# Session #5: Pregnancy and Lactation Labeling Rule (PLLR) Labeling

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# The old USPI pregnancy classification system

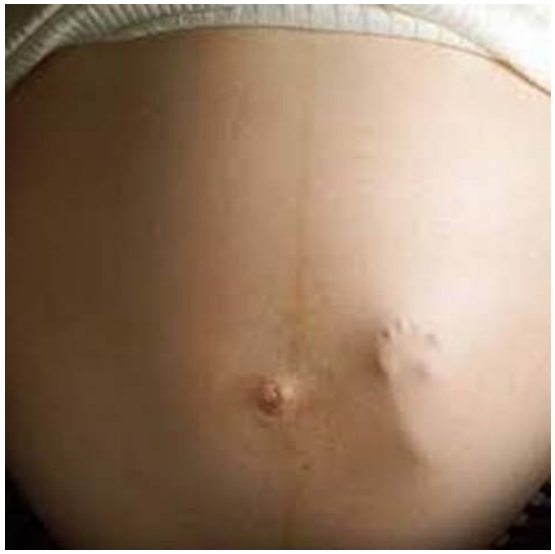
- Failed to advise prescribers and patients of the potential harm from with-holding a medication in pregnancy
- Inaccurately thought of as a grading system where risk increased from lowest (Category A) to highest (Category X)
- Led to incorrect assumptions that drugs in a particular category carry a similar risk
  - Most approved drugs are old Category C
  - Includes drugs with adverse animal data or no animal data at all (significance of adverse animal data may vary)

# The PLLR narrative structure will allow for

- Prominent listing of contact information for Pregnancy Exposure Registries for the drug
- Narrative presentation of information related to use of a drug during pregnancy & lactation including:
  - Risk Summary
  - Clinical considerations for use
  - Supporting data
- A lactation subsection that provides information about using the drug while breastfeeding, including, the amount of drug in breast milk and potential effects on the breastfed infant
- A subsection on females and males of reproductive potential with information about the need for (1) pregnancy testing, (2) contraception, and (3) infertility

# Better addresses how to communicate important information

Source: http://www.sheknows.com/pregnancy-and-baby/day/271



Source: www.Wildbox.com

Source: www.bryanterril.com

- **Pregnant women and females of reproductive potential**
- **Developing fetuses and nursing infants**
- **Men with female partners of reproductive potential**



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# Implementing the PLLR 'Final Rule'

- Within the Company

1. How best to implement the US Pregnancy and Lactation Labeling Rule (PLLR) across the US portfolio of products
2. Implications on the global Core Data Sheet (CDS)
3. Implications for clinical development programs


72064 Federal Register / Vol. 79, No. 233 / Thursday, December 4, 2014 / Rules and Regulations

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. FDA–2006–N–0515 (formerly Docket No. 2006N–0467)]

RIN 0910–AF11

Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending

DATES: This rule is effective June

FOR FURTHER INFORMATION CONTACT

Kathy Schwiter, Center for Drug Evaluation and Research, Food an

Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6246, Silver Spring, MD 20993–0002, 301–796–3432; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911.

SUPPLEMENTARY INFORMATION:

Table of Contents

Executive Summary

Purpose of the Regulatory Action

Summary of the Major Provisions of the Regulatory Action in Question

Costs and Benefits

to the content and format requirements for prescription drug and biological product labeling are authorized by the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and by the Public Health Service Act (PHS Act).

Summary of the Major Provisions of the Regulatory Action in Question

The final rule requires that for the labeling of certain drug products (as described in the "Implementation" section of this document), the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery" be replaced by three subsections entitled "Pregnancy," "Lactation," and

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

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 comments to the Division of Dockets Management (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 Rosemary Addy (CDER) at 301-796-2200, or Office of Communication, Outreach and Development (CBER) at 240-402-7800.

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

# Assembling & maintaining a cross-functional implementation team

- What expertise is needed?
  - ✓ Regionally focused (US only) +/- Global
  - ✓ Cross-portfolio considerations
  - ✓ Clinical Development (Maternal-Fetal, epidemiology)
  - ✓ Developmental & Reproductive Toxicology (DaRT)
  - ✓ Labelling (US and global), labelling sciences
  - ✓ Drug Regulatory Affairs, Policy
  - ✓ Legal, Compliance
- What is the estimated contribution of time?

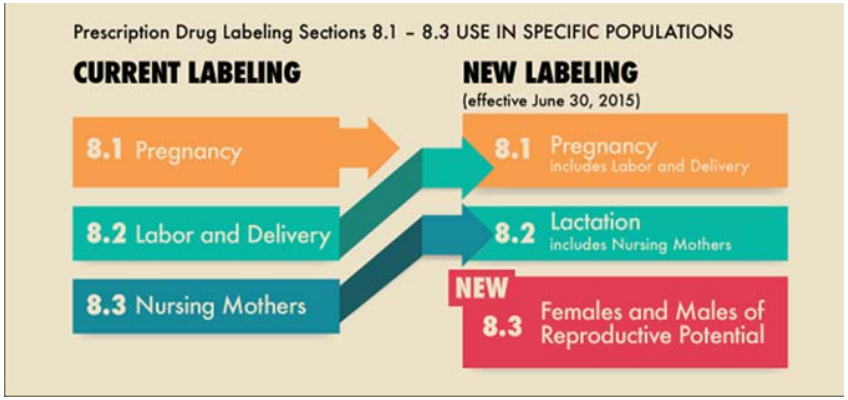
# Alignment of interpretation (1)

- Expert review of key documents
  - Final Rule (21 CFR Part 201)
  - PLLR Draft Guidance for Industry (GfI)
  - USPIs utilizing new PLLR format
- Consultation with program teams that have already been requested to comply with PLLR Guidance (*e.g.*, pending applications)
- Insights obtained through cross-industry discussions and within the ILSI HESI DaRT Committee

ILSI = International life Sciences Institute; HESI = Health and Environmental Sciences Institute; DaRT = Developmental & Reproductive Toxicology

# Alignment of implementation (2)

- How to incorporate information not necessarily required in PLR format to inform prescribing and risk-benefit counseling




Section 8.1 & 8.2

- ✓ Narrative Risk Summary
- ✓ Clinical Considerations

Section 8.3

- ✓ Contraception
- ✓ Pregnancy Testing



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# Development of an Action Plan

- Scope of work
  - What part of the business (OTC not in scope)
  - How many approved labels? Pending applications? Upcoming submissions?
  - USPI only? Core Data Sheet (CDS)?
  - Ensuring governance endorsement at regional level
- Evaluating *in scope* products to draft conversion schedule as mandated within the Final Rule
- Overlay of priority list based on understanding of upcoming submissions

# Example

*U.S. scope of work**


* All marketed products, pending applications, and planned submission



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# Building company efficiency into Implementation process (1)

- Feedback from teams preparing upcoming submissions
  1. Draft GfI is dense rendering it difficult to distinguish how to incorporate information into new PLLR format
  2. '*Appendix A: Organization and Format for PLLR sub-sections*' is a good overview but too simple to understand key elements that are program specific
- Discussed need for hybrid Internal PLLR guidance to facilitate label revisions and governance activities
- Developed internal template text with instructional guidance taken from Final Rule and Draft GfI

# Building company efficiency into Implementation process (2)

- Implemented a PLLR cross-functional awareness and educational ‘Communication Plan’
- Previewed all products that are in ‘old’ (pre-2001) format to assess need for full PLR/PLLR conversion
- Assessed resource need of key functions who will be involved in conversion to PLLR format
  - Can work be done in-house OR will it need to be contracted out?
- Incorporation of a refinement plan
  - How to track feedback from across Divisions, CBER and CDER?
  - How often and based on what insights will we refine the hybrid internal PLLR guidance?

# Experience to date

- 1 NDA & 1 sBLA submitted in PLLR compliant format in 2015 → hybrid internal guidance appears to be providing valuable guidance to teams
- 2 NDAs previously submitted did not receive a request for PLLR conversion in labeling comments received from Agency after 30 June 2015
- 2 program teams have received requests from the Agency for PLLR conversion in midst of old PLR label conversion
- 2 program teams have received requests from the Agency for PLLR conversion during review of non-efficacy supplements (both due for PLLR conversion no later than 2018 - *Appendix B PLLR Draft Gfl*)

# Impact on internal PLLR Implementation activities

- Implementation team reconsidering internal ‘prioritized’ timetable for PLLR conversion
  - Key consideration is impact on resource capacity in specific line functions
- Utilizing feedback from Agency to date, minor revisions to instructional text provided via hybrid internal PLLR guidance

# Final Thoughts

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# The challenge of prescribing in pregnancy

- "*Prescribing in pregnancy can be challenging for providers facing insufficient information about drug safety, overestimation of the risk of medications by both the patient and the care provider, and increasing litigation costs*."[1]

- Pregnant women face the difficult choice between taking untested drugs or foregoing necessary treatment during pregnancy

[1]Mehta et al. Prescribing for the pregnant patient. Cleveland Clinic J of Med. 2014. 81(6). 367-372.

# The value of the ‘Final Rule’

- It has laid the groundwork for more informed communication between

✓Companies and prescribers

✓Prescribers and patients

when pregnancy is a consideration

# Thank You

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