CDER Prescription Drug Labeling Conference
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U.S. FOOD & DRUG ADMINISTRATION

The Pregnancy and Lactation Labeling Rule (PLLR): Four Years In- What's Next?

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Disclaimer

- The views and opinions expressed in this presentation represent those of the speaker, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Learning Objectives

- To discuss the Agency's key considerations for PLLR labeling conversion, including omission of clearly inapplicable or misleading information, and when to include labeling recommendations for pregnancy testing, contraception and infertility.
- To discuss recently published guidances and the steps that the Agency is taking to increase research specific to pregnant and lactating women.

Outline

- Introduction
- PLLR Implementation and Tracking
- Submission of PLLR Compliant Labeling
- PLLR Content Considerations
- New Guidances
- Efforts to Advance Research in Pregnant and Lactating Women

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Introduction

Division of Pediatric and Maternal Health (DPMH)

- Located within Office of New Drugs/Center for Drug Evaluation and Research(CDER)/FDA
- Comprised of Maternal Health Team, Pediatrics Team, and Pediatrics Regulatory Team
- DPMH oversees quality initiatives which promote and necessitate the study of drug and biological products in the pediatric population and improve pregnancy and lactation-related information in prescription drug labeling.

DPMH's Role with PLLR

- To provide consultation to CDER and Center for Biologics Evaluation and Research (CBER) review divisions in issues related to maternal health, including pregnancy and lactation.
- To collaborate within the Agency for consistency of process (including revision of the draft PLLR guidance).
- To track the drug product labeling compliance with PLLR.
- To raise awareness of PLLR amongst external and internal stakeholders.

PLLR Implementation

PLLR Implementation

Table 1: NDAs, BLAs, Efficacy Supplements (ESs) Required to Have Labeling Meet PLLR Format and Content Requirements (Effective Date of PLLR Final Rule: 6/30/2015)[1,2]

	NDAs, BLA, ESs	Required Submission Date for PLLR Format/Content[3]
New NDAs, BLAs, and ESs	Initially submitted on or after 6/30/2015	At time of submission of new NDA, BLA, or ES
NDAs, BLAs, or ESs approved 6/30/2001 through 6/30/2015 or "*pending*"[4] on 6/30/2015	Approved 6/30/2001 through 6/29/2002 Approved 6/30/2005 through 6/29/2007	6/30/2018
	Approved 6/30/2007 through 6/30/2015	6/30/2019
	"*Pending*"[4] on 6/30/2015	6/30/2019 or at the time of approval, whichever is later
	Approved 6/30/2002 through 6/29/2005	6/30/2020
NDAs or BLAs approved prior to 6/30/2001 (with no ES approved on or after 6/30/2001)	Voluntary PLR conversion originally submitted on or after 6/30/2015	At time of submission of voluntary PLR conversion labeling supplement

[1] See PLLR final rule for all the PLLR format and content requirements: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

[2] Includes 505(b)(1) and 505(b)(2) NDAs and 351(a) and 351(k) BLAs

[3] If more than one required submission date for PLLR format/content applies to an NDA, BLA, or ES, choose the earliest required submission date. For example, if an NDA was approved in 2003 (PLLR required submission date is 6/30/2020), an ES was approved in 2004 (PLLR required submission date is 6/30/2020), and another ES was approved in 2006 (PLLR required submission date is 6/30/2018); the required PLLR submission date is 6/30/2018.

[4] For the purposes of PLLR implementation, "*pending*" applications are those that are either under review, have received a complete response (CR), or have received a tentative approval as of 6/30/2015. For example, if an NDA was originally submitted in July 2014, received a CR in May 2015, and was resubmitted on or after the PLLR effective date (i.e., 6/30/2015), the NDA is considered "*pending*" on 6/30/2015 and the required submission date for PLLR format and content is 6/30/2019 or at the time of approval (whichever is later).

Tracking PLLR Converted Labeling*

- Between June 30, 2015 and June 30, 2019, >1300 applications approved with labeling that complies with PLLR
- 2018 cohort:
  - ~294 were required to comply with PLLR format and content requirements
  - 286 applications were submitted to comply with PLLR
    - 208 applications were approved in PLLR format
    - 78 applications are under review
  - 8 applications were not submitted

*Applications (including NDA, BLA, and Efficacy Supplements) approved on or after June 30, 2001 required to comply with PLLR

Tracking PLLR Converted Labeling

- 2019 cohort:
  - ~730 applications were required to comply with PLLR format and content requirements
  - 620 applications were submitted to comply with PLLR
    - 335 applications were approved in PLLR format
- 2020 cohort:
  - ~367 are anticipated

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Submission of PLLR Compliant Labeling

PLLR Labeling Submission

- Include labeling that complies with the PLLR content and format
- Include a review and summary of all available published literature regarding the drug and use in pregnant and lactating women and effects on male and female fertility
- Include a cumulative review and summary of relevant cases reported to your pharmacovigilance database (from the time of product development to present)
- Include a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval
- Include an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry (if applicable)
- Include the updated PLLR labeling and supportive information in Module 1 of the submission

Recommendation for Submission of PLLR Compliant Labeling

- Applicants should also review and update other sections of labeling pertinent to the PLLR (e.g., DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, CLINICAL PHARMACOLOGY, PATIENT COUNSELING INFORMATION) and Patient Labeling as necessary when updating the labeling to the PLLR format.

PLLR Content Considerations

Omissions*

- In some circumstances, applicants must omit certain subsections or specific information otherwise required under the PLLR because it is clearly inapplicable or misleading.
- The applicant should provide the rationale and justification for any proposed PLLR labeling omissions.

*[21 CFR 201.56(a)(2) and 21 CFR 201.56(d)(3)]

PLLR Omissions Example

- TRADENAME is a surfactant indicated for the rescue treatment, including the reduction of mortality and pneumothoraces, of Respiratory Distress Syndrome (RDS) in **premature infants**
- 8.1 Pregnancy and 8.2 Lactation were omitted from labeling because the information is clearly inapplicable.

8.1 Pregnancy, Risk Summary

- **Risk statement based on human data**
  - Determining whether pregnancy exposure data establish a drug-associated risk is a complex process that requires an assessment of the quality and quantity of available data.
  - Helps the prescriber to understand the benefit/risk of the drug
  - The types of available data should be specified (e.g., pregnancy registry, cohort, case-control, case series, case reports, etc.).
  - The focus is on evaluating the **safety** of drug use during pregnancy.

8.1 Pregnancy, Risk Summary

- **Risk statement based on animal data**
  - There are multiple considerations when determining potential human risks from animal data
    - Does the adverse developmental outcome occur in more than one animal species?
    - Is the adverse developmental outcome consistent across animal species?
    - What is the relative animal to human exposure?
    - Does the adverse developmental outcome occur in the absence of maternal toxicity?
    - Are there positive signals in other drugs of the same class or with the same mechanism of action?

8.1 Pregnancy, Risk Summary

- **Risk statement based on pharmacology***
  - When a drug has a well-understood pharmacologic mechanism of action that may result in adverse developmental outcomes, the Risk Summary must explain the mechanism of action and potential associated risks.
  - A cross-reference should be provided to CLINICAL PHARMACOLOGY, where the pharmacologic data on which this Risk Summary is based are more fully described.

*21 CFR 201.57(c)(9)(i)(B)(3)).

8.1 Pregnancy, Risk Summary-Example

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, TRADENAME can cause fetal harm when administered to a pregnant woman. Available human data are insufficient to inform the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies in mice and rabbits, embryo and fetal toxicity were observed with administration of drug name at doses approximately 0.33 and 0.18 times the human therapeutic dose, respectively *(see Data).* Advise pregnant women of the potential risk to a fetus.

8.2 Lactation, Risk Summary*

- For drugs absorbed systemically by the mother, unless breastfeeding is contraindicated during drug therapy, the labeling under the Risk Summary heading must include the following risk and benefit statement at the end of the labeling under the Risk Summary heading:

  The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breastfed child from (name of drug) or from the underlying maternal condition.

*21 CFR 201.57(c)(9)(ii)(A)(3)]

8.2 Lactation, Risk Summary

- When the drug is not contraindicated for use in breastfeeding women, but breastfeeding is not recommended during drug use because of the potential risk to the breastfed child (e.g., cytotoxic drugs), the labeling should include a statement describing the reason(s) to avoid breastfeeding.
  - Additionally, if breastfeeding is not recommended (e.g., cytotoxic drugs), the risk and benefit statement should be omitted because including such a statement may be misleading.
- When human data are available, animal data must not be included unless the animal model is specifically known to be predictive for humans.*

*21 CFR 201.56(d)(4) and 21 CFR 201.56(a)(2)]

8.3 Females and Males of Reproductive Potential

- Pregnancy Testing
- Contraception
- Infertility

8.3 Females and Males of Reproductive Potential, Pregnancy Testing*

- When FDA has determined that pregnancy testing is required or recommended, the labeling under the Pregnancy Testing heading must include this information.
- Timing and frequency of pregnancy testing and the type of pregnancy test used should be individualized to the patient.
- A statement regarding pregnancy testing should also be added to other sections of labeling, as applicable (e.g., DOSAGE AND ADMINISTRATION).

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Contraception*

- When FDA has determined that contraception is required or recommended before, during, or after drug therapy for the appropriate use of a drug with potential risk of adverse developmental outcomes, the Contraception heading must include this information.
- This information should also be included in other sections of labeling (e.g., PATIENT COUNSELING INFORMATION)

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Contraception*

- If data from nonclinical studies or mechanism of action raise concerns about mutagenesis
  - A summary of this information and its clinical implications must appear under the Contraception heading.
  - When pertinent, a cross-reference to the NONCLINICAL TOXICOLOGY section should be included for a detailed discussion of the nonclinical studies.
- If data from the nonclinical studies do not raise concern with respect to mutagenesis
  - Information should be described only in the NONCLINICAL TOXICOLOGY section.

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Contraception*

- If there are pharmacokinetic studies of semen that inform the need for contraception recommendations,
  - A summary statement of pertinent findings and recommendations should be included under the Contraception heading
  - There should be a cross-reference to the *Pharmacokinetics* subsection of the CLINICAL PHARMACOLOGY section for a more detailed study description.

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Contraception*

- If there is an interaction between the drug and hormonal contraception, a summary statement concerning the interaction and a recommendation to use a nonhormonal or additional method of contraception could be included.
  - A cross-reference to the DRUG INTERACTIONS section (and, if applicable, to other relevant sections of labeling) should be included for a more detailed description of the interaction

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Infertility*

- Describe the availability of human data that demonstrate adverse effects on male or female fertility
- Include a description of what is known about the potential reversibility of the adverse effect(s).
- If there are no available human fertility data, then no statement is needed.

*21 CFR 201.57(c)(9)(iii)

8.3 Females and Males of Reproductive Potential, Infertility*

- If data from animal studies or mechanism of action raises concerns about impairment of human fertility,
  - Include a summary of this information and its clinical implications under the Infertility heading.
  - When pertinent, cross-reference to the NONCLINICAL TOXICOLOGY section for a detailed discussion of the animal studies.
- If data from the animal studies do not raise concerns with respect to impairment of human fertility,
  - Information should be described only in subsection 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility*.

*21 CFR 201.57(c)(9)(iii)

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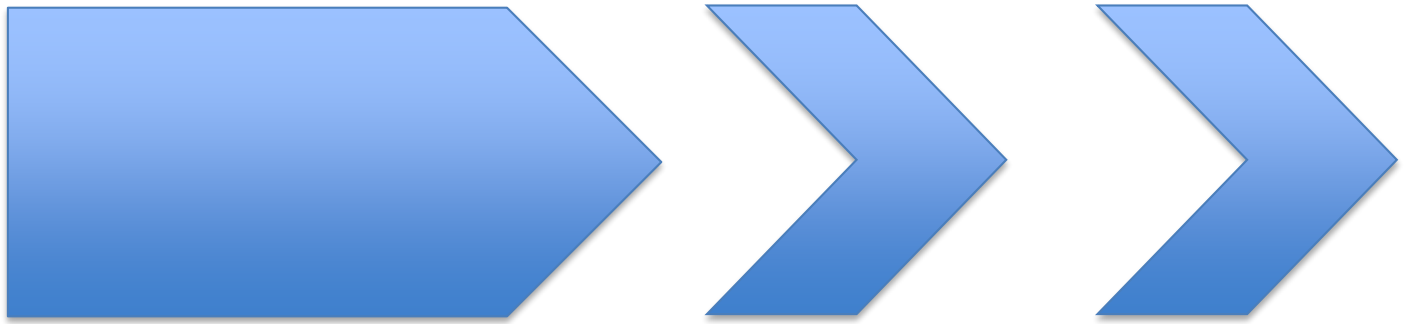
What's Next?



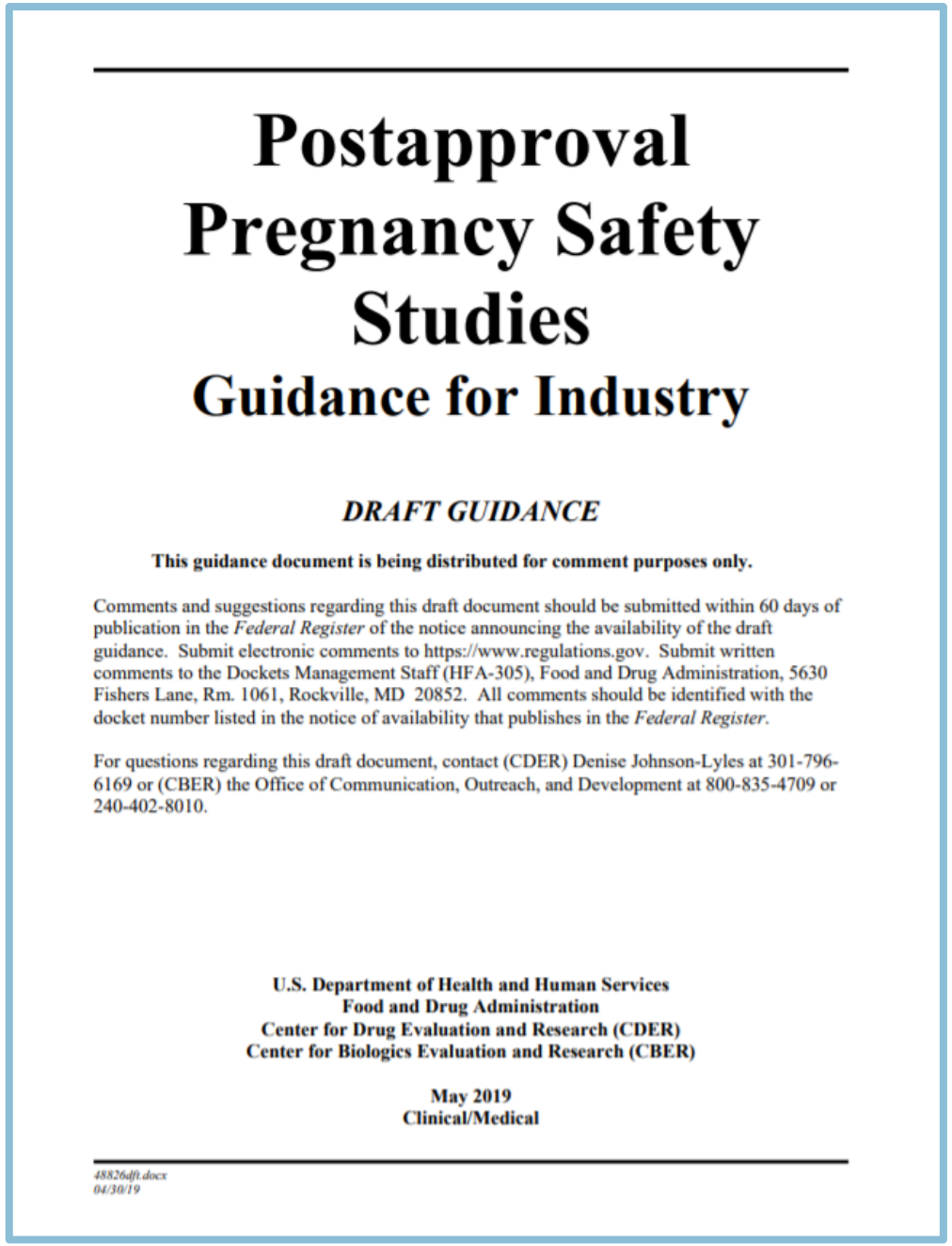
PLLR Research

- **Project:** “PLLR End User Testing to Improve Health Communications”
- **Aims:**

  -Identify gaps in HCP understanding of the PLLR content in labeling to improve risk communication between HCP and pregnant women.

  -Develop approaches for the presentation of pregnancy information in labeling (e.g., graphical representations) to improve risk communication.

New Guidances



Postapproval Pregnancy Safety Studies

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 (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)

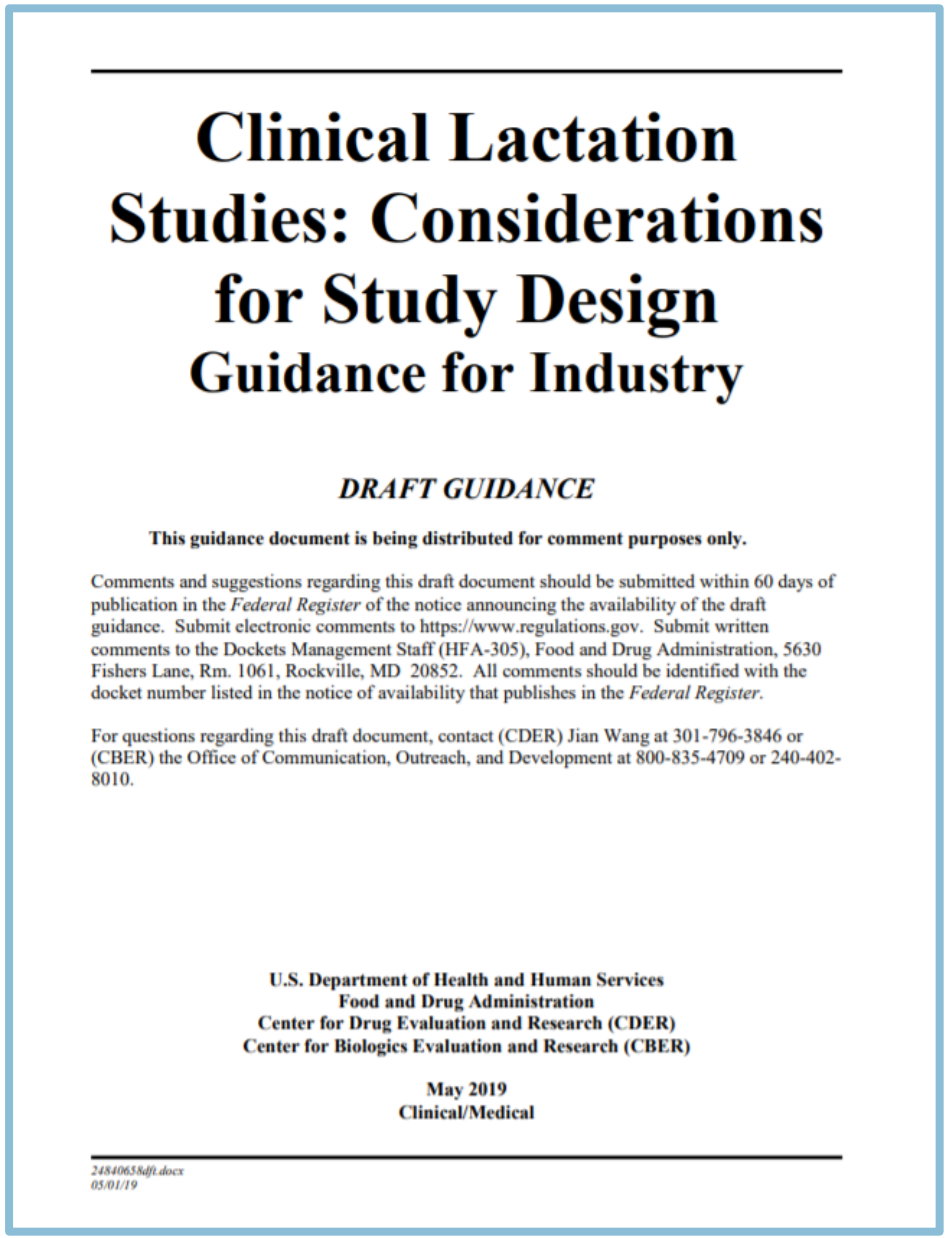
May 2019
Clinical/Medical

48826dft.docx
04/30/19

- Published May 9, 2019
- Replaces 2002 Pregnancy Registry Guidance
- Reflects recommendations from 2014 FDA public meeting of stakeholders on how to best collect safety data in pregnant women after a drug is approved
- Guidance available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

Highlights of Draft Guidance

- Expands on previous pregnancy registry guidance to also include other types of epidemiologic studies (e.g., electronic healthcare data studies) and pregnancy surveillance programs.
- Describes three general approaches used in postmarketing setting to evaluate drug or biological product safety during pregnancy
  - Pharmacovigilance
  - Pregnancy registries
  - Complementary data sources



Clinical Lactation Studies: Considerations for Study Design

Guidance for Industry

DRAFT GUIDANCE

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

May 2019
Clinical/Medical

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05/01/19

- Published May 9, 2019
- Replaces draft guidance published in 2005
- This guidance provides information to facilitate the conduct of lactation studies. Such studies can inform breastfeeding with drug use recommendations included in the *Lactation* subsection of labeling
- Guidance available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design

Highlights of Draft Guidance

- Describes specific study designs that can be considered (e.g., milk only study; milk/plasma study; mother-infant pair study)
- Clinical pharmacology considerations
  - Milk sampling methods
  - Pharmacokinetic analyses
  - Calculation of estimates of infant dosage
- Infant safety considerations

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Efforts to Advance Research in Pregnant and Lactating Women

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
- **Phase I**: PRGLAC Task Force prepared a report of 15 recommendations to the Secretary of the Department of Health and Human Services (completed September 2018)

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

- **Phase II**: HHS reauthorized PRGLAC Task Force to continue work on implementation of recommendations (Task Force charter extended to 3/2021)
  - FDA representation on the PRGLAC Task Force, including representatives from DPMH
  - Four working groups (Research/Training, Regulatory, Communication and Discovery) were established to develop a plan for implement the recommendations

For more information, visit https://www.nichd.nih.gov/about/advisory/PRGLAC

PLLR Resources

- Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf
- Pregnancy and Lactation Labeling Final Rule http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
- Prescription Drug Labeling Resources

  https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources

Where to find product labeling and other resources

- FDALabel: Full-Text Search of Drug Labeling https://www.fda.gov/scienceresearch/bioinformaticstools/ucm289739.htm
- Drugs @FDA http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- Daily Med (National Library of Medicine) http://dailymed.nlm.nih.gov/dailymed/about.cfm
- LactMed (National Library of Medicine) http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- CDC (Centers for Disease Control) http://www.cdc.gov/pregnancy/meds/index.html
- FDA Office of Women's Health Pregnancy Registry Website https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm

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Thank You

Challenge Question 1

Question #1: True/False: In some circumstances certain subsections or specific information that is otherwise required under PLLR must be omitted because it is clearly inapplicable or misleading.

Challenge Question 1

- Answer: True

Challenge Question 2

Question #2: What are the main topics discussed in the Clinical Lactation Studies Guidance?

A. Clinical lactation studies can inform breastfeeding with drug use recommendations included in the *Lactation* subsection of labeling
B. It describes specific study designs that can be considered (e.g., milk only study; milk/plasma study; mother-infant pair study)
C. It describes clinical pharmacology considerations (milk sampling methods, pharmacokinetic analyses, calculation of estimates of infant dosage)
D. It describes infant safety considerations
E. All of the above

Challenge Question 2

- Answer E: All of the above

Back-up Slides

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

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

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 *(extended 3/2019 to 3/2021)*
15. Establish an Advisory Committee to monitor and report on the implementation of the Taskforce recommendations *(Deferred)*