Pregnancy and Lactation Labeling Rule (PLLR): Placement of Human Data in Labeling

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The speaker has nothing to disclose.

Overview

- Introduction
- Overview of Pregnancy and Lactation Labeling Rule
- Inclusion of Human Data in Labeling
- Conclusions

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.

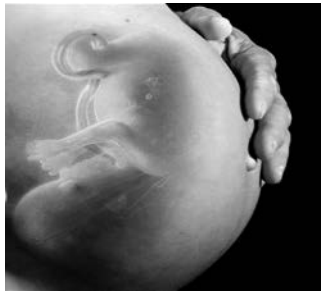
The Information Gap

- Human data about medical product safety in pregnancy at time of market approval are limited or absent
  - Pregnant women are usually actively excluded from clinical trials.
  - Women who become pregnant during clinical trials are discontinued but followed.
- Consequently, almost all clinically relevant human data are collected post-approval

- Important goal of the PLLR conversion process is accurate and up-to-date labeling recommendations which reflect the post-approval experience

Human Data Sources for Pregnancy

- Clinical Trials
  - Trials for drugs specifically to treat a pregnancy-related condition
  - Inadvertent pregnancy reported in clinical trials for non-pregnancy-related condition
- Observational Studies
  - Pregnancy Exposure Registries (Drug or Disease based)
  - Cohort Studies, Case-Control Studies
  - Enhanced Pregnancy Surveillance Program
  - Case Reports or Case Series



Overview of Pregnancy and Lactation Labeling Rule (PLLR)

PLLR

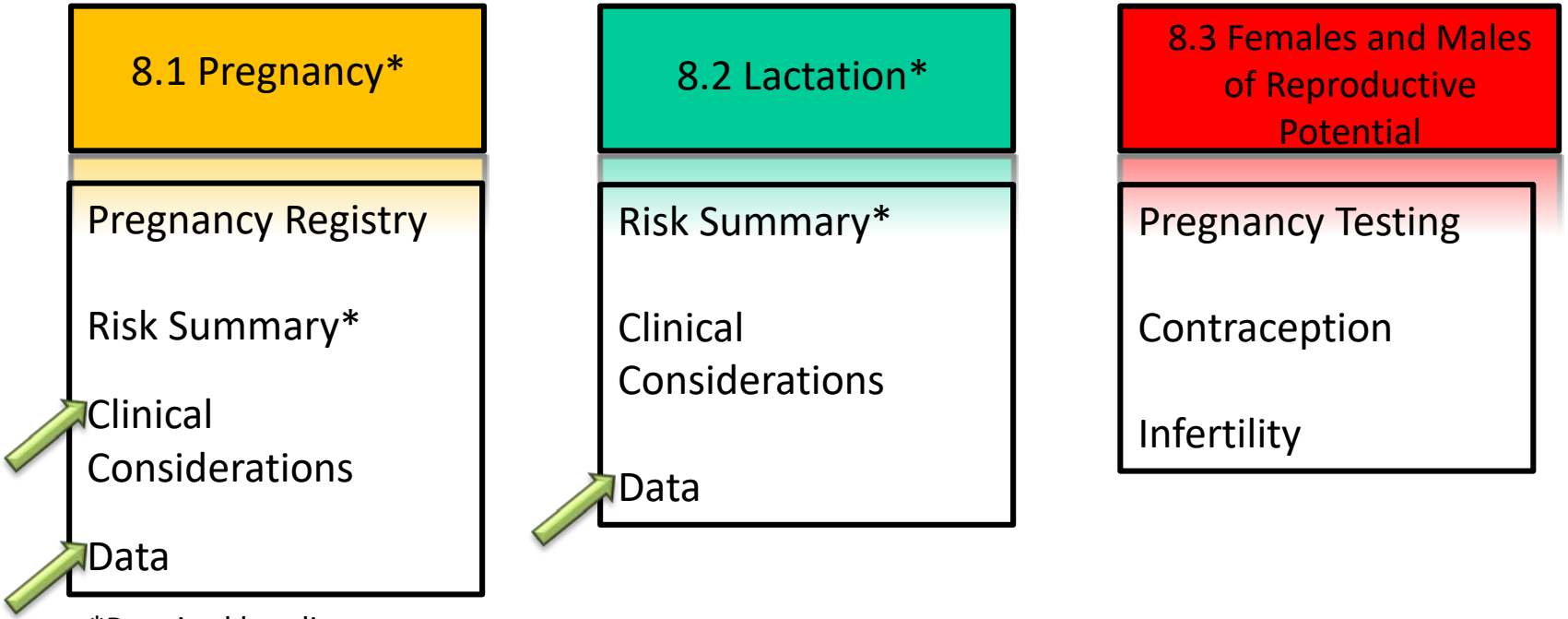
- Effective date **June 30, 2015**.
- **ALL** prescription drugs to remove pregnancy letter categories by June 2020, gradual process
- Prescription drugs approved on or after June 30, 2001 have additional content and formatting requirements

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 Changes to Labeling

8. USE IN SPECIFIC POPULATIONS



*Required heading

See draft guidance: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

8.1 Pregnancy- Clinical Considerations

- Provides information to prescriber to further inform medical/disease factors and benefit/risk counseling to be considered (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, Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

- Describes serious known or potential risks to the pregnant women and/or embryo/fetus associated with the underlying disease or condition for which the drug is indicated
- Not an exhaustive textbook review of the untreated disease/condition and pregnancy outcomes
- Example - Asthma

  "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 in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control."

8.1 Pregnancy- Data, Human Data

- Human Data subheading
  - Describe any potential risk mentioned in Risk Summary
  - Describe clinical trials, pregnancy exposure registry studies, large epidemiologic studies, or well-described case series
  - Should not be lengthy
  - Succinctly describe study design, drug exposure, pregnancy outcomes
  - Describe any limitations of the data

Example: Adalimumab : 8.1 Pregnancy

Data

Human Data

In a prospective cohort pregnancy exposure registry conducted in the U.S. and Canada between 2004 and 2013, 74 women with RA treated with adalimumab at least during the first trimester, 80 women with RA not treated with adalimumab and 218 women without RA (non-diseased) were enrolled. Excluding lost-to-follow-up, the rate of major defects in the adalimumab-exposed pregnancies (N=72), disease-matched (N=77), and non-diseased comparison groups (N=201) was 5.6%, 7.8% and 5.5%, respectively.

Example: Adalimumab : 8.1 Pregnancy

Data

Human Data (continued)

However, this study cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design. Data from the Crohn's disease portion of the study is in the follow-up phase and the analysis is ongoing.

In an independent clinical study conducted in ten pregnant women with inflammatory bowel disease treated with [TRADENAME], adalimumab concentrations were measured in. . .

Example: Methotrexate: 8.1 Pregnancy

Data

Human Data

Published data from cases, literature reviews, and observational studies report that methotrexate exposure during pregnancy is associated with an increased risk of embryo-fetal toxicity and fetal death. Methotrexate exposure during the first trimester of pregnancy is associated with an increased incidence of spontaneous abortions and multiple adverse developmental outcomes, including skull anomalies, facial dysmorphism, central nervous system abnormalities, limb abnormalities, and sometimes cardiac anomalies and intellectual impairment. . . .

Example: Methotrexate : 8.1 Pregnancy

Data

Human Data (continued)

A prospective multicenter study by U.S. and European teratology information services evaluated pregnancy outcomes in women taking methotrexate less than or equal to 30 mg/week after conception. The rate of spontaneous abortion/miscarriage in pregnant women exposed to methotrexate was 42.5% (95% confidence interval [95% CI] 29.2-58.7), which was higher than in unexposed autoimmune disease comparators (22.5%, 95% CI 16.8-29.7) and unexposed nonautoimmune disease comparators (17.3%, 95% CI 13-22.8). . . .

8.2 Lactation – Data

- 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)
- Note: If considered meaningful for information on concentration in breast milk or adverse reactions in infants, information from case reports may be reflected briefly under the Risk Summary or Data headings

Example: Adalimumab : 8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. 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.

Inclusion of Human Data in Labeling

Challenges

Because most human data related to drug use during pregnancy and lactation do not come from adequate and well-controlled trials.

Ongoing discussions about when:

1. Data are limited
2. Lack of a specific or consistent safety finding
3. Whether to include case reports

Considerations of Limited Data

- Limited data may represent
  - A small number of case reports with no safety signal
  - Case reports with missing information and/or confounding
  - A single, small study without control population
- No conclusions about adverse developmental outcomes may be determined.
- Labeling may only have a simple statement in Risk Summary.

Considerations with Lack of a Specific or Consistent Safety Finding

- In some situations, there are a large amount of data on use during pregnancy, however, no clear conclusion may be drawn.
  - Does not necessarily establish or exclude absence of a risk
  - Detailed description of every study is not the goal; however, a conclusion about the safety message from this data is most valuable.
  - This situation may only include simple statements in Risk Summary and Data. Any further description of data must be balanced and present meaningful information to the prescriber.

Lack of a Specific or Consistent Safety Finding: Examples (1)

- Risk Summary statement, nothing under Data

"Available data from published literature on the use of infliximab products during pregnancy have not reported a clear association with infliximab products and adverse pregnancy outcomes."

Lack of a Specific or Consistent Safety Finding: Examples (2)

- Human Data

"Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish or exclude the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups."

Considerations on Case Reports

- Approach should be similar to how cases inform subsection 6.2 *Postmarketing Experience* of labeling, however, some questions and caveats
- Would inclusion in labeling change our understanding of risk message in a clinically meaningful way?
- When the available information is small, as with lactation, even case report descriptions may be helpful
- Determine on a case-by-case basis

Best Practices

- Applicants provide the Agency with a review and summary of the available published literature, relevant cases from their pharmacovigilance databases, and interim or final report of a pregnancy registry study
- Applicants ensure that changes to labeling recommendations are supported by the available data
- Both applicant and Agency need to plan for assessment of safety with drug use in pregnant and lactating women especially with a new drug or when use in pregnant women is highly anticipated for new or chronic disease/conditions

Conclusions

Conclusions

- Goal is to accurately communicate known information about the risks with prescription drug use in pregnant and lactating women
- PLLR format improves presentation of currently available data, but does not help when there are poor quality or sparse data
- Important to have applicant's input on the available data and rationale for updates to safety messaging in the labeling
- Ongoing evolution of Agency thinking on how to include human data such that it is both accurate and meaningful to the prescriber
- Data collection in pregnant and lactating women is a shared responsibility among all stakeholders

Resources

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

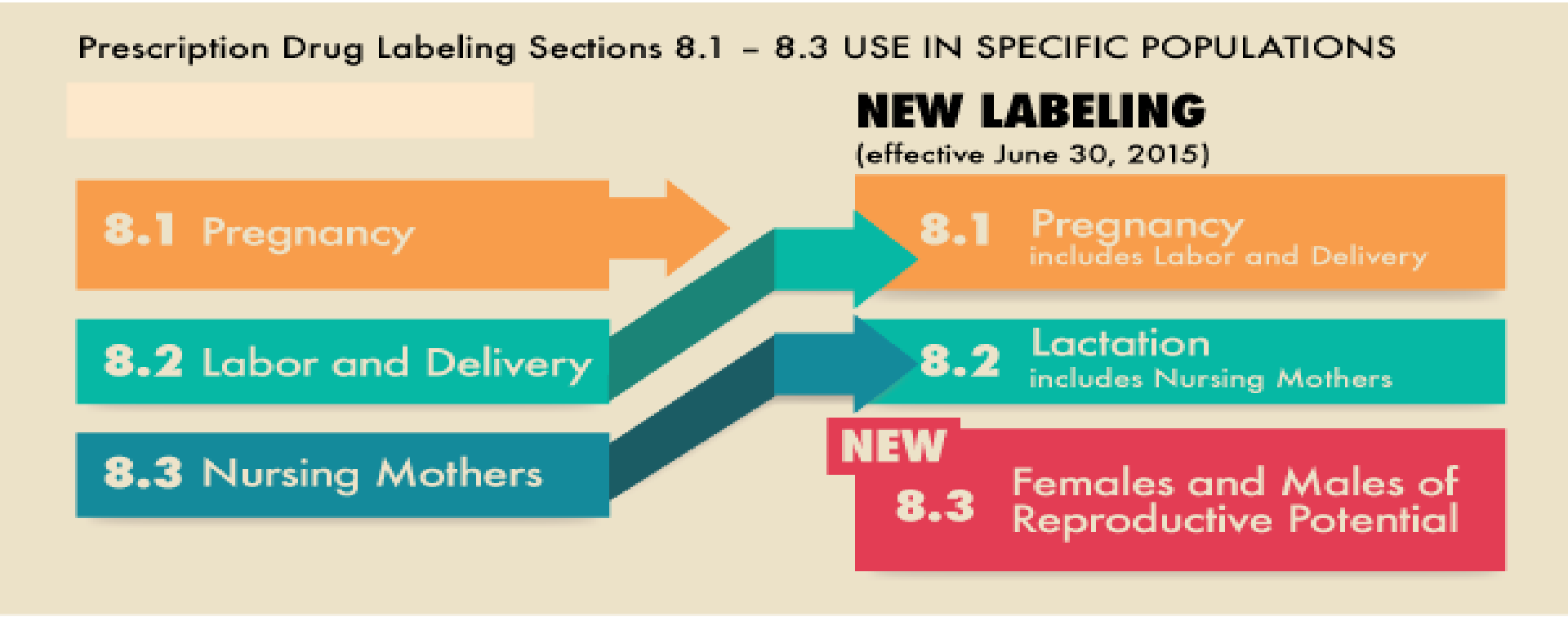
Where to find product labeling and other resources

- Drugs @FDA
  http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- FDALabel: Full-Text Search of Drug Labeling
  https://www.fda.gov/scienceresearch/bioinformaticstools/ucm289739.htm
- 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

Pregnancy Registry Website

https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm

PLLR Changes to Labeling

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