GENERAL REGULATORY CONSIDERATIONS

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Director, Office of Pediatric Therapeutics
Office of Clinical Policy and Programs
Office of the Commissioner

Fetal Pharmacology & Therapeutics Workshop
FDA-MCERSI
October 21, 2021

Disclaimer

- This presentation reflects the opinions and views of the speaker and should not necessarily be interpreted as the position of the US Food and Drug Administration

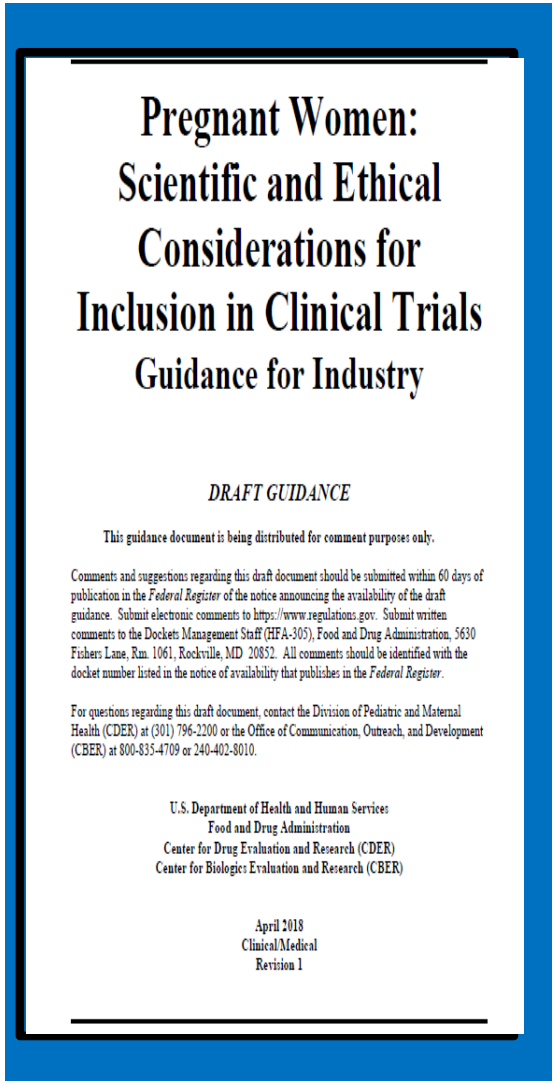
Outline

- Regulatory considerations when evaluating therapies intended for pregnant individuals and/or their fetuses
- Opportunities and challenges of using quantitative models to advance the science of fetal therapeutics

US Regulations Governing Maternal-Fetal Research

- Pediatric regulations do NOT apply to the fetus
- HHS* regulations (Common Rule) include specific protections for human subjects, children, pregnant women and fetuses
- FDA has parallel regulations for the protections for human subjects and children, but does not have regulations pertaining to fetal research

*Department of Health and Human Services



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

Guidance for Industry

DRAFT GUIDANCE

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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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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.

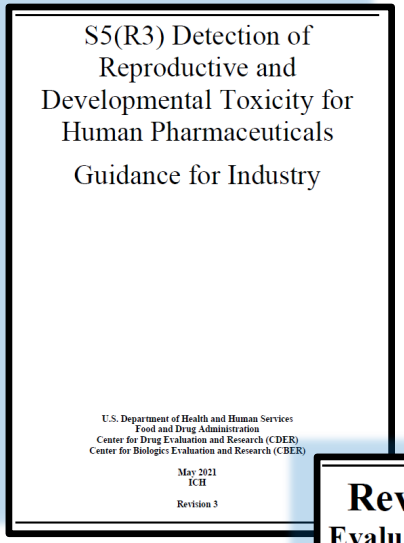
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical
Revision 1

- Reasons for including pregnant persons in clinical trials:
  - Need safe and effective treatments during pregnancy
  - Failure to establish dosing, safety and efficacy of treatments may compromise health
  - Possibility of direct benefit that is unavailable outside the research setting
  - Limited accessible treatment options is a significant public health issue
- Decisions for inclusion of pregnant women necessitate complex risk benefit analyses that **take into account both the pregnant individual and fetus**
- General considerations:
  - Postmarketing setting (i.e., FDA-approved drugs)
  - Premarketing setting (i.e., investigational drugs)
- PK data:
  - Phase 2 trials
  - Phase 3 trials
- **Sponsors should consider meeting with the appropriate FDA review division early in development**

https://www.fda.gov/media/112195/download

FDA Guidances Pertaining to Maternal-Fetal-Neonatal Studies

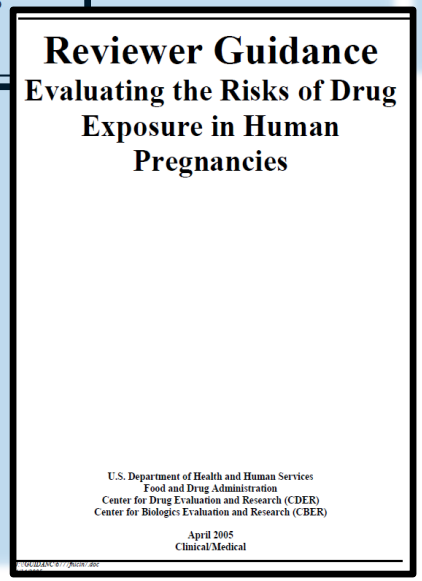

S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals

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)

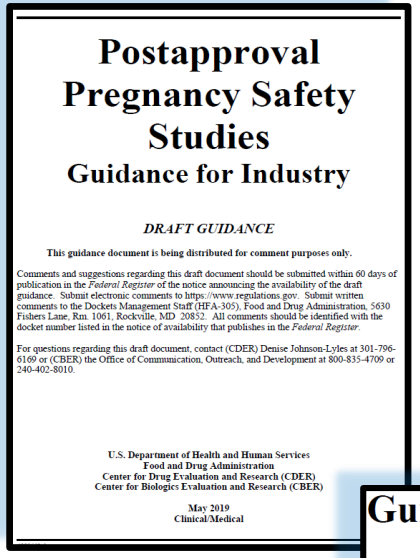
May 2021
ICH

Revision 3


Reviewer Guidance
Evaluating the Risks of Drug Exposure in Human Pregnancies

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 2005
Clinical/Medical


Postapproval Pregnancy Safety Studies
Guidance for Industry

DRAFT GUIDANCE

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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.

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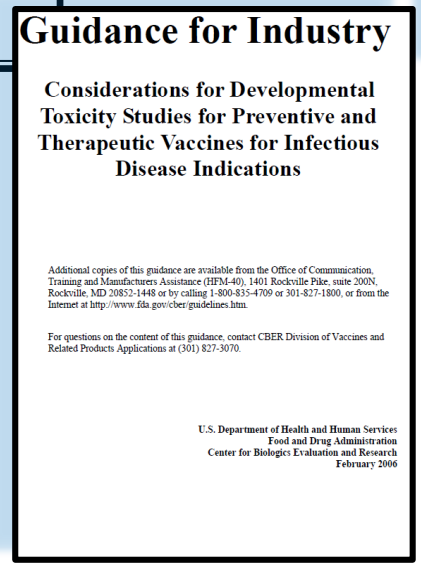
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Clinical/Medical

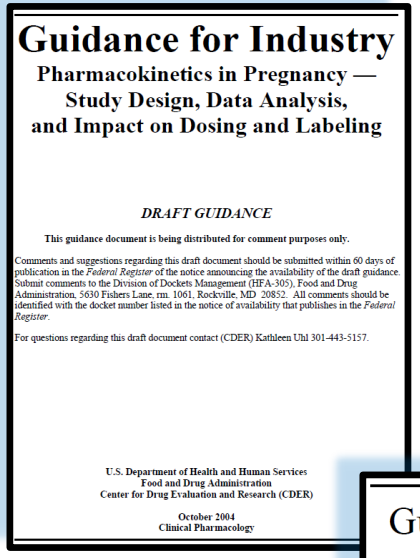

Guidance for Industry

Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448 or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact CBER Division of Vaccines and Related Products Applications at (301) 827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2006


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

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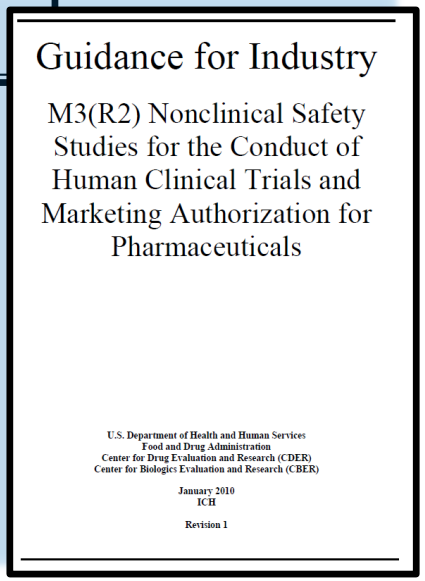
For questions regarding this draft document contact (CDER) Kathleen Uhl 301-443-5157.

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

October 2004
Clinical Pharmacology


Guidance for Industry

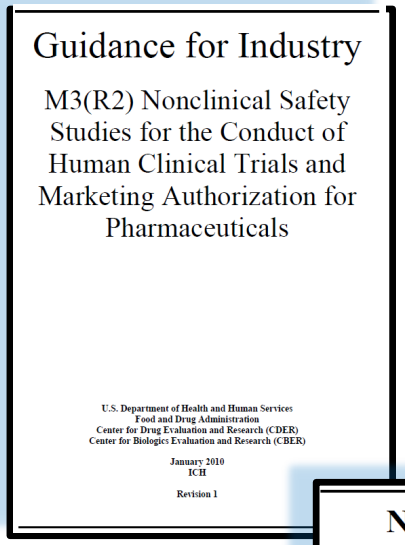
M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

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)

January 2010
ICH

Revision 1

Guidances (cont.)

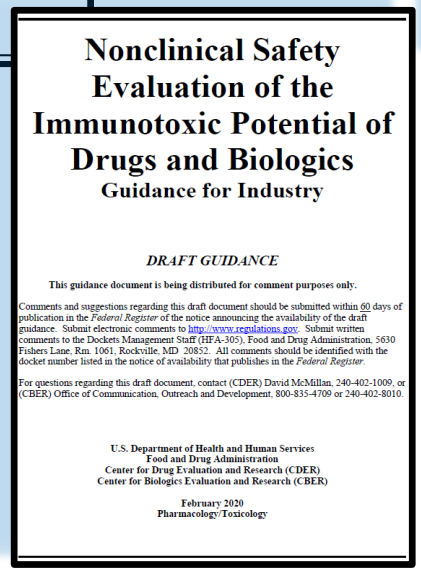

Guidance for Industry

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

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)

January 2010
ICH

Revision 1


Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics
Guidance for Industry

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For questions regarding this draft document, contact (CDER) David McMillan, 240-402-1009, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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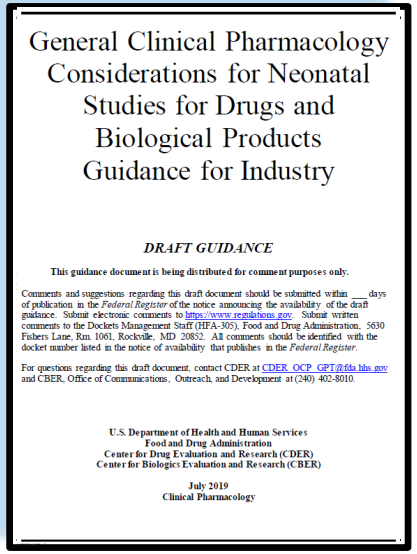
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2020
Pharmacology/Toxicology


General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products
Guidance for Industry

DRAFT GUIDANCE

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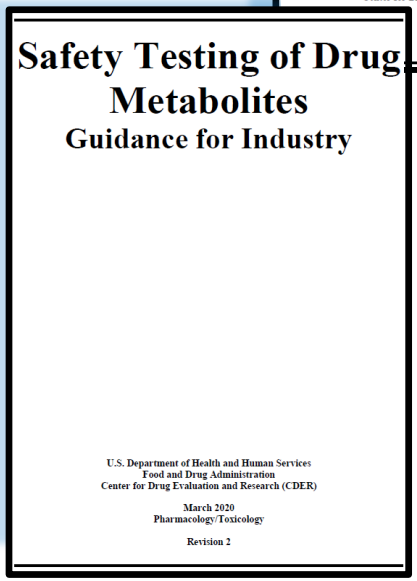
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2019
Clinical Pharmacology

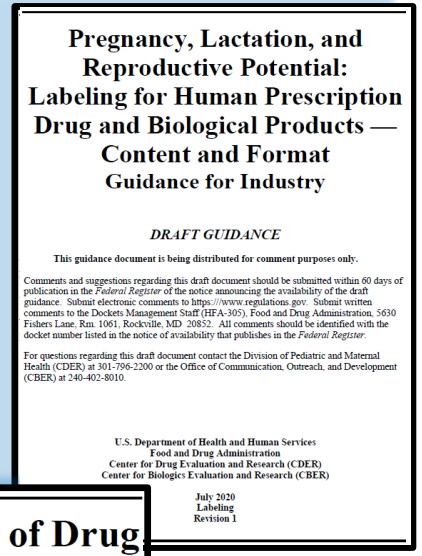
"A starting dose based on a minimal anticipated biologic effect level (MABEL) or a pharmacological effect level (PEL) may be more appropriate than a starting dose based on toxicology endpoints such as the no observed adverse effect level (NOAEL)"


Safety Testing of Drug Metabolites
Guidance for Industry

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

March 2020
Pharmacology/Toxicology

Revision 2


Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format
Guidance for Industry

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2020
Labeling
Revision 1

"When a drug is intended for use in a population that includes women of childbearing potential, sponsors should conduct embryo-fetal development toxicity studies with the drug metabolite."

Fetal Therapeutics

Disease	Drug(s)	Reference
Prematurity	Corticosteroids	Shanks et al[6]
Fetal tachyarrhythmia	Digoxin, flecainide, Sotalol, verapamil	Giacoia et al[7]
Fetal bradyarrhythmia	Dexamethasone, IVIG, hydroxychloroquine	Kumar et al[8]
Multiple genetic	Gene/stem cell therapy	O'Connell et al[1]

JAMA Pediatrics | Review

Gene and Stem Cell Therapies for Fetal Care
A Review

Amy E. O'Connell, MD, PhD; Stephanie Guseh, MD; Larissa Lapteva, MD, MHS, MBA; Christy L. Cummings, MD; Louise Wilkins-Haug, MD, PhD; Jerry Chan, MB BCh BaO, MA, PhD; William H. Peranteau, MD; Graça Almeida-Porada, MD, PhD; Stella Kourembanas, MD

Box. Partial List of Genetic Disorders Amenable to Fetal Intervention

Hemophilia A
Alpha- and beta-thalassemia
Ectodermal dysplasia
Spinal muscular atrophy
Zellweger disease
Niemann-Pick disease
Surfactant deficiency

Skeletal dysplasia
Congenital disorders of glycosylation
Osteogenesis imperfecta
Cystic fibrosis
Leber congenital amaurosis
Alport syndrome
Urea cycle disorders

Slide courtesy of Dr. Gilbert Burckart

O'Connell et al. JAMA Pediatr. 2020 Oct 1;174(10):985-991.

Model-Informed Drug Development (MIDD)

- Development and application of exposure-based, biological and statistical models to inform drug development and decision-making
- In 2018, FDA introduced the MIDD Pilot Program to:
  - Provide an opportunity for drug developers and FDA to discuss the application of MIDD approaches
  - Provide advice about how particular MIDD approaches can be used in a specific drug development program
- Submissions can be related to any relevant MIDD topic; prioritization has been given to strategies for:
  - Dose selection or estimation
  - Clinical trial simulation
  - Predictive or mechanistic safety evaluation

https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

Quantitative Models to Advance the Science of Maternal/Fetal Therapeutics: Opportunities

- Quantitative modeling approaches are routinely used in drug development and can:
  - Leverage all prior knowledge and integrate information from diverse data sources
  - Reduce unnecessary studies
  - Decrease uncertainty and attrition
  - Provide a regulatory pathway forward for practically challenging drug development contexts
  - Inform appropriate use of a drug once approved

- Maternal-fetal PBPK models have the potential to:
  - Increase the mechanistic understanding of PK of drugs in pregnancy
  - Estimate the drug concentration that the fetus is exposed to
  - Predict product safety
  - Investigate associations between in-utero drug exposure and long-term outcomes
  - Advance knowledge of fetal pharmacology
  - Inform target concentrations for fetal therapeutics
  - Select doses and explore optimal dosing regimens

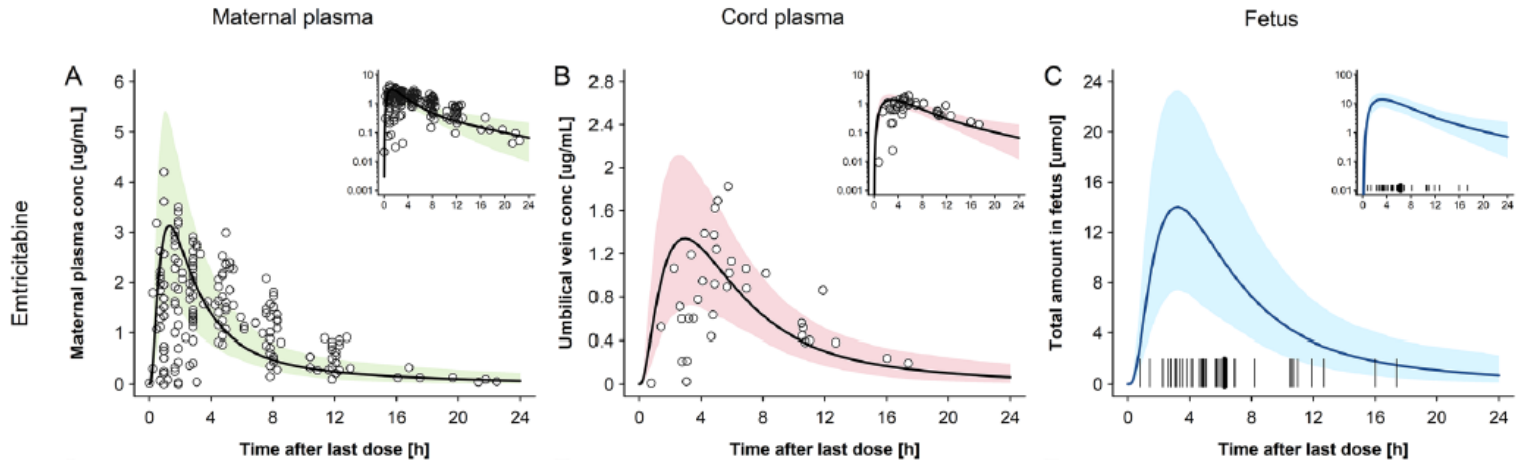
New Tools for Examining Fetal Concentrations

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

ORIGINAL RESEARCH ARTICLE

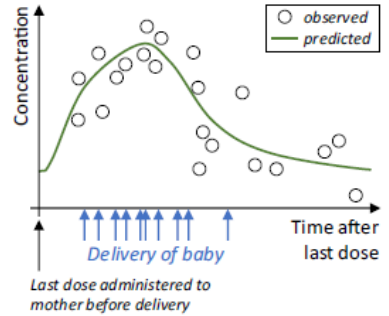
Physiologically Based Pharmacokinetic Modeling Framework to Predict Neonatal Pharmacokinetics of Transplacentally Acquired Emtricitabine, Dolutegravir, and Raltegravir

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]

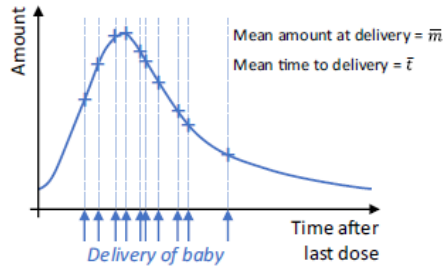


Maternal-fetal PBPK model

1. Predict drug concentrations in umbilical vein around delivery



2. Predict total drug amount in fetal compartment at delivery



Slide courtesy of Dr. Gilbert Burckart

Liu et al. Clin Pharmacokinet (2021).
https://doi.org/10.1007/s40262-020-00977-w

Quantitative Models to Advance the Science of Maternal/Fetal Therapeutics: Challenges

- Prediction accuracy dependent on quality (and quantity) of prior data and assumptions
- Need for increased transparency of model assumptions
- Need for further basic science research on:
  - Physiologic and pharmacokinetic changes in pregnancy
  - Placenta transfer and distribution of drugs
  - Ontogeny of enzyme systems, transporters, and receptors in the fetus/neonate

Summary

- Additional regulatory protections govern the inclusion of pregnant individuals and their fetuses in research
- An increasing number of FDA guidances discuss topics such as:
  - Evaluating the risks of drug exposure in human pregnancies
  - Developmental toxicity studies
  - Scientific and ethical considerations for inclusion in research
  - PK assessment in pregnancy
- MIDD is regularly being integrated into drug development programs
- Modeling approaches, such as maternal-fetal PBPK models, have the potential to help advance the science of fetal pharmacology and therapeutics

Acknowledgements

- Gilbert Burckart, PharmD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