The Pregnancy and Lactation Labeling Rule (PLLR)

Labels without Categories: A Workshop on FDA's Pregnancy and Lactation Labeling Rule

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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.

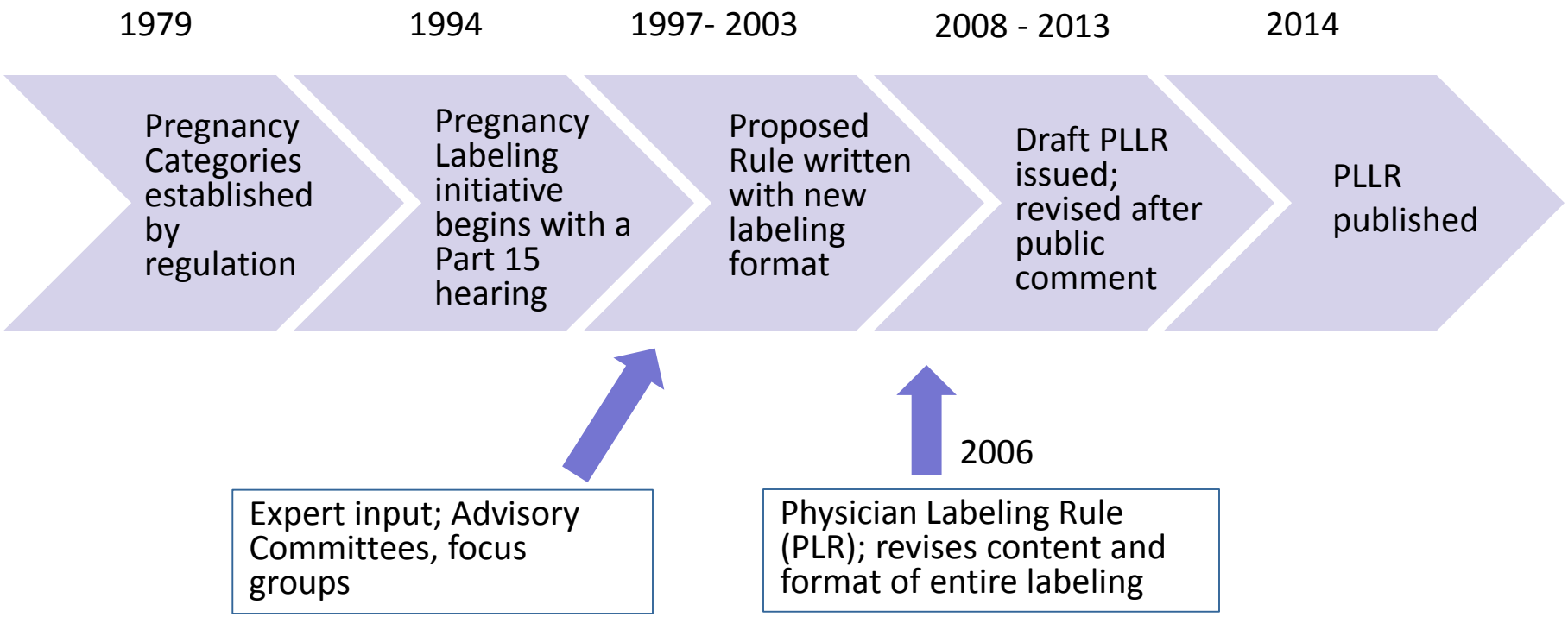
Overview

- Background
- Overview of the rule
- Draft Guidance

The Pregnancy and Lactation Labeling Rule (PLLR) December 4, 2014

- Addresses long standing problems with pregnancy and lactation labeling
- Amends the Physician Labeling Rule (PLR)
  - Pregnancy and Lactation labeling subsection revisions were deferred when PLR was published in 2006

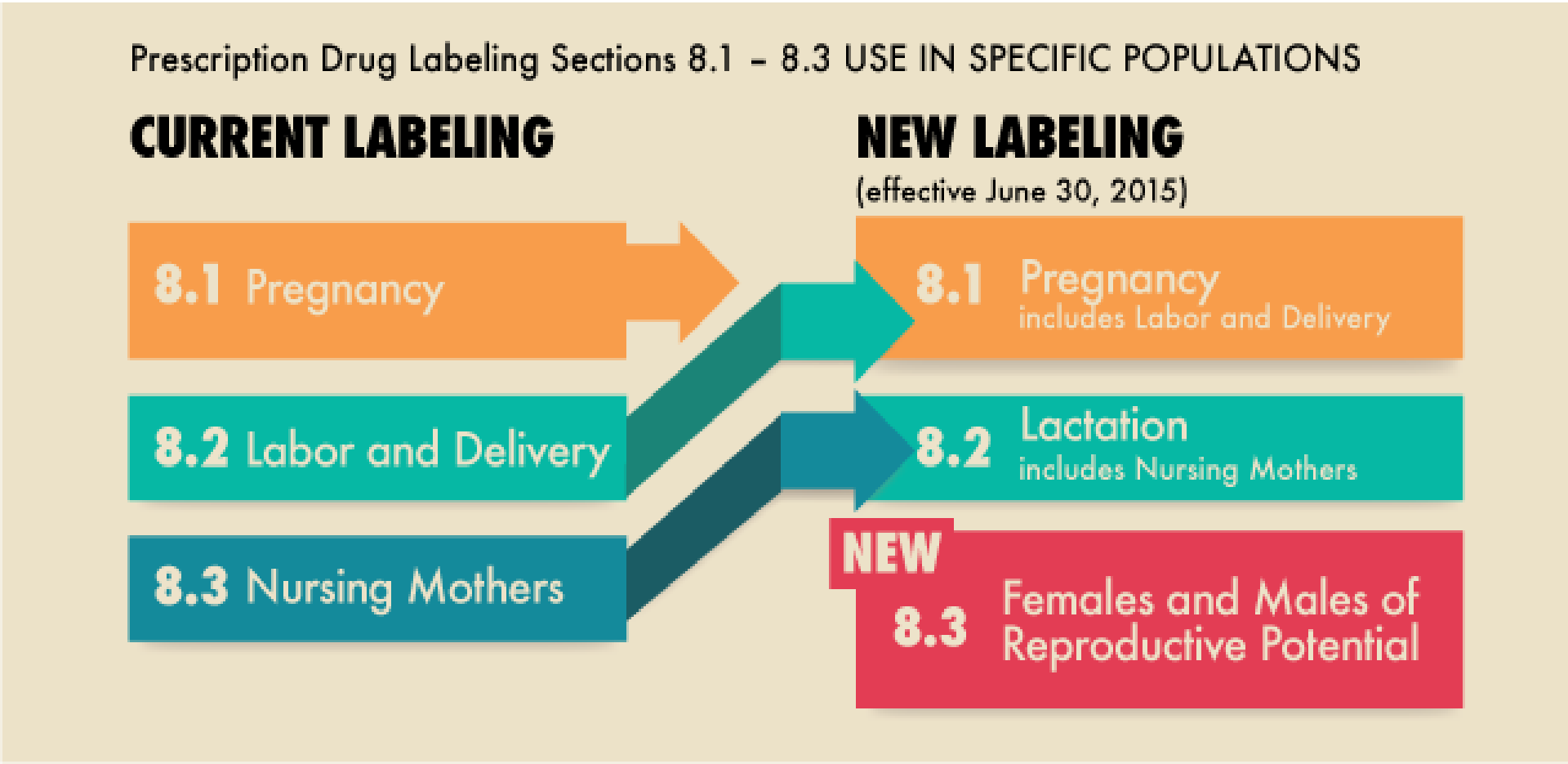
PLLR: a brief history



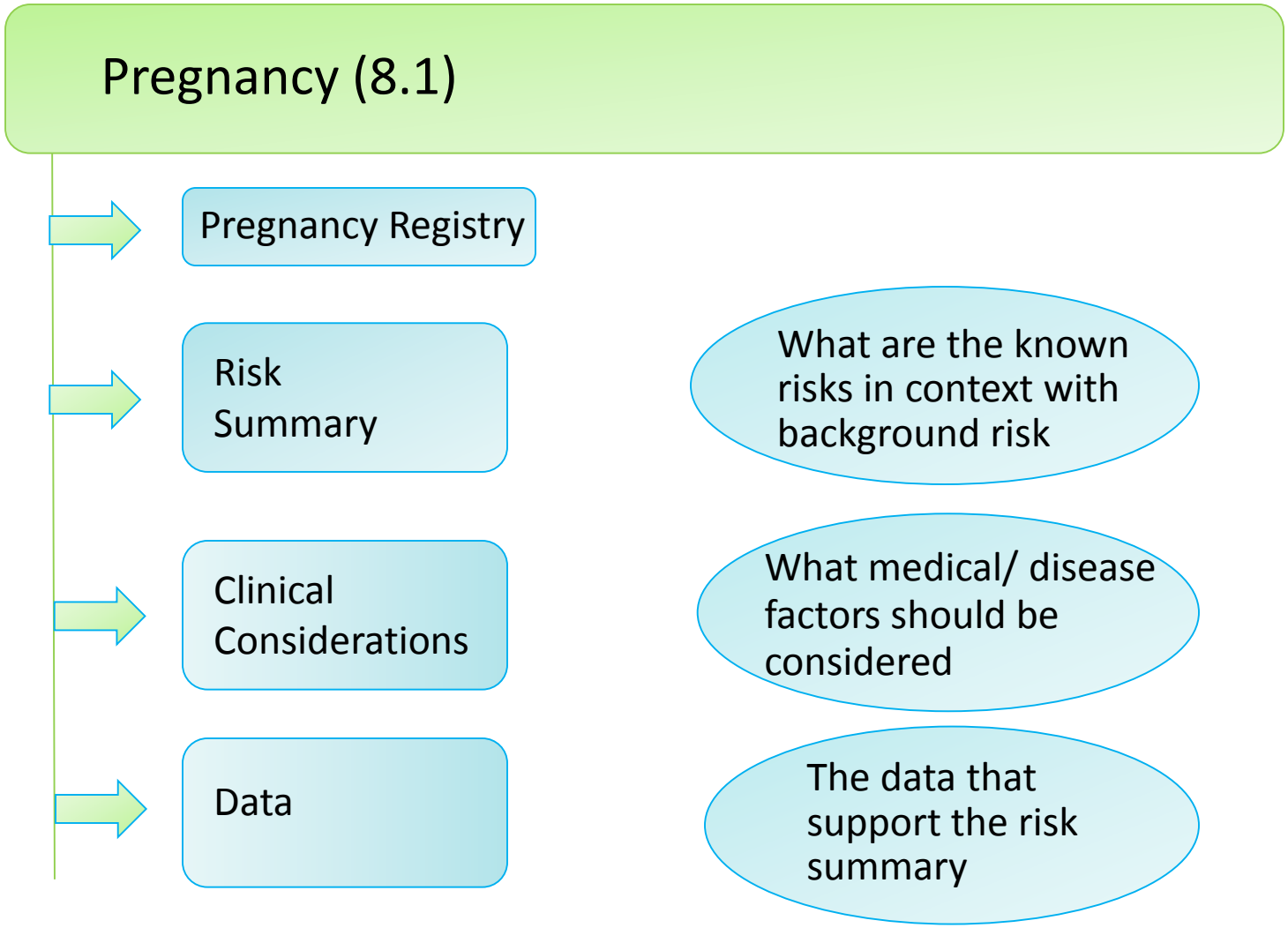
Pregnancy and Lactation Labeling Rule

- Published on December 4, 2014
- Amends the Physician Labeling Rule (PLR)
  - Pregnancy and Lactation labeling subsection revisions were deferred when PLR was published in 2006
- All prescription drugs approved on or after June 30, 2001 must revise content and format of the Pregnancy and Nursing Mothers (Lactation) subsections of labeling
  - Pregnancy letter categories are replaced with an integrated Risk Summary
- **ALL** prescription drugs are required to remove pregnancy letter categories
- Staggered implementation over 3-5 years

Labeling Changes with PLLR



Revised Format



Required Labeling Elements

Pregnancy Exposure Registry*

"There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (name of drug) during pregnancy."

- Contact information listed

The availability of a pregnancy registry is also noted in the PATIENT COUNSLEING INFORMATION section.

*is not included if there is no available registry

Required Labeling Elements

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 heading

**is not included if there is no risk information

Pregnancy - Risk Summary

Drug systemically absorbed:

- When use of a drug is contraindicated during pregnancy, this information must be stated first in the Risk Summary
- Human data:
  - A summary of the available human data or a statement there are no available human data to establish a drug-associated risk
- Animal data:
  - A summary of the available animal data; a statement if studies do not meet current standards; a statement when no data exist
- Pharmacology:
  - A statement regarding the mechanism of action and potential associated risks when the drug has a well-understood MOA
- Background Risk:
  - A statement about the estimated background risk of major birth defects and miscarriage in the US general population or the estimated background risk in the diseased population.

Pregnancy - Risk Summary

- No drug systemic absorption:
  - If drug is not systemically absorbed, Risk Summary will only contain the following statement:

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

Pregnancy - Clinical Considerations

Clinical Considerations: provides information to further inform prescribing and risk-benefit counseling (Five 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

* Heading and subheadings are optional; use when needed to convey information

Examples of Clinical Considerations

Clinical Considerations

Disease-Associated Maternal and Fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight and small for gestational age for the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Dose Adjustments during Pregnancy and the Postpartum Period

Dosage adjustments of TRADENAME are necessary for pregnant women to maintain adequate drug plasma concentrations *[see Dosage and Administration (2.x) and Clinical Pharmacology (12.3)].*

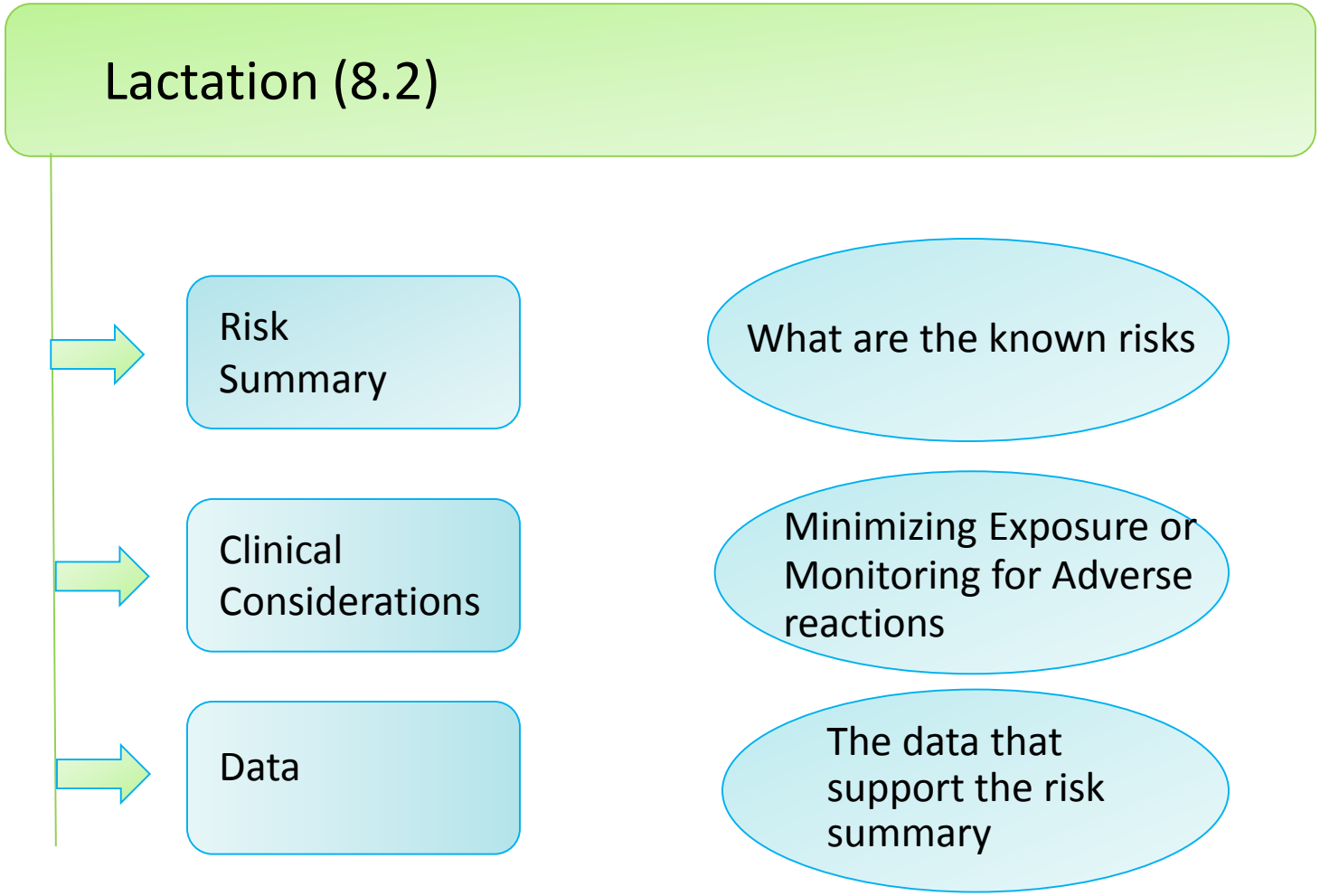
Pregnancy - Data

Data: Description of the data that provide the scientific basis for the summary information presented in the Risk Summary and Clinical Considerations headings*

- Human Data
  - Description of the studies includes type of study, number of subjects, study duration, exposure information and limitations of the data
- Animal Data
  - Description of the studies includes, type of study, species studied, animal doses and the basis for the exposures described in terms of the human dose or exposure, duration and timing of exposure, study findings, presence (or absence) of maternal toxicity, limitations of the data.

* Heading and subheadings; only include if there are data

Revised Format



Risk Summary - Lactation

Drug systemically absorbed:

- When use of a drug is contraindicated during lactation, this information must be stated first in the Risk Summary
- Presence of drug in human milk
- Effects of drug on the breastfed child
- Effects of drug on milk production
- Risk and benefit statement

  "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 infant from (name of drug) or from the underlying maternal condition."

- Animal data are not included if human data are available

Risk Summary - Lactation

No drug systemic absorption:

"(Drug name) 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)"

Clinical Considerations and Data - Lactation

Clinical Considerations - include only when information available:

- Minimizing Exposure
- Monitoring 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)

New labeling elements

8.3 Females and Males of Reproductive Potential*

Include when there are requirements or recommendations for pregnancy testing and/or contraception and when human and/or animal data suggest drug effects on fertility (three headings)

- Pregnancy Testing
- Contraception
- Infertility

*included when this information is needed

8.3 Females and Males of Reproductive Potential

- Moves recommendations for contraception and pregnancy testing information from the pregnancy subsection of labeling and section 13 Nonclinical Toxicology
- Moves human infertility statements and considerations from nonclinical subsection of labeling
- Details of animal studies remain in section 13 Nonclinical Toxicology

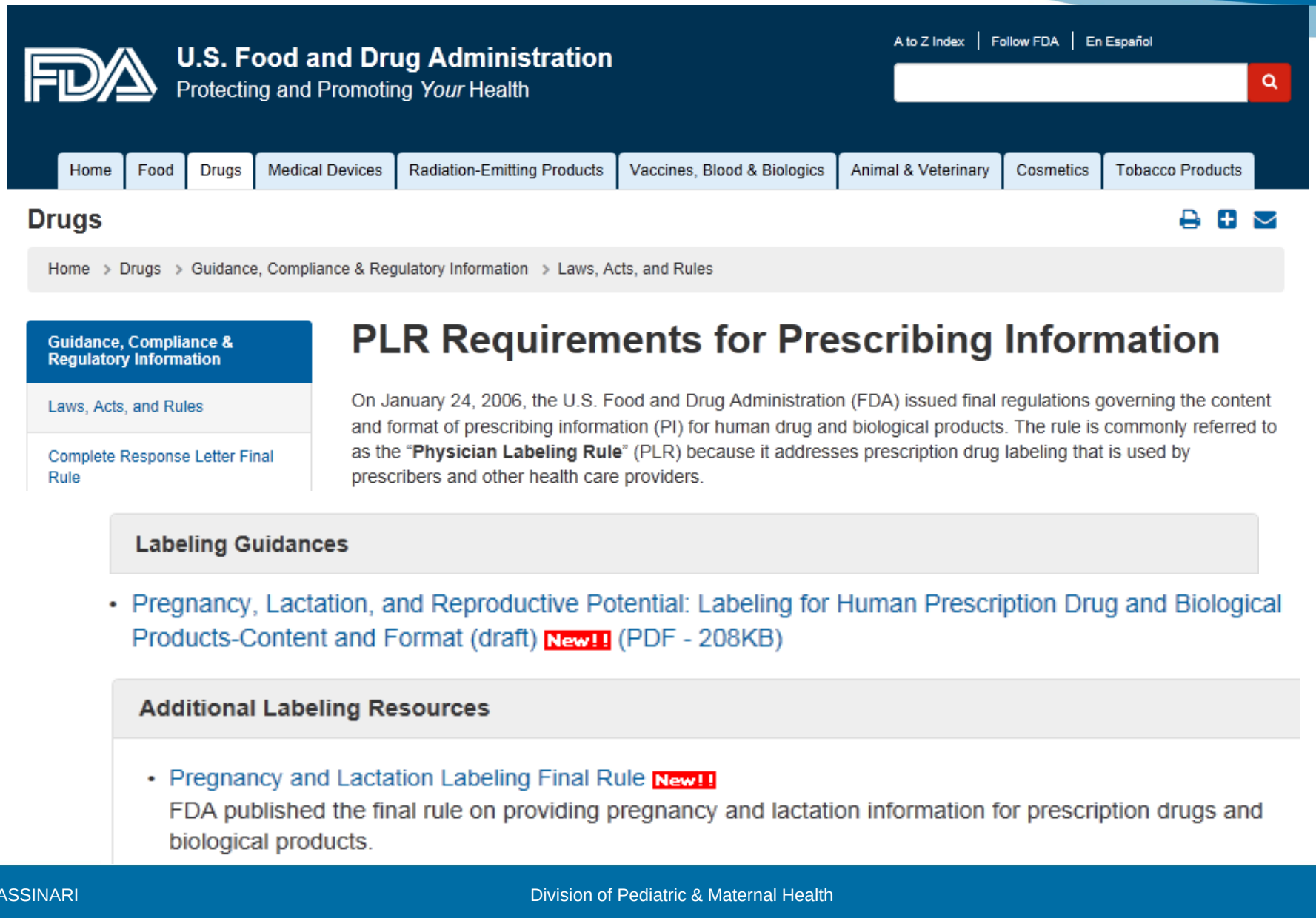
PLLR Implementation Schedule

	NDAs, BLA, ESs	Required Submission Date of PLLR Format
New Applications (prospective cohort)	Submitted on or after 6/30/2015	At time of submission
Start (6/30/15) ----------		
Older Approved Applications (retrospective cohort)	Approved 6/30/2001 to 6/29/2002 Approved 6/30/2005 to 6/29/2007	6/30/2018
	Approved 6/30/2007 to 6/29/2015 or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 to 6/29/2005	6/30/2020
	For applications approved prior to 6/30/2001 in old format labeling	Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018

Older Labeling

- Drugs approved before June 30, 2001 are required to remove the pregnancy letter category by June 30, 2018 (3 yrs after PLLR goes into effect)
- But, the labeling for these drugs is not required to conform to the Physician Labeling Rule (PLR)
  - Consequently are not required to revise the Pregnancy and Nursing Mothers sections under PLLR
- Efforts underway to encourage conversion of the older labeling to the PLR (and PLLR) format

PLLR Resources (1 of 2)



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Guidance, Compliance & Regulatory Information

Laws, Acts, and Rules

Complete Response Letter Final Rule

PLR Requirements for Prescribing Information

On January 24, 2006, the U.S. Food and Drug Administration (FDA) issued final regulations governing the content and format of prescribing information (PI) for human drug and biological products. The rule is commonly referred to as the "**Physician Labeling Rule**" (PLR) because it addresses prescription drug labeling that is used by prescribers and other health care providers.

Labeling Guidances

- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (draft) New!! (PDF - 208KB)

Additional Labeling Resources

- Pregnancy and Lactation Labeling Final Rule New!!
  FDA published the final rule on providing pregnancy and lactation information for prescription drugs and biological products.

PLLR Resources (2 of 2)

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Drugs

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Development & Approval Process (Drugs)

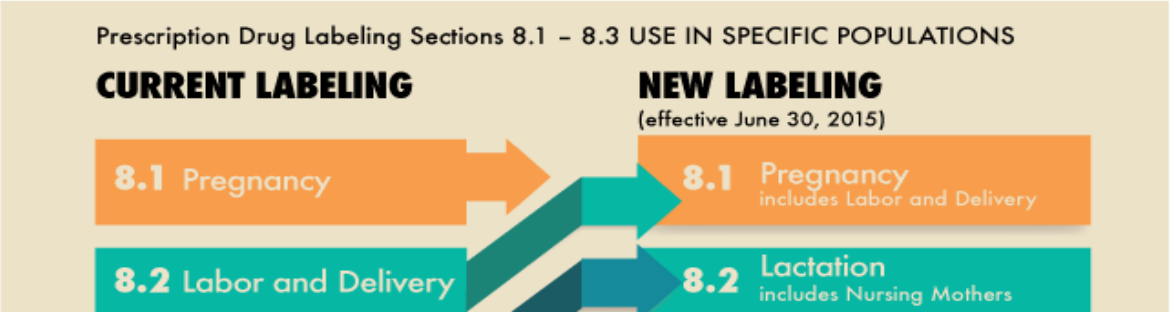
- Development Resources
- Labeling
- **Pregnancy and Lactation Labeling Final Rule**

Pregnancy and Lactation Labeling Final Rule

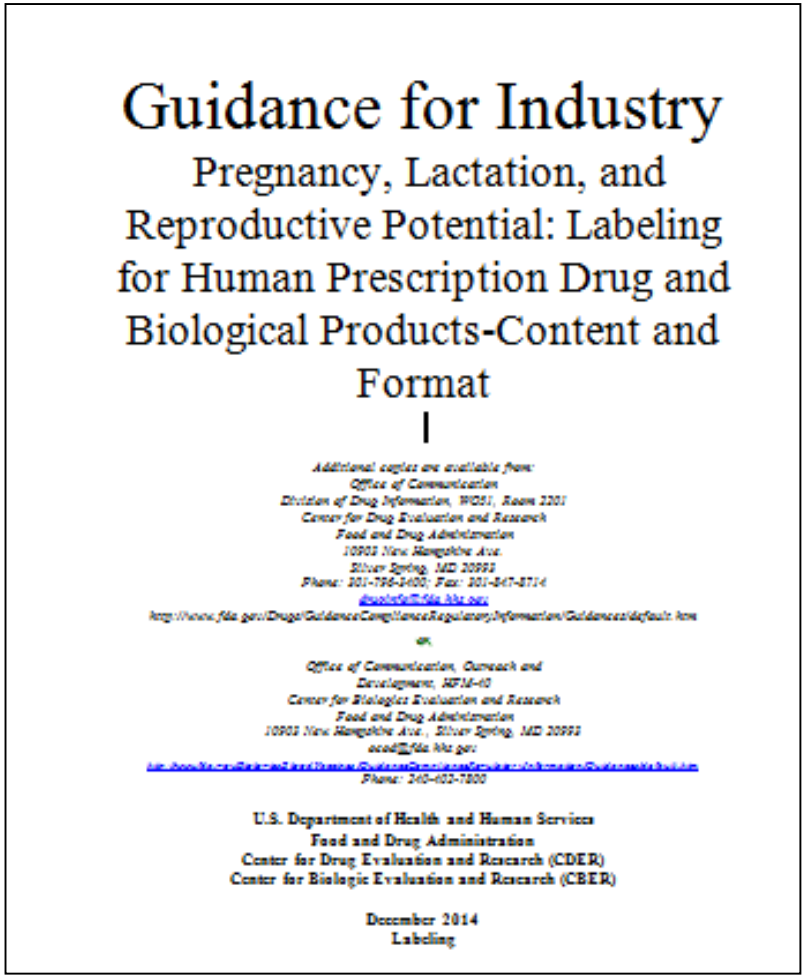
[12/3/14] The FDA published the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule).

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.



Draft Guidance



Guidance for Industry

Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format

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

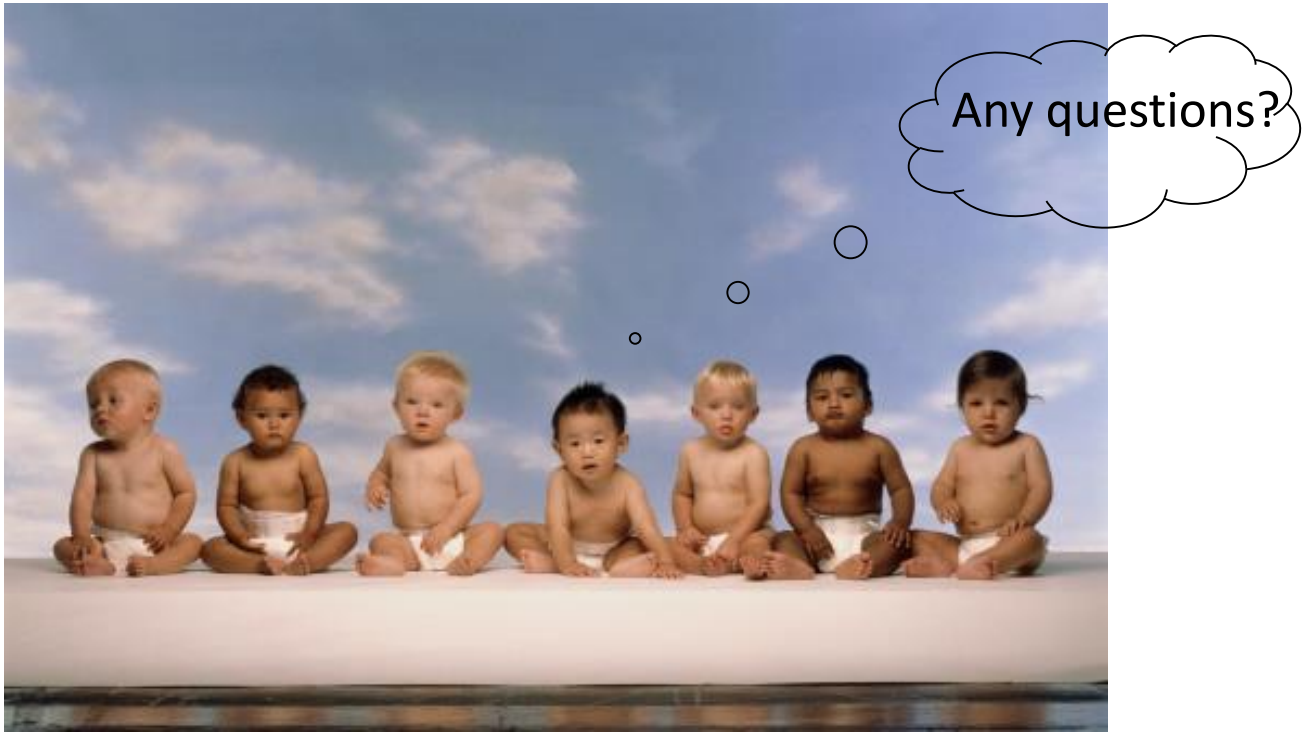
December 2014
Labeling

- Issued with the PLLR
- Comments received from public
- Review and revisions then published in final form

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf

PLLR Labeling Revisions

- PLLR amends the PLR
- Information in current labeling reformatted
  - Replaces pregnancy letter categories with a Risk Summary
  - Concise risk statements based on current data
  - When there are no data – it says so
- Consolidate relevant information in one place
- Lists available pregnancy registries
- Human data added when it is available
- Risk assessment based on animal data will be put in context of human exposure
- As before, drugs contraindicated in pregnancy will say so, in all important sections of the labeling, in addition to section 8.1
- The result is a more complete assessment of the known risks based on the available data


Any questions?

Back ups

Pregnancy Categories

A	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	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).
C	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. OR animal studies have not been conducted and there are no AWC studies in humans.
D	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).
X	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).