American Academy of Pediatrics Webinar

Medication Prescribing for Pregnant and Childbearing-aged Women: Resources for the Practicing Clinician

January 26, 2016
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Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects Defects and Developmental Disabilities
Centers for Disease Control and Prevention

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School of Medicine
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Learning Objectives

- Recognize medications that are known teratogens
- Recognize the importance of discussing medication use with women who are or could become pregnant
- Access resources available through MotherToBaby affiliates and other relevant organizations to help counsel women regarding treatment decisions before and during pregnancy
Part 1: Preventing Teratogenic Exposures

Cheryl S. Broussard, PhD
Division of Birth Defects and Developmental Disabilities

January 26, 2016
National Birth Defects Prevention Month 2016

- **Theme:**
  
  Making Healthy Choices to Prevent Birth Defects – Make a **PACT** for Prevention

  **P**lan ahead
  **A**void harmful substances
  **C**hoose a healthy lifestyle
  **T**alk with your healthcare provider

- #LivingMyPACT
Birth Defects

- Birth defects are common, costly, and critical

- 1 in every 33 babies are born with a birth defect in the United States

- Preconception health is key
HOW SOME MEDICATIONS CAN BE HARMFUL

Birth defects

Pregnancy loss

Prematurity

Infant death

Developmental disabilities

Unknown outcomes
Medication Safety Information is Lacking

Fewer than 10% of medications have enough information to determine fetal risks.

Some women need to take medication during pregnancy.
Misinformation is Abundant
Medication Use in Pregnancy is Common

Is this medication safe for me and my baby?

9 OUT OF 10 WOMEN IN THE UNITED STATES TAKE A MEDICATION DURING PREGNANCY

5.4 MILLION PREGNANCIES ARE EXPOSED TO MEDICATIONS EACH YEAR
How Do We Study Medication Use in Pregnancy?

- Animal toxicology
- Exclusion of pregnant women from clinical drug trials due to ethical concerns places heavy reliance on observational studies.
- Prospective studies are usually not feasible for rare outcomes such as birth defects.
- Retrospective studies are the only realistic options:
  - Cohort
  - Case-control
- Methodological challenges exist for both types.
How Do We Recognize Teratogenic Exposures?

- Teratogens are agents that act to irreversibly alter growth, structure or function of the developing embryo or fetus

- Only way to know with certainty that a prenatal medication is teratogenic in humans is to observe birth defects in babies

- Which study designs were responsible for producing the first signals for subsequent recognition of 17 teratogens?

Friedman JM. ABCDXXX: The obscenity of postmarketing surveillance for teratogenic effects. Birth Defects Res Part A Clin Molec Teratol 2012 (OTIS Special Issue)
Sources of Information about Potential Teratogens

- Case reports* / case series
- Pregnancy registries*
- Birth defects surveillance systems
- Epidemiologic studies
  - Cohort
  - Case-control
- FDA adverse event reporting system

*first-line sources

Sources of Information about Potential Teratogens

- Case reports*/ case series 11
- Pregnancy registries* 5
- Birth defects surveillance systems
- Epidemiologic studies
  - Cohort 3
  - Case-control 1
- FDA adverse event reporting system 1

*first-line sources
Papers that shaped pharmacoepidemiology:

#1

Tribute:
Frances Oldham Kelsey, who
Saved U.S. Babies from
Thalidomide, Dies at 101 –
The New York Times

'Heroine' of FDA Keeps Bad Drug Off Market

By Morton Mintz
Washington Post Staff Writer
July 15, 1962

This is the story of how the skepticism and
stubbornness of a Government physician
prevented what could have been an appalling
American tragedy, the birth of hundreds or indeed
thousands of armless and legless children...

Frances O. Kelsey received the President's Award for Distinguished Federal
Civilian Service from President John F. Kennedy, 1962
National Library of Medicine, Images from the History of Medicine, A018057

Thalidomide-associated phocomelia – 1960s
http://toxipedia.org/display/toxipedia/Thalidomide
## Teratogenic Exposures

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Sedative/antiemetic</td>
<td>Thalidomide embryopathy (including phocomelia)</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Severe cystic acne</td>
<td>Isotretinoin embryopathy (craniofacial, ears, heart, CNS)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Ectopic pregnancy, some autoimmune diseases, malignancies</td>
<td>Fetal methotrexate/aminopterin syndrome (CNS and palate)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anticoagulant</td>
<td>Warfarin embryopathy (hypoplastic nose, limb, CNS, eye, spontaneous abortion)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Spina bifida, atrial septal defect, cleft palate, hypospadias</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Anticonvulsant embryopathy (spina bifida)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Anticonvulsant embryopathy (dysmorphic facial features and distal limb defects)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Anticonvulsant embryopathy (IUGR, dysmorphic facial features, CNS anomalies, cleft lip/palate, and distal limb defects)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Facial clefts</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Facial clefts</td>
</tr>
</tbody>
</table>

Teratogenicity of AEDs

- Exposure to AEDs during pregnancy has been consistently associated with increased risk for birth defects overall

<table>
<thead>
<tr>
<th>Monotherapy Treatment</th>
<th>Prevalence of Birth Defects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women without epilepsy</td>
<td>3.3 (1.4-5.2)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.9 (2.0-3.8)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4.6 (3.5-5.8)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4.9 (3.2-6.6)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>7.4 (3.6-11.1)</td>
</tr>
<tr>
<td><strong>Valproic Acid</strong></td>
<td><strong>10.7 (8.1-13.3)</strong></td>
</tr>
</tbody>
</table>

Current Treatment Guidelines (AAN and AES*)

- Optimize treatment prior to conception
- Choose the most effective AED for seizure type and syndrome
- If possible, avoid valproic acid and AED polytherapy during the first trimester (and throughout pregnancy)
- Use monotherapy and lowest effective dose
- Supplement with folic acid (0.4 mg = recommendation for all women)

*AAN: American Academy of Neurology; AES: American Epilepsy Society*
## Teratogenic Exposures

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<tr>
<th>Medication</th>
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<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misoprostol</td>
<td>Prevent gastric ulcers, abortifacient</td>
<td>Mobius syndrome (skull, cranial nerves), limbs (clubfoot)</td>
</tr>
<tr>
<td>Methimazole</td>
<td>Antithyroid</td>
<td>Aplasia cutus of the scalp</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Immunosuppressant</td>
<td>Mycophenolate embryopathy (ear, facial clefts, conotruncal heart defects)</td>
</tr>
<tr>
<td>Lithium</td>
<td>Antimanic</td>
<td>Ebstein anomaly (rare heart defect)</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Treatment for Wilson disease, rheumatoid arthritis, cystinuria</td>
<td>Connective tissue disorder resembling cutis laxa</td>
</tr>
</tbody>
</table>

## Teratogenic Exposures

<table>
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<th>Medication</th>
<th>Description</th>
<th>Exposure</th>
<th>Pregnancy Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors (Angiotensin</td>
<td>Antihypertensive</td>
<td>2(^{\text{nd}}) and 3(^{\text{rd}}) trimesters of pregnancy</td>
<td>Fetal renal failure, renal dysplasia, hypocalvaria (skull), fetal death</td>
</tr>
<tr>
<td>converting enzyme)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DES (Diethylstilbestrol)</td>
<td>Prevent pregnancy complications</td>
<td>During pregnancy</td>
<td>Vaginal adenocarcinoma in young women</td>
</tr>
</tbody>
</table>
Medication Safety

- Medications not mentioned today as teratogenic exposures are not necessarily “safe”!

- Many commonly used medications require further study
  - Prescription medications
    - Antidepressants
    - Opioid analgesics
    - Antibacterials
    - Others
  - Over-the-counter medications
  - Herbal products
Research Study Sites across the US

CBDRP State Participation

- 1997 - current
- 2003 - current
- 2003 - 2011
- 1997 - 2011
- 1997 - 2003
Key Messages:

Women: Pregnant or thinking about pregnancy? Don’t stop or start taking any medications without first talking with a healthcare provider.

Healthcare Providers: Discuss the potential risks and benefits of [xyz] medication use with women of reproductive age, prior to prescribing. You might be treating for two.
For more information, contact CDC
1-800-CDC-INFO (232-4636)

Visit: [www.cdc.gov/treatingfortwo](http://www.cdc.gov/treatingfortwo)
Contact: cbroussard@cdc.gov

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Part 2: When & How to Assess & Advise

Christina Chambers, PhD, MPH
Department of Pediatrics
University of California, San Diego
La Jolla CA
Prevention of Risky Exposure in Pregnancy and Lactation

- Therapeutic and safety goals
  - Best (most effective) medication for treatment of mother
  - Among choices of medications and based on best-quality evidence, safest treatment for both mother and baby
  - Prevention of exposure to teratogenic medications at critical times in gestation if possible
  - Reassurance for mother that lack of treatment or inappropriate/under-treatment may be harmful for mother and baby
When to Assess and Advise

- Most pregnancies are unplanned
- Exposures to potentially harmful medications can easily take place in the first few weeks of embryonic development when many mothers do not yet know they are pregnant
When and How to Assess and Advise

- Routine health visits for women with the potential to become pregnant even if not planning to do so
- At dispensing of a known teratogen or medication that may pose risks during lactation to a female of reproductive age
  - Assess current medication use and any risks associated with the underlying condition being treated if the woman were to become pregnant
  - Review plans for pregnancy and contraceptive practices as appropriate
When and How to Assess and Advise

- Upon first positive pregnancy test
- When discussing plans for breastfeeding
- Postpartum visit
- Inter-pregnancy/pediatric visits
Resources for Information on What and How to Advise

- Even with known teratogens, often not an easy yes/no answer
- Choice of medications often made in the context of inadequate safety data for any of the available options
- Timing, dose and route of administration matter
- Can require assistance with accessing the most current reliable data
- Can require assistance in interpretation and communication of the information
Sources of information for clinicians
http://mothertobaby.org
866-626-6847 phone; 855-999-3525 text
Benzodiazepines and Pregnancy

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to benzodiazepines may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your health care provider.

**What is a benzodiazepine?**

Benzodiazepines are medications used to treat anxiety, sleeplessness, seizures, muscle spasms, and alcohol withdrawal. Valium (diazepam), Xanax (alprazolam), Klonopin (clonazepam), Restoril (temazepam), and Ativan (lorazepam) are a few examples of benzodiazepines, but there are many others. While it is best to study medicines individually, benzodiazepines are often studied together during pregnancy.

**Should I stop taking my benzodiazepine once I find out I’m pregnant?**

No. You should always talk to your health care provider before making any changes in your medication. If you suddenly stop taking your medication you may have withdrawal and we don’t know what effect withdrawal might have on a pregnancy. Your health care provider can help you decide if the benefit of taking the medicine outweighs any possible risk to your pregnancy.

**I’ve heard that benzodiazepines can cause birth defects like cleft lip and palate. Is this true?**

Some early studies in animals and humans suggested a slight increase in the risk for cleft lip and/or cleft palate if a benzodiazepine was taken during the first trimester. Since these early reports, there have been studies and reviews that have not supported these earlier results or birth defects in general. It is generally felt that exposure to a benzodiazepine does not increase the risk for birth defects.

**Can taking benzodiazepines cause other pregnancy problems?**

Two studies have suggested a higher rate of preterm deliveries and low birth weight in infants when women take benzodiazepines during pregnancy. However, a third study did not find these risks, so more research is needed to accurately answer this question. It is possible that other factors and not the medicine were responsible for these findings.

**I need to continue taking my benzodiazepine medication. Will it cause any harmful effects in my baby after birth?**

If you are taking a benzodiazepine near the time of delivery, your baby may have withdrawal symptoms such as difficulty breathing, muscle weakness, irritability, crying, sleep disturbances, tremors, and jitteriness. It is important that you inform your obstetrician and your baby’s pediatrician so extra care can be provided should your baby need it. These symptoms resolve over a period of time as the drug leaves the baby’s system and are not expected to have any long-term effects.

**Will taking a benzodiazepine have any effect on my baby’s behavior and development?**

Some studies in animals have suggested an effect on behavior in exposed offspring. However, since animals do not always predict the effects in humans, no conclusions can be made. Presently, there are no well-done, long-term studies looking at children exposed to benzodiazepines during pregnancy. However, these drugs have been on the market for more than 40 years and there has been no evidence to suggest that they have long-term harmful effects on the child’s brain or development.
Drugs in Pregnancy and Lactation, 10th Edition

A Reference Guide to Fetal and Neonatal Risk

Gerald G. Briggs
Roger K. Freeman

Includes interactive eBook with complete content
Reprotox – On-Line Subscription Service/App
TERIS – On-Line Subscription Service

Teratogen Information System

and the on-line version of

Shepard's Catalog of Teratogenic Agents
Drugs and Lactation Database (LactMed) - A peer-reviewed and fully referenced database of drugs to which breastfeeding mothers may be exposed. Among the data included are maternal and infant levels of drugs, possible effects on breastfed infants and on lactation, and alternate drugs to consider.

Select Database
- ChemIDplus
- HSDB
- TOXLINE
- CCRIS
- DART
- GENETOX
- IRIS
- ITER
- LactMed
- Multi-Database
- TRI
- Haz-Map
- Household Products
- TOXMAP
- TOXNET Home

Search LactMed

(e.g. Advil, oral contraceptives, Prozac)

Search  Clear

For chemicals, add synonyms and CAS numbers to search:
- Yes
- No

Limits  Browse the Index

Support Pages
- LactMed Record Format
- Database Creation & Peer Review Process
- Help
- Fact Sheet
- Sample Record
- TOXNET FAQ
- Glossary
- Breastfeeding Links
Revised Pregnancy and Lactation Labeling
The Pregnancy and Lactation Labeling Rule (PLLRL) 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
## Pregnancy Categories

<table>
<thead>
<tr>
<th></th>
<th>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).</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</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>B</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>C</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>D</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>
</tr>
<tr>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
PLLR: 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: PLLR published

- 2006: Physician Labeling Rule (PLR); revises content and format of entire labeling
- Expert input; Advisory Committees, focus groups
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

MotherToBaby
Medications & More During Pregnancy & Breastfeeding
Ask The Experts

UC San Diego
School of Medicine
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
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

Drugs systematically 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.
## PLLR Implementation Schedule

<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></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 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
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" (PLLRR or final rule).

The PLLRR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist healthcare 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 PLLRR removes pregnancy letter categories – A, B, C, D and X. The PLLRR also requires the label to be updated when information becomes outdated.

Below is a comparison of the current prescription drug labeling with the new PLLRR labeling requirements.
Questions & Answers

All live Webinar participants will be contacted via email following the presentation with instructions for completing the session evaluation.