Regulatory Perspective on Advancing Pharmacokinetic and Lactation Studies in Pregnant and Lactating Women

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IMPAACT-WHO Meeting June 13, 2019

Objectives

Historical perspective

FDA efforts to advance research in pregnant and lactating women

Clinical Trials in Pregnant Women draft Guidance

Considerations for Antiretroviral (ARV) Pharmacokinetic (PK) trials

Enhancing the Diversity of Clinical Trial Populations draft Guidance

Postapproval Safety Studies draft Guidance

Lactation Studies draft Guidance

Considerations for ARV lactation trials

Disclaimer

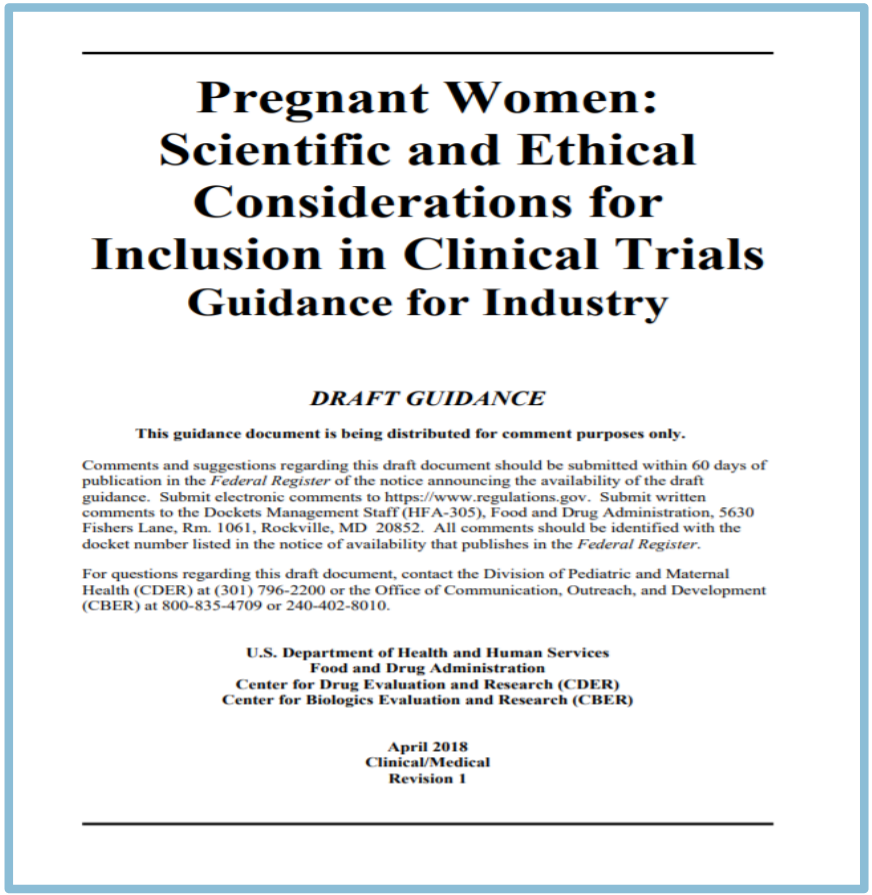
- I do not have any financial disclosures to report
- This presentation represents the views of the speaker, and not the official position of the FDA

Historical Perspective: Thalidomide and FDA's Culture of Safety

Advancing Research in Pregnant Women and Lactating Women

FDA' s perspective

- Committed to advancing research in pregnant and breastfeeding women
  - Clinical trials/PK trials; Lactation studies
  - Safety studies
- Regulatory advances
  - Common Rule: has removed reference to pregnant women as "vulnerable"
  - FDA is working to harmonize its regulations with the Common Rule
- Participant in Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- Participated in Congressional Briefing 5-29-2019



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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

Published
April, 2018

Guidance: Clinical Trials in Pregnant Women

- Ethical and scientific considerations
  - For when it would be appropriate to include pregnant women in clinical trials
  - Follows HHS framework of human subject protection regulations
  - Considerations for postmarket vs. premarket setting
  - Women who become pregnant during a trial
- FDA is reviewing public comments

Federal Regulations 45 CFR part 46, subpart B Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (10 requirements)

1. Nonclinical and clinical studies have been conducted and provide risk information
2. Prospect of direct benefit to the woman or fetus; if no benefit, the risk must be minimal
3. Least possible risk
4. Informed consent is obtained
5. If the prospect of direct benefit is solely for the fetus, then additional consent from the father is needed, unless he is unavailable, incompetent, has temporary incapacity or the pregnancy results from rape or incest

45 CFR 45, Subpart B :10 Requirements

6. Participants are fully informed of the risks to the fetus or neonate
7. For children who are pregnant, assent and permission are obtained
8. No inducements for pregnancy termination
9. Investigators not involved in decisions re: pregnancy termination
10. Investigators not involved in determining the viability of a neonate

PK Trials: Postmarketing vs Premarketing Setting

- Considerations:
  - All 10 regulatory requirements of Subpart B have to be met (these are federal regulations and are followed by FDA)
  - Risk-benefit may vary depending on the setting (i.e. amount of data available to inform safety, efficacy, and dosing; gestational age, etc.)

Nonclinical Studies

- *ICH M3(R2) Nonclinical Safety Studies for the Conduct of Human Trials and Marketing Authorization for Pharmaceuticals*
- Before pregnant women can be included in clinical trials, all female reproduction toxicity studies AND standard battery of genotoxicity studies should be conducted
  - Drug substance
  - Novel excipients
  - Drug substance impurities

Nonclinical Studies

- *ICH S5A Detection of Toxicity to Reproduction for Medicinal Products**
  - Fertility and Early Embryonic Development to Implantation (Fertility)
  - Effects on Embryo-Fetal Development (EFD) (Teratogenicity Study)
  - Prenatal and Postnatal Development, Including Maternal Function (PPD)

**Undergoing revision*

PK Trials in the Postmarketing Setting

- Considerations:
  - Most likely scenario as regulatory requirements have probably been met
  - Opportunistic PK studies
  - Considerations for when a single dose PK study in virologically suppressed women may be possible:
    - What is the drug's safety profile ?
    - Would it be considered a minimal risk study?

PK Trials in the Pre-marketing Setting

- More challenging due to limited safety, efficacy, and dosing information
- Scenario 1: Women who become pregnant during a trial

  Considerations to allow continued participation and PK data collection:

  – Are the nonclinical data adequate to support lack of risk?

  – Do the benefits of continued treatment outweigh the risks (1. to the fetus, 2. the risk of discontinuation and 3. switching to another drug(s) with potential fetal exposure to an additional drug)
- Consent and unblinding

  – Unblinding for adequate risk-benefit considerations

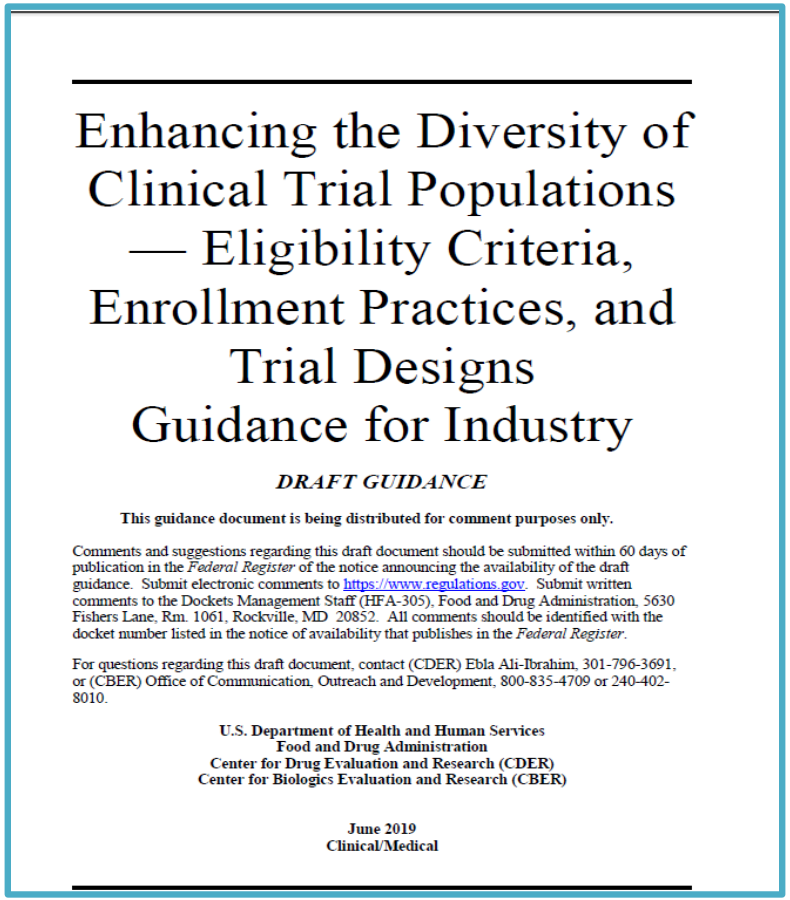
  – Re-consent as a pregnant participant

PK Trials in the Pre-marketing Setting

- Scenario 2: Include in the development plan
  - Considerations : Many questions
  - When ? Phase 3 ? Phase 2b ?
  - Restrict enrollment to pregnant woman with no alternative effective regimen to justify exposure to an investigational drug ? Do the benefits of treatment outweigh the risks?
  - If nonclinical study results not available, consider the inclusion of pregnant women when available ?
  - Labeling considerations: would still need to state that there are no human data to assess the risk of major birth defects and miscarriage

Safety Monitoring

- Consideration for increased safety monitoring
- Cord blood collection at time of delivery
- Pregnancy outcome data
- Follow infant until 1 year of age in a pregnancy registry or other observational study



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

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For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

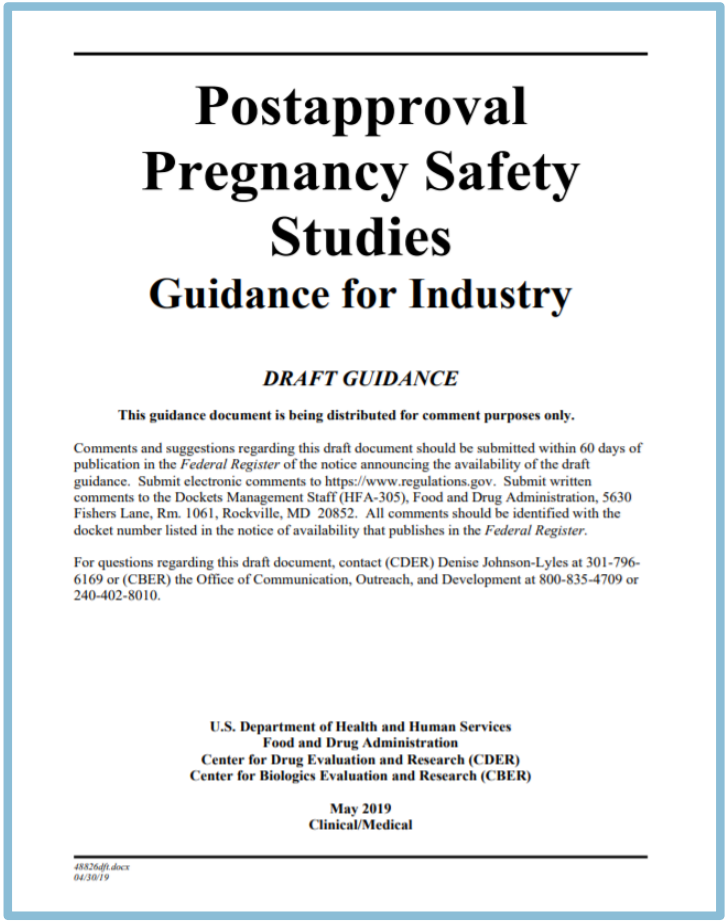
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2019
Clinical/Medical

Published June 7, 2019

Innovation to Advance the Science

- Industry needs to initiate nonclinical studies earlier in development
- Pro-active approach to women who become pregnant in a trial
- Discussions with FDA need to occur early
- Evolving understanding of the need to include pregnant women in research



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.

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

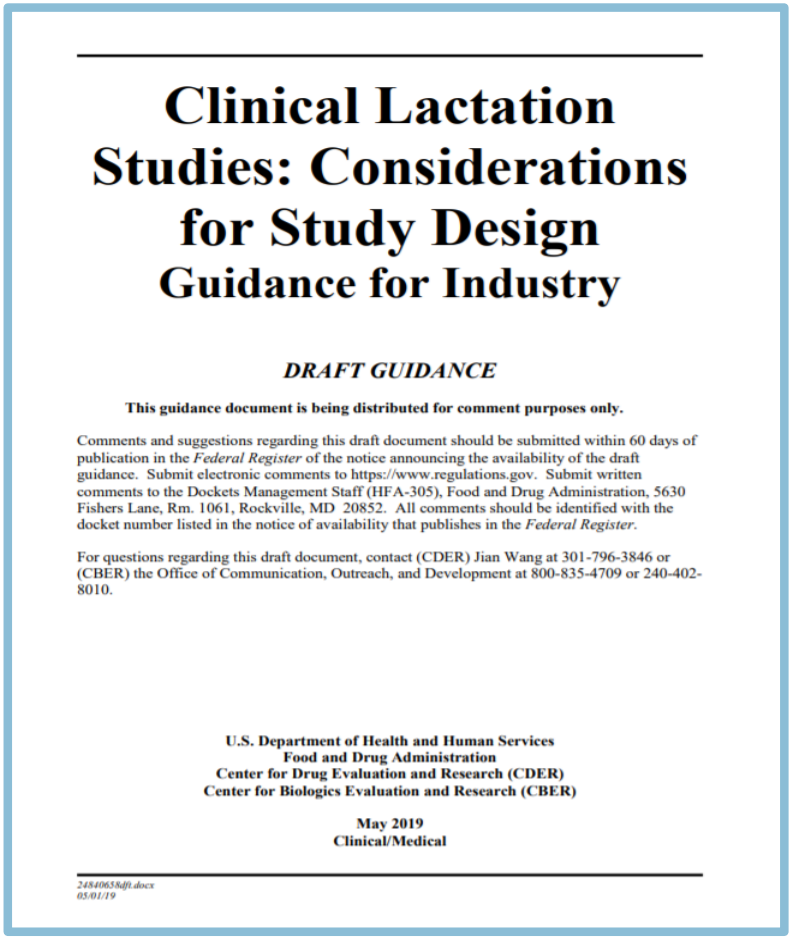
May 2019
Clinical/Medical

48826dft.docx
04/30/19

Published May 9, 2019

Guidance: Postapproval Pregnancy Safety Studies

- Replaces 2002 Pregnancy Registry Guidance
- Broadens the scope to include pharmacovigilance, pregnancy registries, and database studies
- Recognition that a single study is not sufficient for adequate safety assessment
- Rare outcomes are difficult to assess e.g. dolutegravir neural tube defect signal
- Advantages and limitations to each study design



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.

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

248406558dft.docx
05/01/19

Published May 9, 2019

Guidance: Clinical Lactation Studies

- General Considerations (non ARV/HIV context):
  - Opportunistic studies are appropriate: no study related risk to infant
  - Investigational drug/study drug :
    - Study risk: infant exposure to drug is a concern
    - Recommend pump and discard during the milk collection and clearance interval, and feed the infant stored breastmilk

Conduct of Lactation Studies

- Preferable in fully breastfeeding women
- Mature milk (>10 days postpartum)
- At steady state
- No interruption of breastfeeding (opportunistic studies)
- Milk only studies may be sufficient
- Pump and discard if investigational drug
- Safety data collection in infant

Lactation Studies Considerations

- ARV/HIV context : Many Questions
  - Ex US vs US?
  - HIV infection transmission and need for prophylaxis
- Opportunistic studies
- Interventional Trials
  - Prospect of direct benefit (to reduce HIV transmission to the breastfeeding infant)
  - FDA and HHS Subpart D regulations apply (Additional Safeguards for Children)

Summary re: Pregnancy PK and Lactation Studies

- Many Considerations
  - Human Subject Protection Regulations applied broadly
  - Every situation is unique: toxicity profile, available nonclinical, safety, efficacy, dosing data; prospect of direct benefit vs. minimal risk
  - Need to engage with FDA early
  - FDA is open to innovative study designs

FDA's Role in Addressing PRGLAC Recommendations

1. Include and integrate pregnant/lactating women in the clinical research agenda
2. Increase the quantity, quality, and timeliness of research involving therapeutic products used by pregnant/lactating women
3. Expand the workforce of clinicians and research investigators with expertise in obstetric and lactation pharmacology
4. Remove regulatory barriers to research in pregnant women
5. Create a public awareness campaign to engage the public and healthcare providers in research on pregnant/lactating women
6. Develop and implement evidence based communication strategies with health care providers on information relevant to research on pregnant/lactating women

FDA's Role in Addressing PRGLAC Recommendations

7. Develop programs to study products used off-patent in pregnant/lactating women using NIH Best Pharmaceuticals for Children Act as a model
8. Reduce liability to facilitate research in women who are or may become pregnant and in lactating women
9. Implement a proactive approach to protocol development and study design to include pregnant/lactating women in research
10. Develop programs to drive discovery/development of new therapeutics for conditions specific to pregnant/lactating women

FDA's Role in Addressing PRGLAC Recommendations

11. Utilize and improve existing resources for data to inform the evidence and provide a foundation for research on pregnant/lactating women
12. Leverage established and support new infrastructures/collaborations to perform research in pregnant/lactating women
13. Optimize registries for pregnancy and lactation
14. Extend the charter for the Taskforce
15. Establish an Advisory Committee to monitor and report on the implementation of the Taskforce recommendations

Summary

- FDA is committed to advancing research in pregnant and breastfeeding women
- Regulatory advances are occurring
- Reflection of growing consensus on the need to include pregnant and breastfeeding women in research
- Challenges: industry is risk averse; adequate resources are not allocated to study these populations
- Stakeholder collaboration is essential

Acknowledgments

- Yodit Belew, MD, Division of Antiviral Products
- Kimberly Struble, Pharm D, Division of Antiviral Products
- Paul Brown, PhD, Office of New Drugs

Questions

Useful Links

- Clinical Trials in Pregnant Women Draft Guidance
  https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM603873.pdf
- Clinical Lactation Studies: Considerations for Study Design Draft Guidance

  https://www.fda.gov/media/124749/download
- Postapproval Pregnancy Safety Studies Draft Guidance

  https://www.fda.gov/media/124746/download
- Enhancing the Diversity of Clinical Trial Populations-Eligibility Criteria, Enrollment Practices, and Trial Designs Draft Guidance

  https://www.fda.gov/media/127712/download