

# **An Evolution of Labeling Information for Pregnant Women: PLLR History and Background**

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# Disclaimer

- No conflicts of interest to disclose, financial or otherwise.

# Overview

- Introduction
- Brief History of PLLR
- Overview of labeling changes
- Lessons learned
- Summary



# Introduction

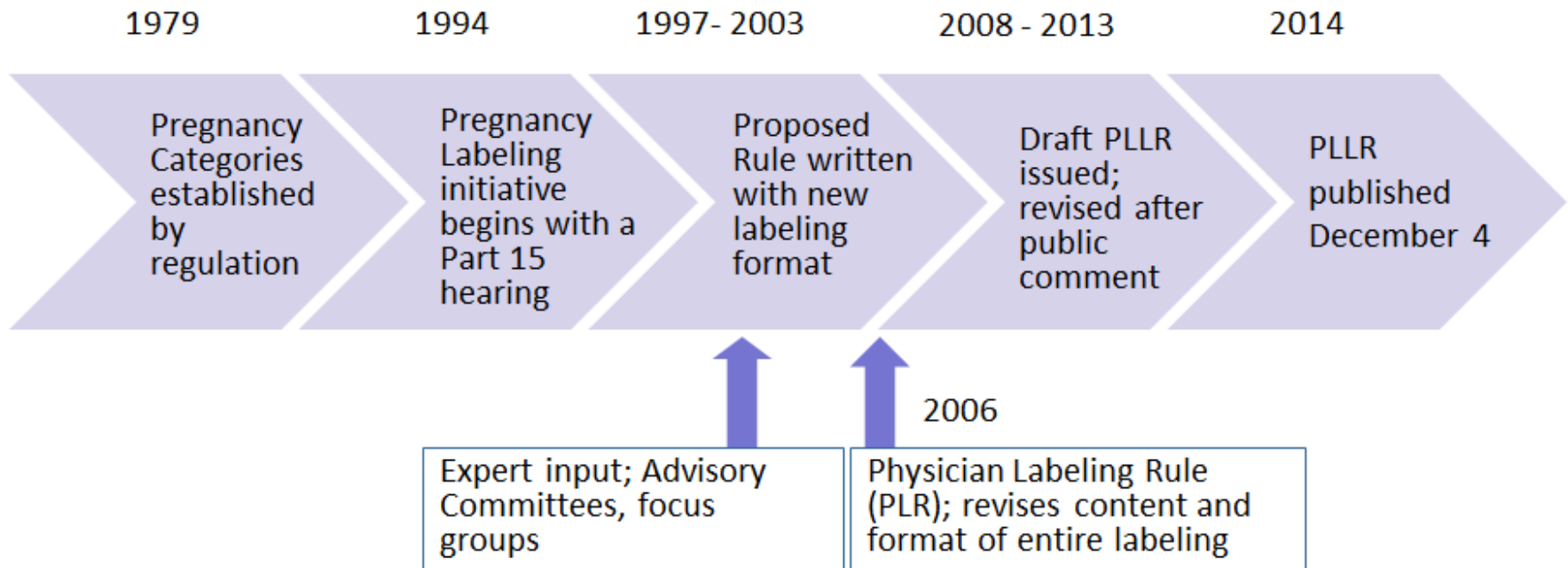
# Pregnancy and Medication Use

- Approximately six million pregnancies in US every year
- 50% of pregnant women reported taking at least one medication
- Pregnant women take an average of 3-5 medications at any time during pregnancy
- Between 1976 and 2008, first trimester use of prescription medications increased by more than 60%
- Use of 4 or more medications in the first trimester has tripled (9.9% to 27.6%)

Curtin SC., et al. Pregnancy rates for U.S. women continue to drop. NCHS Data Brief. 2013;136:pg 2.

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.

# PLLR: Historical Overview



# History of Pregnancy Labeling

- **Early 1960s:** Thalidomide teratogenicity was first described
  - Thousands of infants were born in Western Europe with severe limb deformities
- **November 1960:** Dr. Frances Kelsey refused to approve Thalidomide in the U.S.
- **1962:** Congress enacted the Kefauver-Harris amendments to the Federal Food, Drug and Cosmetic Act. Manufacturers had to:
  - prove that a drug was safe and effective.
  - monitor safety reports that emerged post-market
  - adhere to good manufacturing practices leading to safe products
- **1970s:** Clinicians were faced with an increase in information

# The Pregnancy Categories are Established

- In **1979**, FDA introduced pregnancy labeling categories
- Pregnancy labeling categories standardized the presentation of experimental animal and human data on potential pregnancy effects of medications and provided a risk-benefit formula for practitioners

**A B C D X**



# The Problem with Letters

- Pregnancy letter category system was overly simplistic
- Misinterpreted as a grading system
- 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
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information at all.
- Pregnancy Category X
  - Drugs that were contraindicated because they were teratogenic or,
  - Drugs that had no use during pregnancy [contraceptives]

A B C D X



# Advocating for Change - the Pregnancy Labeling

TERATOLOGY 49:446-447 (1994)

1994 Public Affairs publication

## **FDA Classification of Drugs for Teratogenic Risk**

TERATOLOGY SOCIETY PUBLIC AFFAIRS COMMITTEE

“...The Society recommends that drug labeling should include narrative statements that summarize and interpret available data regarding hazards of developmental toxicity and provide estimates of potential teratogenic risk.”

# The Pregnancy Labeling Initiative Begins

- **Part 15 Public Hearing - September, 1997**
  - Public input on current system of pregnancy labeling
    - *Is it relied on by practicing providers?*
    - *Is it useful? How?*
    - *What is good and bad about it?*
    - *If overall, it is not informative or excessively problematic, what can be done to improve it?*
- **Changes to Labeling supported by:**
  - Teratology Society, American College of Obstetricians and Gynecologists (ACOG), American College of Dermatology, American Psychiatric Association, Pharmaceutical firms, Women's health groups, Reproductive toxicologists, Organization of Teratology Information Specialists, and others

## **1999 -Focus Groups during the 15<sup>th</sup> Annual Clinical Update in Ob/GYN Conference**

- Participants provided with sample “Pregnancy subsections” for comment
- Major concern was lack of human data
- Willing to rely on animal data if there was correlation to human dosing
- Concern about being too directive in clinical management
- Present most important information first
- Uniform labeling format for all drug products

# Discussion of Concept Paper 1999

Pregnancy Labeling Subcommittee of the  
 Reproductive Health Drugs Advisory Committee

June 3, 1999 SEP 14 AB 57

Holiday Inn, Silver Spring, MD

## Committee

Greene, Michael M.D.  
 Dattel, Bonnie J., M.D.  
 Hammond, Mary G., M.D.  
 Lemons, James A., M.D.  
 Conover, Elizabeth Ann, M.S.  
 Chong, Cynthia M., M.D.  
 Scott, Julia R., R.N.  
 Jones, Ken Lyons, M.D.  
 Wisner, Katherine L., M.D.  
 Rosene-Montella, Karen, M.D.  
 Briggs, Gerald, B. Pharm.  
 Wier, Patrick, Ph.D.  
 Andrews, Elizabeth B., Ph.D.,  
 Mitchell, Allen, M.D.\*  
 Cragan, Janet Darden, M.D.  
 Taylor, Alan, Ph.D.  
 O'Loughlin, Victoria, Ph.D.

## FDA

Sandra L. Kweder, M.D.  
 Rose E. Cunningham  
 Kathryn J. Aikin, Ph.D.  
 Joseph J. DeGeorge, Ph.D.  
 Heidi M. Jolson, M.D., M.P.H.  
 Evelyn M. Rodriguez, M.D., M.P.H.  
 Rachel E. Behrman, M.D.  
 Florence Houn, M.D., M.P.H., F.A.C.P.  
 Marianne C. Mann  
 Linda S. Brophy  
 David E. Morse, Ph.D.  
 Murray Lumpkin, M.D.

## Invited Guests/ Guest Speakers

Eric Holmboe, M.D.  
 Francois Meyer, M.D.

## **May 2000 –Focus Groups with American College of Nurse-Midwives and ACOG**

- Participants provided comment on standard statements for labeling to characterize the risk of developmental anomaly associated with a drug.
- Preferred factual statements that allow a clinical judgment based on the circumstances of a patient
- Provide a general statement of background risk

# The Pregnancy Labeling

- Between 1997 and 2003 the proposed PLLR is written
- **January 25, 2006:** Physician Labeling Rule (PLR) is revised
- **May 29, 2008:** Proposed PLLR is published
  - Period of public comment and draft PLLR revised between 2008 to 2013
- **December 4, 2014:** The Final PLLR is published

# PLLR becomes a Reality

- Became effective on **June 30, 2015**.
- Amends the Physician Labeling Rule (PLR) regulations
- 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.
- **ALL** prescription drugs are required to remove pregnancy letter categories by June 2020, gradual process

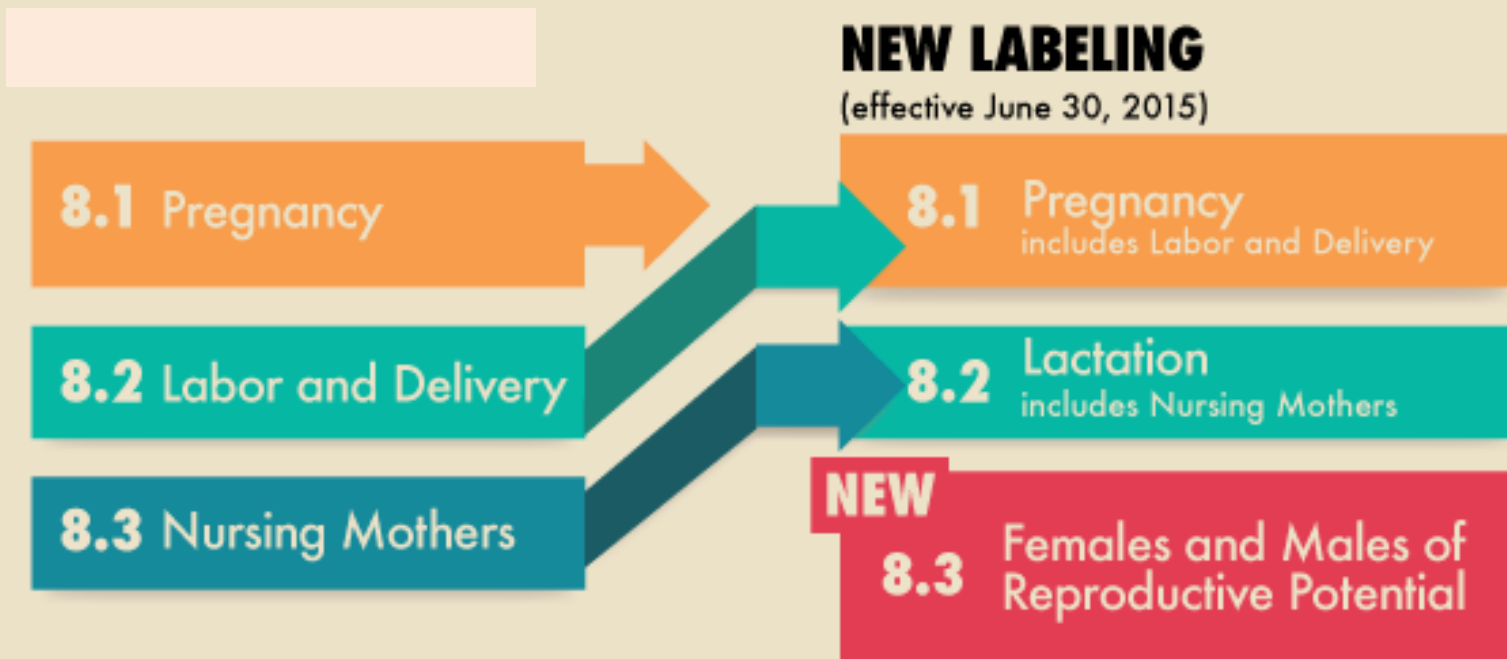


# Intent of PLLR

- 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

# Comparison of Current Labeling with PLLR

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS



# Overview of PLLR Changes to Labeling

## 8. USE IN SPECIFIC 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.

# Lesson Learned to Date

- New format improves presentation of data
- New format does not necessarily help when there are no data
- Absence of a safety finding does not necessarily establish absence of a risk

# Lessons Learned to Date

- Need data to inform the labeling
- Improve ways to systematically collect information post-approval
  - Support and expertise from outside stakeholders
  - FDA Public Meeting December 2012
    - Management of Teratogenic Risk
  - FDA Public Meeting May 2014
    - Revision of 2005 Pregnancy Registry guidance

# Summary

- The PLLR provides a structured approach to labeling to describe available data that can be used to aid in complex risk/benefit discussions between prescribers and their patients.



# QUESTIONS



# **BACK UP SLIDES**



# 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>



# Drug Labeling Information

- 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>

# Pregnancy Categories

<b>A</b>	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
<b>B</b>	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
<b>C</b>	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. <b>OR</b> animal studies have not been conducted and there are no AWC studies in humans.
<b>D</b>	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
<b>X</b>	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).



# PLLR Implementation Schedule

	<b>NDA, BLA, ESs</b>	<b>Latest Submission Date PLLR Format</b>
New Applications (NDAs, BLAs, and ESs)	Originally submitted on or after 6/30/2015	At time of submission
Older Approved Applications	6/30/2001 to 6/29/2015	2018 - 2020
Older Approved Applications	Prior to 6/30/2001	Required to remove pregnancy category by 6/29/2018

NDA = New Drug Application, BLA = New Biologic Application, ES = efficacy supplement

