Life without A, B, C, D & X: How pregnancy and lactation labeling can assist with prescribing decisions when treating pregnant and breastfeeding women

LCDR Miriam Dinatale, D.O.
CDR Carrie Ceresa, Pharm D., MPH

Division of Pediatric and Maternal Health (DPMH)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

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- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
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Overview

- Introduction
- History and Overview of Pregnancy and Lactation Labeling Rule (PLLR)
- Inclusion of Human Data in Labeling
- Challenges to including Human Data in Labeling
- Conclusions
- Resources

Introduction

Pregnancy and Medication Use

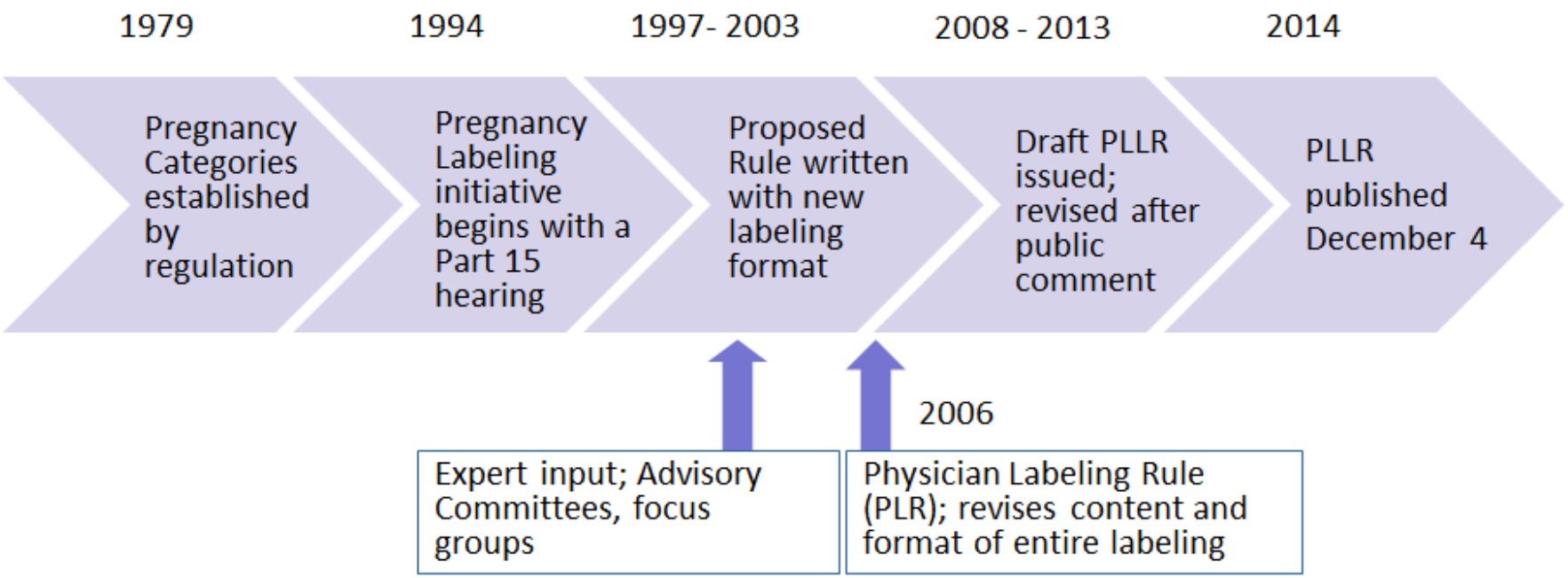
- There were over 3.9 million pregnancies in the US last year
- 50% of pregnant women reported taking at least one medication
- Pregnant women take an average of 3-5 medications at any time during pregnancy
- Between 1976 and 2008, first trimester use of prescription medications has increased by more 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.

History and Overview of the PLLR

PLLR: Historical Overview



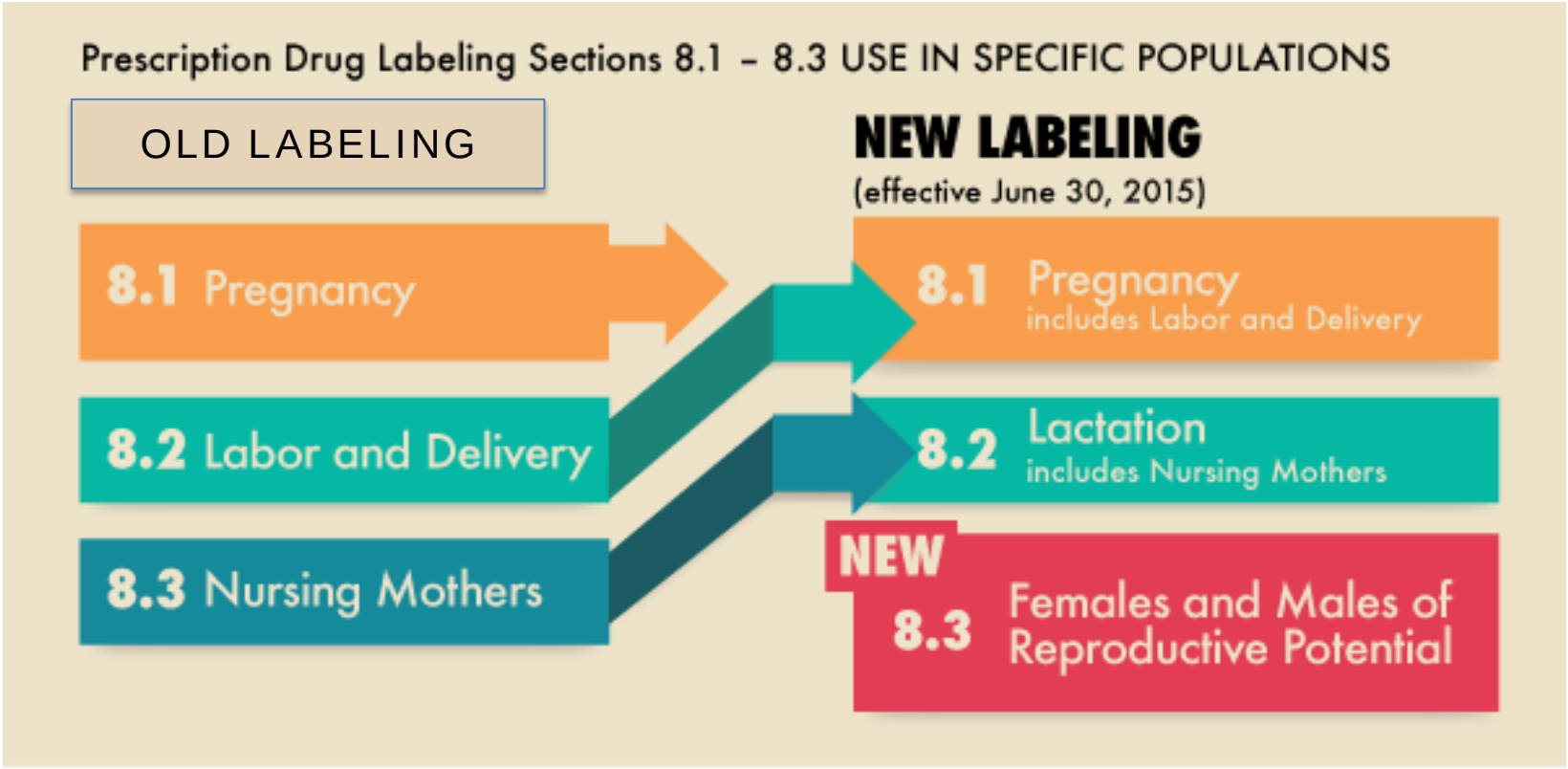
PLLR Implementation

- Effective date **June 30, 2015**.
- **ALL** prescription drugs to remove pregnancy letter categories
- 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

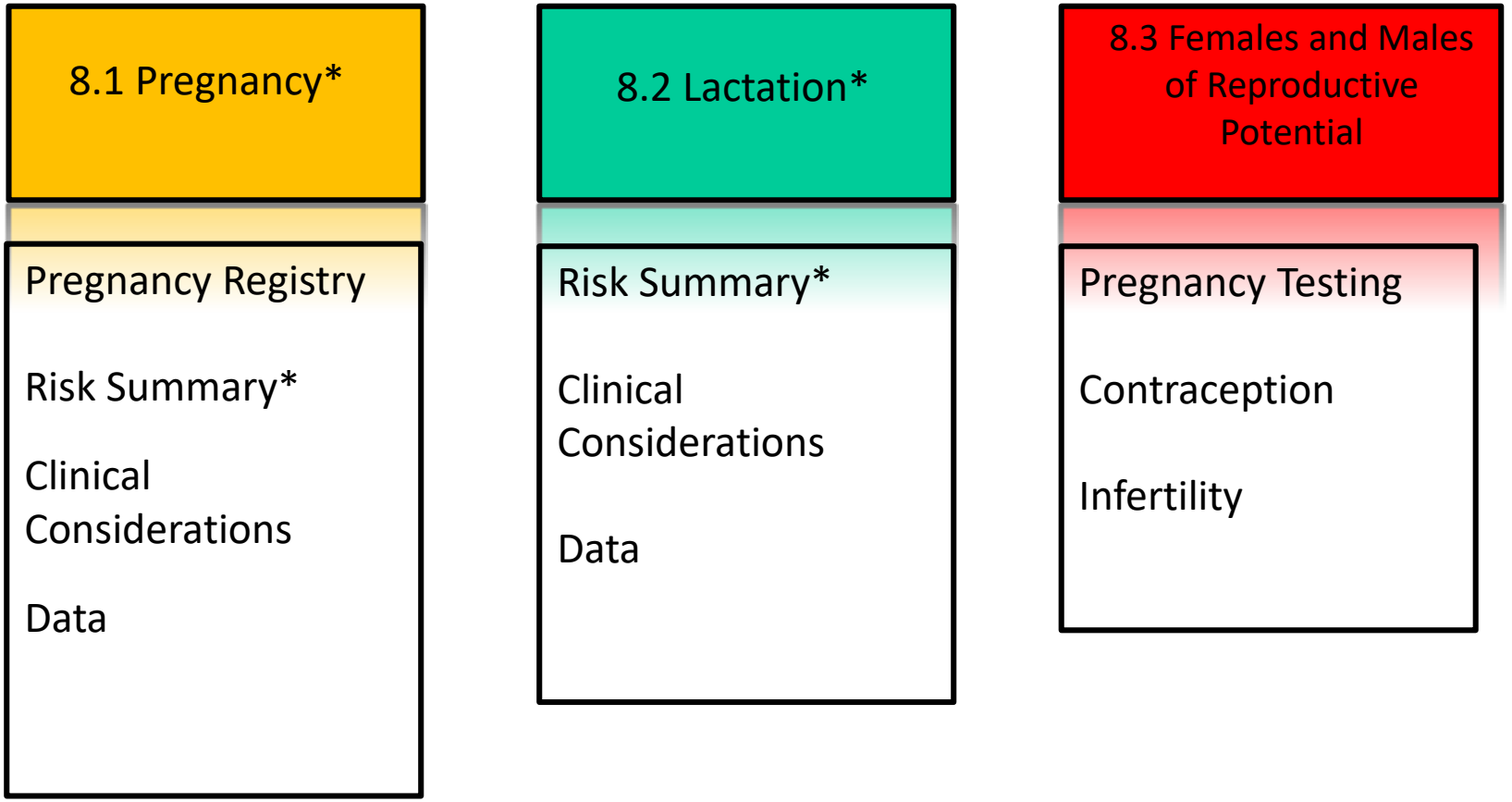
Intent of PLLR

- 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



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.]

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Human Data and Challenges

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 conditions
- Observational Studies
  - Pregnancy Exposure Registries (Drug or Disease based)
  - Retrospective Cohort Studies
  - Case-control Studies
  - Enhanced Pregnancy Surveillance Program
  - Case Reports or Case Series

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Current Approach to the Inclusion of Human Data in Subsection 8.1- Pregnancy

8.1 Pregnancy-Risk Summary

- Drugs without 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."
- 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 information

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

Labeling Example #1:Enbrel (etanercept) Lack of a Consistent Safety Finding

- Data from a pregnancy registry and a retrospective cohort study showed a higher birth defect rate compared to unexposed women with the disease, but no pattern of birth defects

Labeling Example #1:Enbrel (etanercept) Lack of a Consistent Safety Finding

8.1 Pregnancy

Risk Summary

Available studies with use of etanercept during pregnancy *do not reliably support an association between etanercept and major birth defects*. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) Enbrel Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects (*see Data).*

Labeling Example #1:Enbrel (etanercept) Lack of a Consistent Safety Finding

Data

Human Data

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in the first trimester. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

Labeling Example #1:Enbrel (etanercept) Lack of a Consistent Safety Finding

Data

Human Data (continued)

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.

Labeling Example #2: Zofran (ondansetron): Inconsistent Findings

- Varied findings from large epidemiologic studies of varied design (+/- pregnancy registry), with some reporting a potential association of adverse outcomes with drug use and others reporting no association; no consistency or pattern
- Details of the studies are reported under Human Data

Labeling Example #2: Zofran (ondansetron): Inconsistent Findings

8.1 Pregnancy

Risk Summary

Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation *(see Data). …*

Labeling Example #2: Zofran (ondansetron): Inconsistent Findings

Data

Human Data

Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy. Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]).

Labeling Example #2: Zofran (ondansetron): Inconsistent Findings

Data

Human Data (continued)

The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

Labeling Example #2: Zofran (ondansetron): Inconsistent Findings

Data

Human Data (continued)

A case -control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6 th and 9 th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring . In addition, no cases of isolated cleft palate were identified in the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Labeling Example #3: Herceptin (trastuzumab) Clearly Identified Safety Findings

- Case reports/series with quality information to reasonably determine a risk; a rare finding occurs at increased frequency with medication use
- Pregnancy registries or other quality epidemiologic studies report a specific increased risk
- Details of the case reports/series are reported under Human Data

Labeling Example #3: Herceptin (trastuzumab) Clearly Identified Safety Findings

8.1 Pregnancy

Risk Summary

Herceptin can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death *(see Data).* Apprise the patient of the potential risks to a fetus.

Labeling Example #3: Herceptin (trastuzumab) Clearly Identified Safety Findings

Data

Human Data

In post-marketing reports, use of Herceptin during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death. These case reports described oligohydramnios in pregnant women who received Herceptin either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin therapy resumed after amniotic index improved, and oligohydramnios recurred.

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Current Approach to the Inclusion of Human Data in Subsection 8.2-Lactation

8.2 Lactation-Data

- Even less clinical data available on drug use while breastfeeding
- Published clinical studies often not best quality, no information on effects on breastfed infant, and raw data not available for review
- Greater contribution of case reports to risk determination

Example #1: Enbrel (etanercept)

8.2 Lactation

Risk Summary

Limited data from published literature show that etanercept is present in low levels in human milk and minimally absorbed by a breastfed infant. No data are available on the effects of etanercept on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Enbrel and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Example #2: Zykadia (ceritinib)

8.2 Lactation

Risk Summary

There are no data regarding the presence of ceritinib or its metabolites in human milk, the effects of ceritinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions including gastrointestinal adverse reactions, hepatotoxicity, pneumonitis, bradycardia and pancreatitis, advise a woman not to breastfeed during treatment with ZYKADIA and for 2 weeks following completion of therapy.

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Challenges to including Human Data in Labeling

Challenges

- Most human data related to drug use during pregnancy and lactation do not come from adequate and well-controlled trials.
- Ongoing discussions about what to do when:
  - Data are limited
  - Lack of a specific or consistent safety findings
  - Whether to include case reports

Risk Communication Advisory Committee

- **Held on March 5-6, 2018**
- Discussed the impact of pregnancy and lactation labeling information in prescription drug and biological products as modified under the Pregnancy and Lactation Labeling Rule
  - How information in PLLR labeling is being perceived and used by health care providers and other stakeholders
  - Factors that are critical to health care providers' interpretation of the data and counseling of pregnant women on the risks and benefits of a medication, and
  - How to convey risk information to health care providers to accurately and adequately inform risk-benefit considerations for medication use during pregnancy.

Key RCAC Recommendations

- Plain language; Avoid confusing terms
- Upfront pregnancy benefits
- Consider a visual tool
- Develop criteria for strength of evidence, magnitude of evidence
- More message testing

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

- The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant and lactating women.
- PRGLAC is tasked with identifying these gaps and will report its findings back to the Secretary.

PRGLAC Duties

PRGLAC Timeline (1)

PRGLAC Timeline (2)

- Presented Agency methods for disseminating safety information to the public

- new guidance on inclusion of pregnant women in clinical trials
- recommendations from the March 2018 Risk Communication Advisory Committee

- FDA has and will continue to review and contribute to the report

Conclusions

- The goal of PLLR is to accurately communicate known information about the risks with prescription drug use in pregnant and lactating women
- Messaging needs to balance risk with benefit
- Messaging is challenging in the presence of imperfect data.
- There is an ongoing evolution of Food and Drug Administration thinking on how to include human data such that it is both accurate and meaningful to the prescriber

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 Express: mobile application
- 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

Where to find more information about the RCAC and PRGLAC

- Risk Communication Advisory Committee- Recordings and other materials available at:

  https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm594576.htm
- Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) https://www.nichd.nih.gov/About/Advisory/PRGLAC

Pregnancy Registry Website

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Questions

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Back-up Slides

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).


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