# FDA Perspectives on Drug Use in Lactation

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# Outline

- Introduction
- Overview of Postmarketing Requirements
- Overview of PLLR Labeling Changes
- Summary/Conclusion

# INTRODUCTION

# Background

- Six million pregnancies in the US every year
- During postpartum, women use drugs to manage chronic medical conditions, alleviate pain, or treat new conditions (i.e., infections, postpartum depression)
- Collecting data to inform safe use of drugs during lactation is an important public health issue

# Sparse Information on Lactation and Drug Use

- Information on drug use in lactating women is often collected in the post-marketing period
- Information collected at lesser frequency than information on drug use during pregnancy
- The lack of information may lead to a decision to discontinue breastfeeding
- The benefits of breastfeeding for the mother and infant are lost unnecessarily.

# Limitations of Animal Studies and Drug Use during Lactation

- Available pre-marketing data from animal studies often obtained from the pre-/postnatal study
  - Drug is measured for presence in animal milk, sometimes milk:plasma ratio is determined
  - Confounding drug exposure from milk with *in utero* exposure
- Dedicated animal lactation studies are conducted infrequently
- Species-specific differences in lactation physiology, means animal data do not reliably predict levels in human milk

# OVERVIEW OF POSTMARKETING REQUIREMENTS

# Regulatory History

- 2005: Draft Guidance for Industry – Clinical Lactation Studies
- 2007: FDA Amendments Act (FDAAA) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drugs and biologics at the time of approval or after approval if FDA becomes aware of new safety information†
- 2014: Pregnancy and Lactation Labeling Rule is finalized

† Guidance for Industry Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (2011)

# Draft Guidance for Industry (2005)

"Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling"

- Currently undergoing revision
- Will be re-issued as a draft, not final guidance

# Per Draft Guidance: Current Clinical Lactation Study Designs

| Design Options | Human Milk Study | Human Milk/Maternal Plasma Study |
|---|---|---|
| **Data that can be obtained** | | |
| Presence of drug in human milk | ■ | ■ |
| Drug concentration in human milk | ■ | ■ |
| Calculated daily infant dose (based on average infant milk intake or on changes in infant weight from before until after a feeding) | ■ | ■ |
| Effects of a drug on milk production and composition (if the drug is stopped or started during lactation) | ■ | ■ |
| Limited information about adverse effects of drug on breastfed infant | ■ | ■ |
| Maternal pharmacokinetics of a drug in lactating women (including concentration-time profiles) | | ■ |
| Infant plasma levels of drug and active metabolites (via limited sampling) | ■ | ■ |
| Urine concentrations of drug and/or metabolites | ■ | ■ |

# Clinical Lactation Study PMRs

- When drug is absorbed systemically
- When there is a potential safety risk based on mechanism of action, animal data, and/or serious adverse reactions demonstrated in adult clinical trials
- When drug use in females of reproductive potential is anticipated
- A review of ClinTrials.gov showed 8 products have postmarketing clinical lactation studies

# OVERVIEW OF PREGNANCY AND LACTATION LABELING RULE (PLLR) CHANGES

# PLLR

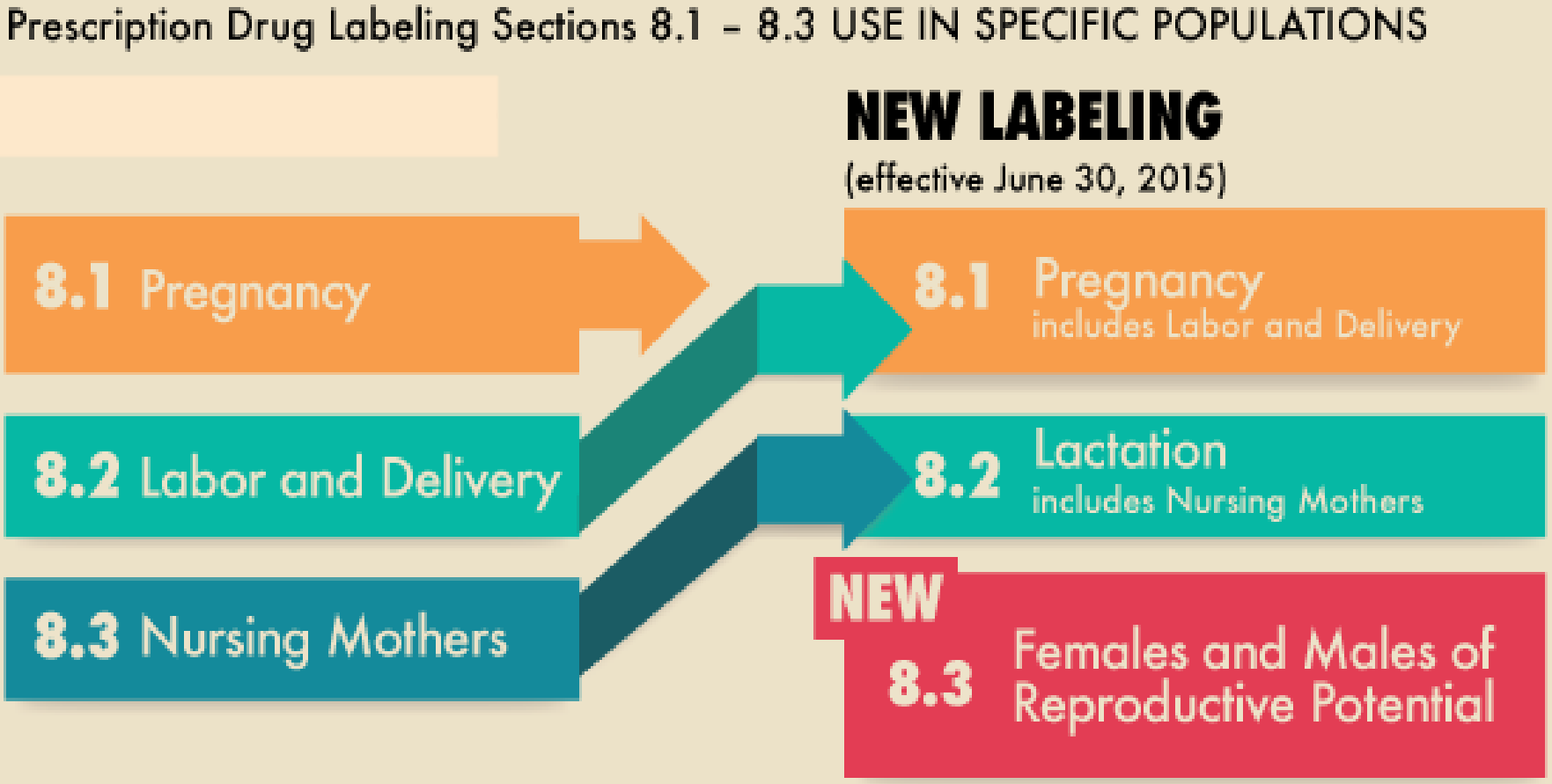
- Effective date **June 30, 2015**.
- **ALL** prescription drugs to remove pregnancy letter categories over the next 2-4 years
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements
- Prescription drugs approved prior to June 30, 2001 must remove pregnancy letter category

The following presentation is for educational purposes only. Questions regarding product specific labeling should be referred to the Center/Division responsible for regulation of that product.

# PLLR

- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs.
- Available information from the post-marketing experience will be used to update labeling
  - Published literature review
  - PMR Clinical Lactation Study Report
  - Relevant cases reported from the applicant's postmarketing database

# PLLR Changes



# PLLR – Changes to Labeling

8. USE IN SPECIAL POPULATIONS

**8.1 Pregnancy***

- Pregnancy Registry
- Risk Summary*
- Clinical Considerations
- Data

**8.2 Lactation***

- Risk Summary*
- Clinical Considerations
- Data

**8.3 Females and Males of Reproductive Potential**

- Pregnancy Testing
- Contraception
- Infertility

*Required heading

See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

# 8.2 Lactation

- Three headings:
  - Risk Summary*
  - Clinical Considerations
  - Data
- Information is summarized to convey the most relevant information

*Required heading

# 8.2 Lactation – Risk Summary

- Systemic drug absorption
  - Presence of drug in milk*
    - Concentration in milk
    - Actual or estimated infant daily dose
  - Effects of drug on the breastfed infant*
  - Effects of the drug on milk production*
  - Risk/Benefit Statement

*if unknown, must state so.

# Example:
# 8.2 Lactation- Risk Summary

Risk Summary

Limited published literature based on breast milk sampling from five mothers, reports that [drugname] is present in human milk, which resulted in infant doses of 0.16% to 0.7% of the maternal

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

maternal condition.

# Example:
# 8.2 Lactation- Risk Summary-
# Safety Concerns

Risk Summary

[Drugname] is present in human milk. A published lactation study reports variab ast milk w mothe assess studie includ s of the dr production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with [TRADENAME] .

Example: Because of the potential for serious adverse reactions, including . . . , advise patients that breastfeeding is not recommended during treatment with TRADENAME.

# 8.2 Lactation – Clinical Considerations and Data

- Clinical Considerations
  - Minimizing exposure to the breastfed infant
  - Monitoring the breastfed infant for Adverse Reactions

- Data - Include only when information are available
  - Description of clinical lactation study/data
  - Description of animal lactation study (only if there are no human data)

# SUMMARY/CONCLUSION

# Summary

- Limited information available on drug use in lactating women.
- Postmarketing studies required when there is a safety concern.
- When new information is available, the labeling must be updated.
- PLLR provides a more structured approach to labeling to help more clearly describe available data that can be used to aid in complex risk/benefit discussions between prescribers and their patients.

# Conclusion

- There remains significant gaps in the information needed to inform safe use of drugs in lactating women
- PLLR propels forward the conversation on how to gather the needed information
- All stakeholders will need to work together to proactively seek information to fill the gaps.

# Thank you

# RESOURCES

# PLLR Website

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

A to Z Index | Follow FDA | En Español

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

**Drugs**

Home > Drugs > Development & Approval Process (Drugs) > Development Resources > Labeling

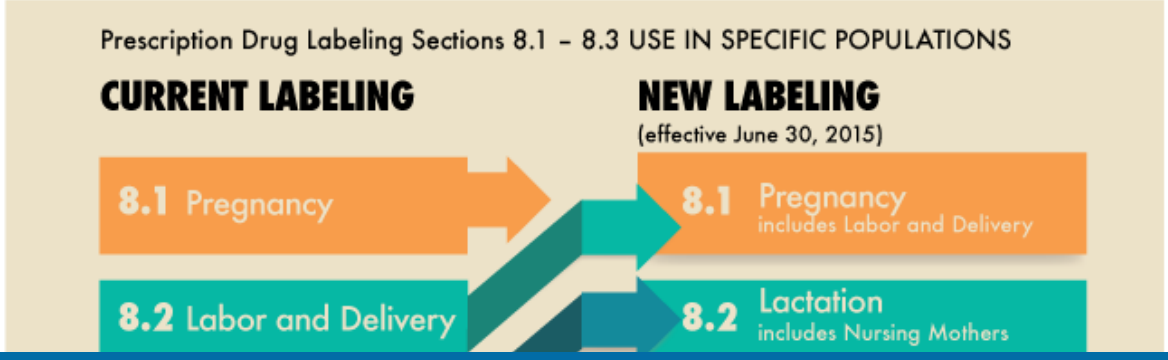
- **Development & Approval Process (Drugs)**
- Development Resources
- Labeling
- **Pregnancy and Lactation Labeling Final Rule**

## Pregnancy and Lactation Labeling Final Rule

[12/3/14] The FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule).

The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories – A, B, C, D and X. The PLLR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLR labeling requirements.



# Pregnancy Registry Website

U.S. Department of Health and Human Services

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

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Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

## Science & Research

Home > Science & Research > Science and Research Special Topics > Women's Health Research

- **Women's Health Research**
- OWH Research and Development Program
- OWH Research Initiatives
- OWH Presentations and Publications
- Understanding Sex Differences
- Women in Clinical Trials
- Pregnancy Registries

## Pregnancy Registry Information for Health Professionals

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Find a Registry

### Sign Up Your Patients

Enrolling your patients in a pregnancy exposure registry can help improve safety information for medicines used during pregnancy and can be used to update drug labeling.

1. **Check the list of registries**. The list includes the website and phone number for you to contact each registry.
2. **Encourage your patients to enroll.** Remind your patients that they will not be given an experimental drug. Pregnancy registries collect information on pregnancy outcomes in women who are already taking medication.

**Buttons**


**Copy this code to add the small size Pregnancy Registry Buttons to your site:**
(150X150 pixels)

# 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
- Physician's Labeling Rule Requirements for Prescribing Information http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

# Where to find product labeling and other resources

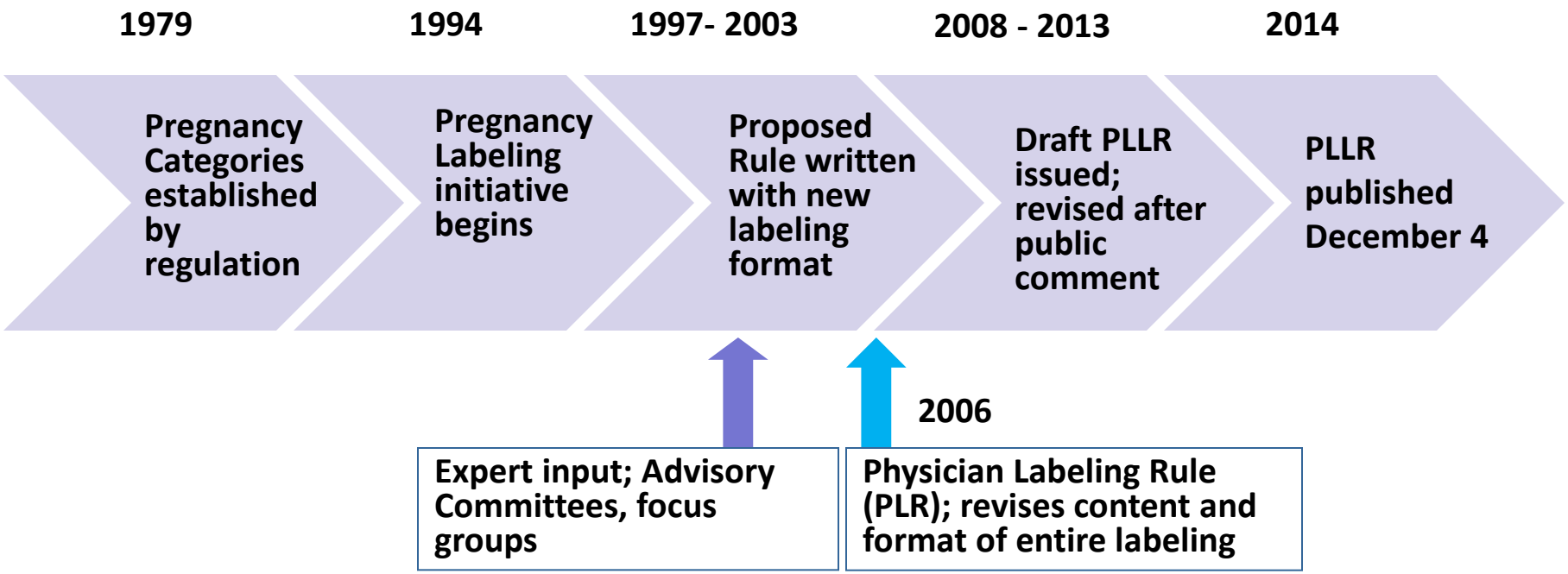
- Drugs @FDA
  http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- Daily Med (National Library of Medicine)

  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

# Questions

# Back-up slides

# Timeline of the PLLR



# Intent of PLLR

- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added when available
- Explicitly states when no data are available

# 8.1 Pregnancy

- Four headings
  - Pregnancy Exposure Registry
  - Risk Summary*
  - Clinical Considerations
  - Data

*Required heading

# 8.3 Females and Males of Reproductive Potential

- Include when there are requirements or recommendations for pregnancy testing and/or contraception and/or when human and/or animal data suggest drug effects on fertility
- Three headings
  - Pregnancy Testing
  - Contraception
  - Infertility