THE PREGNANCY AND LACTATION LABELING RULE (PLLR)

Miriam Dinatale, D.O., LCDR, USPHS
Division of Pediatric and Maternal Health
FDA/CDER/OND/ODEIV

Pediatric Advisory Committee Meeting
September 14, 2016

Disclaimer

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.

Opinions expressed in this presentation are those of the speaker and do not necessarily reflect official positions or policy of the FDA.

The speaker has nothing to disclose.

Overview

- Introduction
- History of Pregnancy Labeling
- Overview of PLLR Labeling Changes
- Summary/Conclusion

INTRODUCTION

Pregnancy and Medication Use

- Six million pregnancies in US every year
- 50% of pregnant women reported taking at least one medication
- Pregnant women take an average of 2.6 medications at any time during pregnancy
- First trimester use of prescription medications has increased by more than 60%
- Use of 4 or more medications in the first trimester has tripled (9.9% to 27.6%)

Mitchell AA, Gilboa SM, Werler MM, et al., Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51.e1-8.

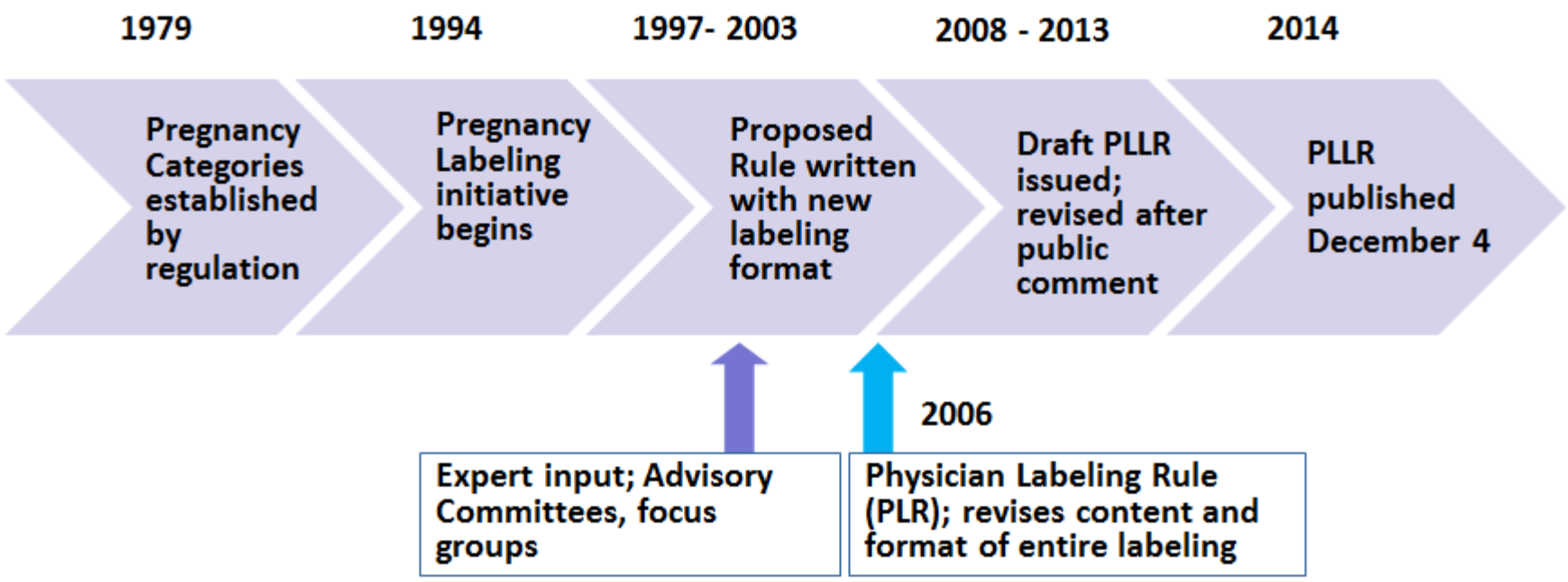
Pregnancy and Medication Use

- Only a small percentage of drugs are contraindicated for use in pregnancy or while breast feeding.
  - e.g., isotretinoin, mycophenolates
- For the majority of drugs, labeling should provide what is known in a way that enables decisions for treatment.

The question is HOW?

HISTORY OF PREGNANCY LABELING

Timeline of PLLR



The Problem with Letters

- Pregnancy letter category system was overly simplistic
- Misinterpreted as a grading system
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information
  - Example: Pregnancy Category C
  - Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, BUT the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
  - Studies in pregnant women and animals are not available

Intent of PLLR

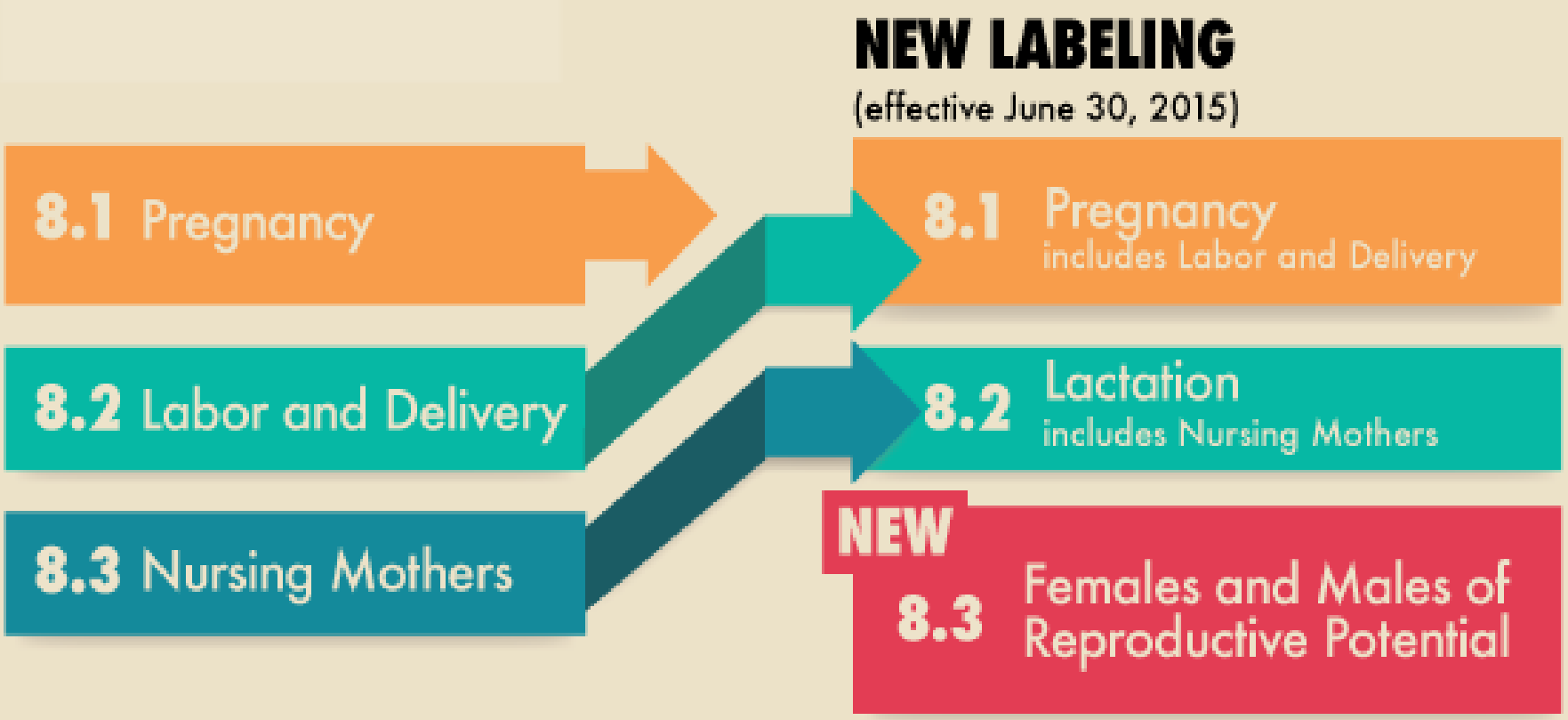
- Provide the prescriber with relevant information for critical decision-making when treating pregnant or lactating women
- More complete statement of the known risks based on the available data
- Considerations of medical/disease factors
- Animal data put in context of human exposure
- Human data added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

PLLR

- Effective date **June 30, 2015**.
- **ALL** prescription drugs to remove pregnancy letter categories by June 2020, gradual process
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements
- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs.

OVERVIEW OF PLLR LABELING CHANGES

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS



8.1 Pregnancy

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

*Required heading

8.1 Pregnancy-
Pregnancy Exposure Registry

- Pregnancy Exposure Registry
  "There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy."
- Includes specific contact information
  - Phone #
  - Website

8.1 Pregnancy- Risk Summary*

- No drug systemic absorption

"[TRADENAME] is not absorbed systemically following (route of administration) and maternal use is not expected to result in fetal exposure to the drug."

*Required heading(s)

8.1 Pregnancy- Risk Summary*

- Drugs with systemic absorption
  - When use of a drug is contraindicated during pregnancy, that information must be stated first in the Risk Summary
  - Risk statement based on human data*
  - Risk statement based on animal data*
  - Risk statement based on pharmacology
  - Background risk information in general population*
  - Background risk information in disease population

*Required

Example:
8.1 Pregnancy – Risk Summary - Risk Based on Animal Data

Risk Summary

There are no adequate and well-controlled studies of [TRADENAME] in pregnant women. The limited available information on [TRADENAME] use during pregnancy is not sufficient to inform a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, oral administration of [drug name] to pregnant rats and rabbits during the period of organogenesis at doses up to 40 and 20 times the maximum recommended human dose (MRHD), respectively, resulted in decreased fetal body weight gain and delayed skeletal ossification but no teratogenic effects were observed. Decreased fetal body weight and delayed skeletal ossification were not observed at doses up to 10 and 5 times the MRHD in rats and rabbits, respectively *[see Data].*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15- 20%, respectively.

8.1 Pregnancy- Clinical Considerations

- Clinical Considerations (five optional subheadings)
  - Disease-Associated Maternal and/or Embryo/Fetal Risk
  - Dose Adjustments During Pregnancy and the Post-Partum Period
  - Maternal Adverse Reactions
  - Fetal/Neonatal Adverse Reactions
  - Labor or Delivery

8.1 Pregnancy- Data

- Data
  - Detailed description of the data that provide the scientific basis for the summary information presented in the Risk Summary and Clinical Considerations headings
  - The applicant provides to the Agency a comprehensive review of relevant published literature, their pharmacovigilance database, and pregnancy exposure registry (if applicable) to support updated language for this section of labeling.
  - Sections
    - Human Data
    - Animal Data

8.2 Lactation

- Three headings:
  - Risk Summary*
  - Clinical Considerations
  - Data

*Required heading

8.2 Lactation- Risk Summary*

- No drug systemic absorption

"[TRADENAME] is not absorbed systemically by the mother following (route of administration) and breastfeeding is not expected to result in exposure of the infant to [drug name]."

*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 – Drug in Human Milk

Risk Summary

There is no information regarding the presence of [drug name] in human milk, the
producti ody,
and imm unts.
[Drug na partum
followin
(8.1)].Th uld be
consider and
any pote AME]
or from t

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.

Example:
8.2 Lactation- Risk Summary- Safety Concerns

Risk Summary

[Drug name] is present in human milk. A published lactation study reports variable

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

breastfed infant, 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
  - The applicant will provide a comprehensive review of published literature and their pharmacovigilance database to update this section.
  - Description of clinical lactation study/data
  - Description of animal lactation study (only if there are no human data)

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

8.3 Females and Males of Reproductive Potential

- Dedicated labeling section consolidates information from other areas of labeling
  - Moves recommendations for contraception and pregnancy testing from section 8.1, Pregnancy and section 13, Nonclinical Toxicology
  - Moves human fertility study descriptions and infertility considerations from section 13, Nonclinical Toxicology
  - Animal fertility study descriptions remain in section 13, Nonclinical Toxicology

Example:
8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, TRADENAME can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Female patients of reproductive potential should have a negative pregnancy test …

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment and for at least 2 weeks after the last dose of TRADENAME. Advise patients that TRADENAME can reduce the effectiveness of oral contraceptives and to use alternative effective contraception during treatment with TRADENAME *[see Warnings and Precautions (5.x), Drug Interactions (7.x), Clinical Pharmacology (12.x)].*

Infertility

Females

Decreased fertility and ovarian toxicity were observed in female rats treated with DRUGNAME. Advise female patients of reproductive potential …

Males

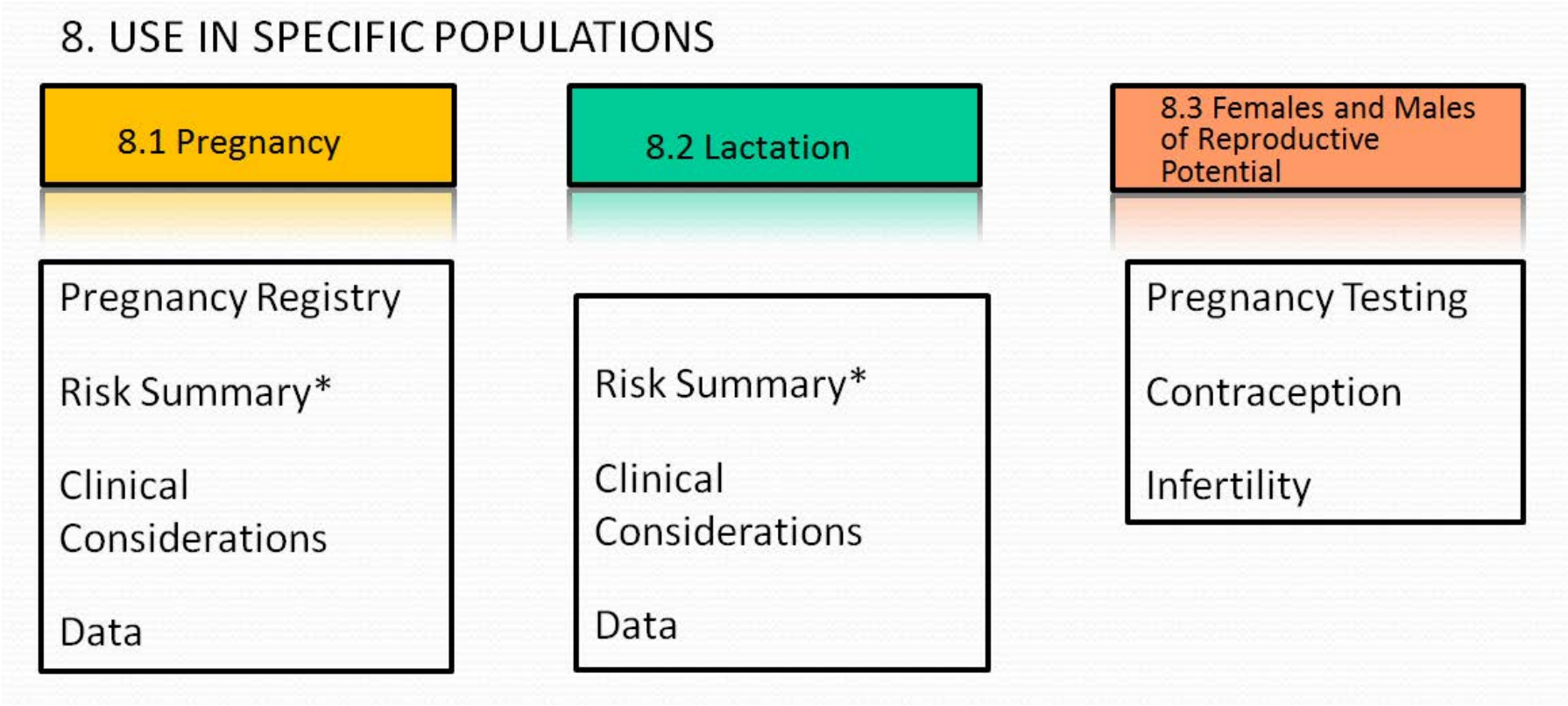
Effects on spermatogenesis have been observed in animals treated with DRUGNAME. Advise male patients of the potential risk…

SUMMARY/CONCLUSION

PLLR Summary

- PLLR implementation is a gradual process that will take another **2 to 4 years**.
- **ALL** prescription drug labeling will be required to remove pregnancy letter categories**.**
- PLLR provides clearer communication of available data to assist the prescriber with critical decision-making when treating pregnant or lactating women
- PLLR notes when there is no available data

PLLR – Changes to Labeling



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

Conclusion

- The 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.
- PLLR includes required statements when data are not available. Hopefully, all stakeholders will work together to proactively seek information to fill the gaps.

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)

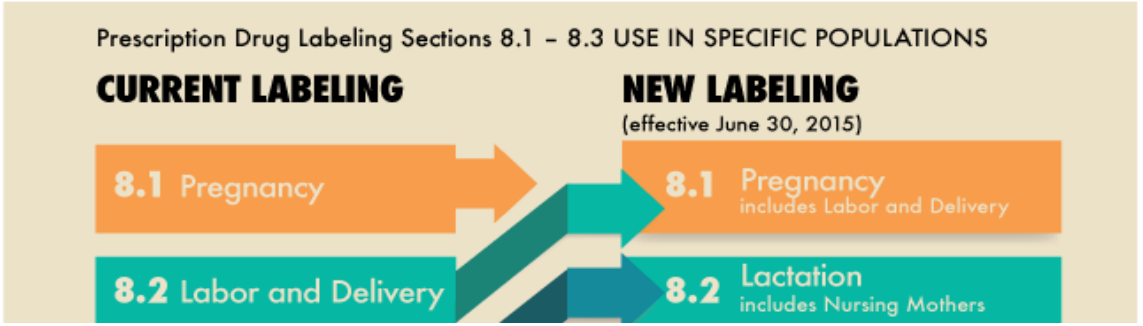
- Development Resources
- Labeling
- **Pregnancy and Lactation Labeling Final Rule**

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

A to Z Index | Follow FDA | En Español

Search FDA

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION