict the PK of the drug in nonpregnant populations
- Can the pregnancy-fetal-neonatal model predict the PK of drug products with similar absorption, distribution, metabolism, and elimination

Summary

- FDA is committed to advancing clinical research in pregnant individuals
- Growing recognition of the critical importance of data when treating pregnant individuals
- Innovative approaches such as pregnancy-fetal-neonatal PBPK modeling have great potential
- Stakeholder collaboration is essential to move forward

Thank You