Prescribing for Pregnant Women

The New Pregnancy and Lactation Labelling Rule (PLLR) and

The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)
The Pregnancy and Lactation Labeling Rule (PLLRR)

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## Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>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).</td>
</tr>
<tr>
<td>B</td>
<td>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).</td>
</tr>
<tr>
<td>C</td>
<td>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.</td>
</tr>
<tr>
<td>D</td>
<td>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).</td>
</tr>
<tr>
<td>X</td>
<td>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).</td>
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</tbody>
</table>
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
PLL: a brief history

1979
Pregnancy Categories established by regulation

1994
Pregnancy Labeling initiative begins with a Part 15 hearing

1997-2003
Proposed Rule written with new labeling format

2008-2013
Draft PLLR issued; revised after public comment

2014
PLL published

1994
1997-2003
2008-2013
2014

Expert input; Advisory Committees, focus groups

2006
Physician Labeling Rule (PLR); revises content and format of entire labeling
Overview

- Background
- Overview of the rule
- Draft guidance
- Challenges
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

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

**CURRENT LABELING**

- **8.1** Pregnancy
- **8.2** Labor and Delivery
- **8.3** Nursing Mothers

**NEW LABELING** (effective June 30, 2015)

- **8.1** Pregnancy includes Labor and Delivery
- **8.2** Lactation includes Nursing Mothers
- **NEW 8.3** Females and Males of Reproductive Potential
Revised Format

Pregnancy (8.1)

- Pregnancy Registry
- Risk Summary
- Clinical Considerations
- Data

- What are the known risks in context with background risk
- What medical/disease factors should be considered
- The data that support the risk summary

Pregnancy Registry
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 COUNSELING 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.
- 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 (2)

- **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
Pregnancy - Risk Summary (3)

• 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
Lactation (8.2)

Risk Summary

What are the known risks

Clinical Considerations

Minimizing Exposure or Monitoring for Adverse reactions

Data

The data that support the risk summary
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.”
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)
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
<table>
<thead>
<tr>
<th>New Applications (prospective cohort)</th>
<th>NDAs, BLA, ESs</th>
<th>Required Submission Date of PLLR Format</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Submitted on or after 6/30/2015</td>
<td>At time of submission</td>
</tr>
<tr>
<td><strong>Start (6/30/15)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older Approved Applications (retrospective cohort)</td>
<td>Approved 6/30/2001 to 6/29/2002</td>
<td>6/30/2018</td>
</tr>
<tr>
<td></td>
<td>Approved 6/30/2007 to 6/29/2015 or pending on 6/30/2015</td>
<td>6/30/2019</td>
</tr>
<tr>
<td></td>
<td>For applications approved prior to 6/30/2001 in old format labeling</td>
<td>Not required to be in PLLR format. However, must remove Pregnancy Category by 6/29/2018</td>
</tr>
</tbody>
</table>
Older Labeling

• Drugs approved before June 30, 2001 are required to remove the pregnancy letter category by June 30, 2018 (3 years 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
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.
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” (PLLIR or final rule).

The PLLIR 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 PLLIR removes pregnancy letter categories – A, B, C, D and X. The PLLIR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLIR labeling requirements.
Meeting the Challenge of Including Human Data in the New Label

• For many drugs, no or limited human pregnancy safety data exist
• When available, typical sources of data have limitations
  – Traditional pregnancy registries
    • Limited sample size/power, inability to control for important confounders, high lost to follow-up
  – Larger cohort studies
    • May be few exposures to drug of interest even in large number of pregnancies - limited power
  – Administrative or claims databases
    • Difficult to confirm if and when exposure took place, may be few exposures to drug of interest even in large databases – limited power, inability to control for important confounders (folic acid, alcohol, tobacco)
When There Are Data: Challenges in Writing Label Content

- Difficult to interpret studies with the limitations described
- Can lead to misunderstandings about relative safety or risk of medication used in pregnancy
- Can lead to frustration in clinical application of the new fetal risk summary
Vaccines and Medications in Pregnancy Surveillance System (VAMPSS)

Allen Mitchell, MD
Director, Slone Epidemiology Center
Boston University
Boston, MA

Michael Schatz, MD, MS
Department of Allergy
Kaiser Permanente Medical Center
San Diego, CA
Goals of VAMPSS

• National systematic post-marketing surveillance system
• Identify as early as possible the circumstances in which a drug or immunization causes harm
• Provide reassuring data to all concerned for those drugs and immunizations (likely the majority) that are safe during pregnancy
• Provide meaningful information for the new pregnancy label that will benefit both providers and patients
Structure of VAMPSS

American Academy of Allergy Asthma and Immunology
Michael Schatz, MD, MS

Prospective Cohort
Organization of Teratology Information Specialists Research Center at the University of California San Diego
Tina Chambers, PhD, MPH
Kenneth Lyons Jones, MD

Case-Control Study
Slone Epidemiology Center at Boston University
Allen A. Mitchell, MD
Carol Louik, ScD

Independent Advisory Committee
Includes:
CDC
NICHD
NIAID
ACOG
AAP
Biostatistician
Consumer Representative

VAMPSS: Vaccines and Medications in Pregnancy Surveillance System
NICHD: National Institute of Child Health and Human Development
NIAID: National Institute of Allergy and Infectious Diseases
ACOG: American Congress of Obstetricians and Gynecologists
AAP: American Academy of Pediatrics
Overall Approach

- Prospective Cohort
  - Wide range of perinatal outcomes
  - Organization of Teratology Information Specialists (OTIS)

- Case-Control Surveillance
  - Birth defects surveillance (specific congenital malformations) and prevalence of drug/vaccine use
  - Slone Epidemiology Center (SEC) at Boston University
Overall Approach (cont.)

- Both arms obtain information directly from the patient
  - Maximizes confounder ascertainment
  - Minimizes exposure misclassification
    - For flu vaccines, capture exposures occurring outside traditional medical settings
    - For medications, *actual use* versus prescriptions filled but not used, or no prescription but medication borrowed from others
OTIS Methods - 1

- OTIS sites ascertain and refer potential participants to coordinating center
- Exposed cohort, disease-matched cohort (if appropriate), healthy unexposed cohort concurrently recruited
- All groups receive multiple maternal structured telephone interviews at standard time points
- Outcome interview, medical records review (including 1 year pediatric record review)
Maternal interviews and medical records review provide detailed information on:

- Dose, timing, duration of medication and vaccine exposure, coded using Slone Drug Dictionary
- Maternal disease or indication for medication
- Pregnancy history, health history, demographics
- Wide range of potential confounders including other prescription or OTC medications, BMI, tobacco, alcohol and vitamin/mineral use
SEC Methods - 1

- Study subjects
  - Infants with specific major malformations
  - Infants without malformations
  - Medical records reviewed to confirm diagnosis
  - Identified at birth hospitals and tertiary hospitals and via state-based surveillance programs
  - Mothers are interviewed by telephone (CATI) by study nurses within 6 months of delivery
SEC Methods - 2

- Interview data include
  - Demographic, reproductive factors
e.g., age, education, parity
  - Medical history
e.g., maternal asthma before and during pregnancy
  - Medication use (prescription, OTC, vitamins/minerals, herbal and other dietary supplements), coded via Slone Drug Dictionary
  - Vaccine exposure
  - Additional critical variables:
e.g. alcohol, smoking, occupation, diet
Data Analyses

• Unadjusted analyses
  – Prospective cohort: Relative risk ratios for outcomes in exposed compared to unexposed women
  – Case control: Odds ratios for exposures in cases versus controls

• Analyses adjusted for confounders
Potential Confounders Captured for Adjusted Analyses

- Demographics (age, ethnicity, SES)
- Family history
- Reproductive history
- Concomitant diseases
- Concomitant medication exposures (including OTC)
- Periconceptional folic acid supplements
- Habits (smoking, alcohol)
- Occupational exposures
Data Output of VAMPSS

• Interim analyses (every 6-12 months) of accumulating data regarding exposure and outcomes
• Point estimates are estimates of the magnitude of the risk
• 95% confidence intervals provide estimates of the certainty of the risk estimate
• Data are presented to the Advisory Committee
• Final report reflects Advisory Committee discussion and recommendations
Advantages of VAMPSS Compared to In Traditional Pregnancy Registry

- Includes an unexposed comparison group
- Much more extensive control for confounders
- Much lower lost to follow-up rate
- Power to evaluate specific birth defects, including testing signals generated from the cohort arm or other sources
- Using non-malformed controls in the case control surveillance, provides estimates of exposure prevalence to given agents in pregnancy
Advantages of VAMPSS Compared to Database Approaches

– Outcome diagnosis verification
– Control for confounders not available without direct contact with patients
– Exposure accuracy
  • For flu vaccines, capture exposures occurring outside traditional medical settings
  • For medications, *actual use* versus prescriptions filled but not used or no prescription but medication borrowed from others
Unique Strengths of VAMPSS
(Cohort and Case-Control Arms)

• Exposures from sources other than those recorded in claims or medical records
• Information on a myriad of potential confounders
• Ability to account for the potential effect of the underlying condition and its severity/control
Unique Strengths of VAMPSS
(Cohort Arm)

- Established method of recruiting exposed pregnancies and appropriate comparison groups
- Prospective ascertainment
- Track record of low lost-to-follow-up (<5%)
- Data on range of potential adverse outcomes from birth defects to growth restriction
Unique Strengths of VAMPSS (Cohort Arm)

- Although limited power for detection of increased risks for specific major birth defects, potential for ‘signal’ detection
- Early data for newly marketed vaccines and medications
- Study designs modifiable to incorporate vaccine- or drug-specific study questions/ biomarker collection, extended follow-up of cohort, etc.
Unique Strengths of VAMPSS (Case-control Arm)

• Sufficient power to evaluate specific birth defects, which can put sporadic reports of birth defects into an appropriate context
• Population-based exposure prevalence information
• Ability to modify design when appropriate
• >35 year track record of productivity and rigor
VAMPSS and the FDA

- FDAAA gives FDA increased mandate for post-marketing surveillance in pregnancy
- VAMPSS is strongly supported by CBER and CDER leadership
- FDA has approved VAMPSS for meeting two companies’ post-marketing commitments regarding pregnancy safety, and one additional protocol is pending
- VAMPSS will provide valuable information for the new label
VAMPSS Data and the PLLR

- Risk statement for the drug based on human data for a wide spectrum of perinatal outcomes
- Background risk information in general population (healthy controls)
- Background risk information in disease population (disease-matched cohort, disease as exposure in case-control arm)
Conclusion

• VAMPSS was developed specifically to provide comprehensive information regarding the risks and safety of vaccines and medications during pregnancy

• We hope that our information will provide valuable information for all potential stakeholders