PHASING OUT CATEGORIES AND PHASING IN THE PREGNANCY AND LACTATION LABELING RULE (PLLR)

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A Presentation for HealthTrust Members
April 2, 2019

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OBJECTIVES

- **PHARMACISTS**:
  - Compare previous pregnancy categories to the new Pregnancy and Lactation Labeling Rule (PLLR)
  - Describe the new addition of reproductive potential to pregnancy guidelines
  - Apply the PLLR in making clinical recommendations and decisions in situations where it was previously unclear within former pregnancy categories
- **PHARMACY TECHNICIANS:**
  - Explain the current components of the Pregnancy and Lactation Labeling Rule (PLLR)
  - Recall the different subsections of pregnancy, lactation, and reproductive potential that are now required on medication labels

PREGNANCY STATISTICS

- 6 million pregnancies occur annually
- 50 percent of these pregnant women report to take at least one medication and can take an average of 2.6 medications at any time during pregnancy
- First trimester use of prescription medications has increased by more than 60 percent
- Use of four or more medications in the first trimester has tripled

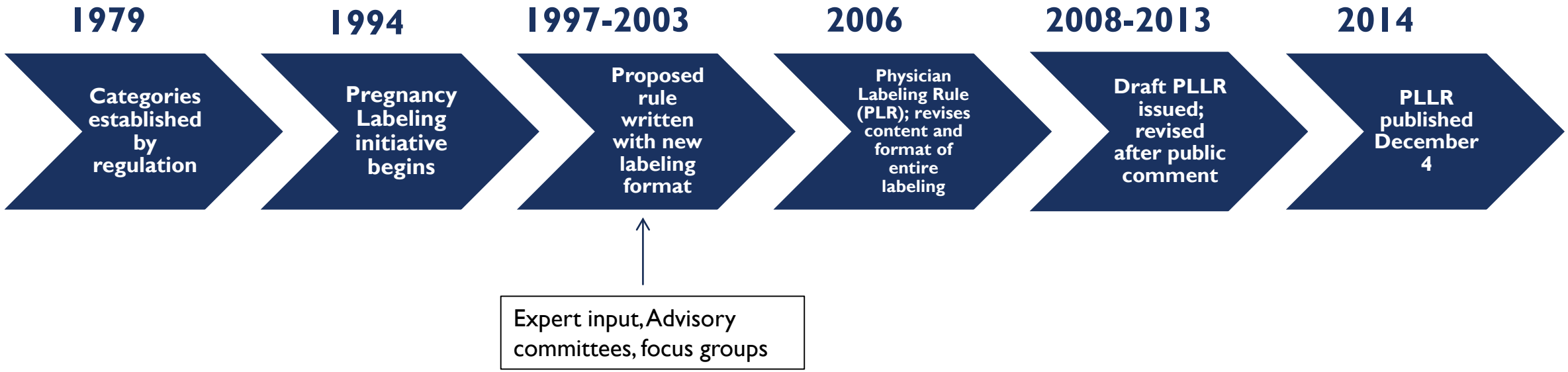
Sources: U. S. Food and Drug Administration, 2014.
Brucker MC, et al. 2017

GAP IN CLINICAL KNOWLEDGE

- Pregnant women usually excluded from clinical studies leading to scarce human safety data in pregnancy
- Study applicants who become pregnant are discontinued from trial but followed
- Most clinically relevant pregnancy data are collected post-approval
- Intent of the PLLR conversion is to fill the clinical knowledge gap of drug therapy in pregnancy by providing accurate and up-to-date labeling recommendations which reflect available data

Source: U. S. Food and Drug Administration, 2016.

HISTORY OF PREGNANCY LABELING RULE



Source: U. S. Food and Drug Administration, 2016.

HISTORY OF PREGNANCY CATEGORIES 1979

- Unless a drug was not absorbed systemically and was not known to have a potential for indirect harm to a fetus, a "Pregnancy" subsection must be included within the "Precautions" section of the labeling
- **8.1 Pregnancy**
  - Contains information on drug's teratogenic effects and other effects on reproduction
  - Description of human studies with drug and data on its effects on later growth, development and functional maturation of the child (if available)
  - Classified as 5 pregnancy categories: **A, B, C, D, X**
    - Categorized on basis of risk of reproductive and developmental adverse effects or risk weighed against potential benefit
- **8.2 Labor and Delivery**
  - Labeling must include information on effects of drugs to mother and fetus
- **8.3 Nursing Mothers**
  - Labeling must include information about excretion of drug in human milk and effects of nursing infant

Source: Fed. Regist. 2014

PREGNANCY CATEGORIES

Pregnancy category	Description
A	Adequate and well-controlled studies in pregnant women have failed to demonstrate 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 adequate and well-controlled studies in pregnant women, **or** animal reproduction studies have shown adverse effects, but well-controlled studies in pregnant women have shown no adverse effects to the fetus.
C	Animal reproduction studies have shown an adverse effect on the fetus, **or** there are no animal reproduction studies and no well-controlled studies in humans.
D	Positive evidence of fetal risk, but benefits may outweigh risks.
X	Positive evidence of fetal risk, and risks clearly outweigh any possible benefit

Source: U. S. Food and Drug Administration, 2016.

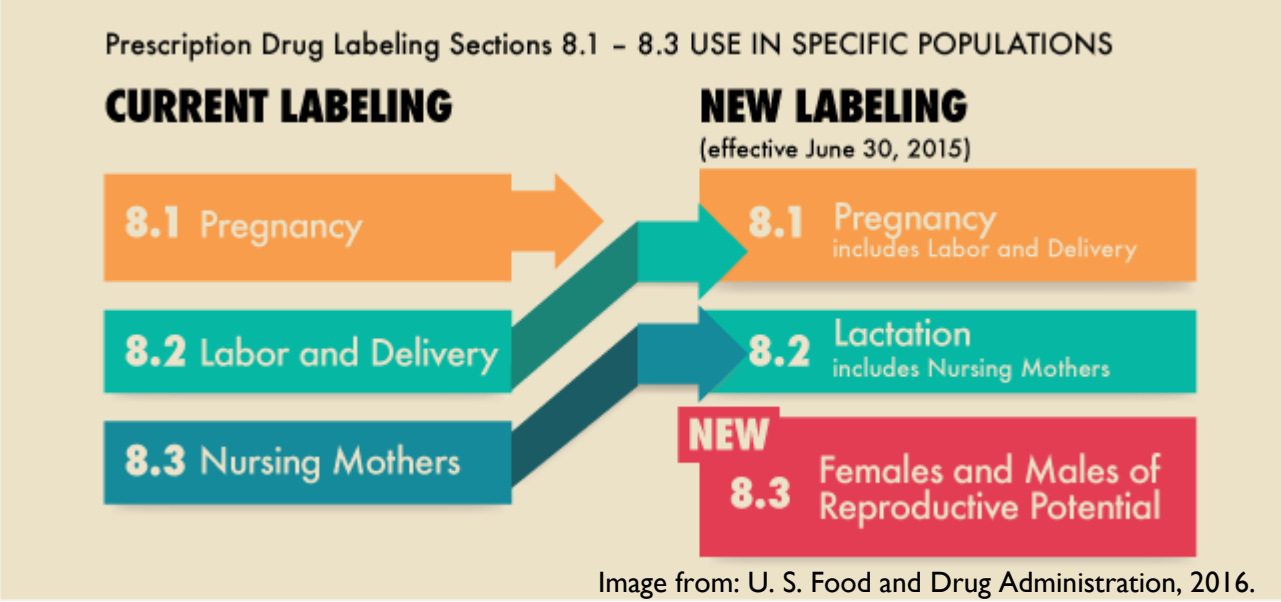
CHALLENGES OF PREGNANCY CATEGORIES

- Pregnancy letter category system oversimplifies a very complicated, and individualized clinical decision
- No information on gestational age and effects of drug exposure at various trimesters
- Does not address differing dosages needed at various stages due to pharmacokinetic changes during pregnancy
- Lack of information on medication use in lactation
- Lack of data on drug effects on humans, resulting in an emphasis on animal data
- An inability to interpret the C category clinically
  - A drug with adverse reactions in animals could be labeled as the same category as a drug with no animal information
- Does not take into account timing of drug exposure during pregnancy
- Categories are not defined by severity of risk but by amount of quality data

Source: Wood, W. 2013.

INTENT OF PLLR

- Remove the pregnancy categories
- Change and combine sections pertaining to pregnancy and lactation and add a new section
- Provide prescriber with relevant information for pregnant or lactating women
- Provide more complete statement of known risks based on available data
- Animal data put into context of human exposure
- Human data added when available
- **Explicitly states when no data are available**



Source: U. S. Food and Drug Administration, 2016.

Image from: U. S. Food and Drug Administration, 2016.

IMPLEMENTATION OF PLLR

- Effective June 30, 2015
- Requires all prescription drugs approved since June 30, 2001 to remove pregnancy categories by 2020 and revise content and format of their pregnancy and lactation sections into new PLLR format
- Drugs approved prior to 2001 are required to remove pregnancy categories within 3 years of implementation date of PLLR
- Must update label as information becomes outdated
- Over-the-counter medications are not affected by PLLR and labeling requirements will not change
- Timely updates may be a challenge to manufacturers due to requirement of close collaboration with FDA
- Encourages consumers to cooperate with pregnancy registry to share their health information for data collection

Source: U. S. Food and Drug Administration, 2016.

ASSESSMENT QUESTION 1

Which of the pregnancy categories defines this statement?

"There are no animal reproduction studies and no well-controlled studies in humans."

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

QUESTION 1 - RESPONSE

Which of the pregnancy categories defines this statement?

"There are no animal reproduction studies and no well-controlled studies in humans."

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

ASSESSMENT QUESTION 2

Which of the pregnancy categories defines this statement?

"Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women."

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

QUESTION 2 - RESPONSE

Which of the pregnancy categories defines this statement?

"Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women."

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

8.1 PREGNANCY

- New 8.1 section will include:
  - **Pregnancy Exposure Registry:** Registry that collect and maintain data on the effects of approved drugs that are prescribed to and used by pregnant women
  - **Risk Summary:** Narrative and summary of any human or animal data; background information regarding major birth defects and miscarriage in United States (U.S.) population
  - **Clinical Considerations [Optional Subheadings]:** Disease-associated maternal and fetal risk, Dose adjustments, Maternal/fetal adverse reactions, and Labor and delivery information
  - **Data:** Summarizes Risk Summary and Clinical Considerations; Human and animal data
  - Also includes labor and delivery information

Source: Fed. Regist. 2014

8.1 PREGNANCY [PREGNANCY EXPOSURE REGISTRY]

"There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TRADENAME during pregnancy."

- Observational study that collects health information from women taking medications or vaccines during pregnancy
- Informs healthcare providers of the availability of a pregnancy exposure registry for a product
  - Phone number and website provided
- Subheading omitted if no registry available

Source: Fed. Regist. 2014

8.1 PREGNANCY [RISK SUMMARY]

HUMAN data	ANIMAL data	PHARMACOLOGY
• Incidence • Effect of dose • Effect of duration of exposure • Effect of gestational timing of exposure	• Number and types of species affected • Timing of exposure • Animal doses expressed in human dose equivalents • Outcomes for pregnant animals and offspring	• Explanation of mechanism of action that may lead to adverse developmental outcomes
If no data available, must clearly be stated in the Risk Summary		

Source: Fed. Regist. 2014

8.1 PREGNANCY [CLINICAL CONSIDERATIONS]

Subheadings	Description
Disease-associated maternal and/or embryo/fetal risk	• Any serious known/potential risk to mother or fetus • Provide information on risks if disease/condition is untreated in pregnancy
Dose adjustments during pregnancy and postpartum period	• Provide information on metabolism if drug is metabolized by P450 enzyme with well-supported activity changes in pregnancy
Maternal adverse reactions	• Any adverse drug reactions (ADRs) unique to pregnancy or occurs with increased frequency or severity in pregnant women • Any available clinical interventions to monitor or mitigate ADRs
Fetal/Neonatal adverse reactions	• Any ADRs that may occur to the fetus or neonate from drug's pharmacologic activity or other data
Labor or delivery	• Any information on drug's effects on labor or delivery to mother, fetus, and/or neonate, duration of labor and delivery • Include severity, reversibility, available interventions that can mitigate ADRs

Source: Fed. Regist. 2014

EXAMPLES OF 8.1 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)]."

Source: Fed. Regist. 2014

8.1 PREGNANCY [DATA]

HUMAN DATA	ANIMAL DATA
• Describes data supporting any risk statements provided in **Risk Summary** and **Clinical Considerations** subsections	• Describes nonclinical developmental toxicity studies that form scientific basis for any risk statements in **Risk Summary**
• Data source • # of subjects • Study duration • Exposure information • Limitations of data	• Types of studies • Animal species • Animal doses in human dose equivalents • Duration/timing of exposure • Study findings • Presence or absence of maternal toxicity • Limitations of data

Source: Fed. Regist. 2014

8.2 LACTATION

- New Section 8.2 will now include:
  - **Risk Summary**: describes presence of drug in human milk (concentration in milk, actual/estimated infant daily dose), and the effects on milk production and the breastfed child, and statement on risk-benefit ratio
  - **Clinical Considerations**: includes information on minimizing exposure and monitoring for adverse reactions in the breastfed infant
  - **Data**: describes clinical studies and data from studies summarized in Risk Summary and/or Clinical Considerations; include only when available
- Risk statement needed

Source: Fed. Regist. 2014

8.2 LACTATION [RISK SUMMARY]

"[TRADENAME] is not absorbed systemically by the mother following (route of administration) and breastfeeding is not expected to result in exposure of the infant to [TRADENAME]."

- Summary of information on the presence of a drug and its active metabolite on:
  - Human milk
  - Breastfed child
  - Milk production
- Contraindications will be stated first in the **Risk Summary** followed by explanation of the risk
- Risk Statement:

"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."

Source: Fed. Regist. 2014

8.2 LACTATION [CLINICAL CONSIDERATIONS]

- Contains information on:
  - **Minimizing Exposure:** Timing of administration relative to breast feedings, pumping sessions, discarding milk for a specific time period ("pump and dump")
  - **Monitoring for Adverse Events:** Description of available ways to monitor and mitigate ADRs in the child who was breastfed as well as counseling information on risks and benefits to the mother
  - **Data:** Description of the data mentioned in Risk Summary and Clinical Considerations sections

Source: Fed. Regist. 2014

8.2 LACTATION [DATA]

- Describe data on which the **Risk Summary** and **Clinical Considerations** are based
- Provide comprehensive review of published literature and their pharmacovigilance database to update this section
- Update new label as data becomes available
- Description of clinical lactation study
- Description of animal lactation study (only if there is no human data)
- If no data, this subheading is omitted

Source: Fed. Regist. 2014

8.3 FEMALES AND MALES REPRODUCTIVE POTENTIAL

- **NEW SECTION ADDED TO LABELING REQUIREMENTS**
- New 8.3 will now include:
  - **Pregnancy testing**
  - **Contraception**
  - **Infertility**
- Section should be utilized in the following situations:
  - Pregnancy testing and/or contraception recommended before, during or after drug therapy
  - Possible drug-associated effects on fertility and/or mutagenesis
- Cross-reference to NONCLINICAL TOXICOLOGY for a detailed discussion of the animal studies

Source: Fed. Regist. 2014

ASSESSMENT QUESTION 3

Which of the pregnancy categories defines this statement?

"Animal reproduction studies have shown an adverse effect on the fetus"

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

QUESTION 3 RESPONSE

Which of the pregnancy categories defines this statement?

"Animal reproduction studies have shown an adverse effect on the fetus"

A. **Pregnancy Category A**
B. **Pregnancy Category B**
C. **Pregnancy Category C**
D. **Pregnancy Category D**
E. **Pregnancy Category X**

ASSESSMENT QUESTION 4

True or False?

The Pregnancy and Lactation Labeling Rule (PLLR) applies to all medications including prescriptions, over-the-counter medications, and herbal supplements.

QUESTION 4 RESPONSE

True or False?

The Pregnancy and Lactation Labeling Rule (PLLR) applies to all medications including prescriptions, over-the-counter medications, and herbal supplements.

False

EXAMPLES OF FORMER CATEGORY C MEDICATIONS

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **PREGABALIN**

PREGABALIN

- **8.1 Pregnancy**
  - Provides Pregnancy Exposure Registry information
  - Risk Summary: States that there are **no** well-controlled studies with pregabalin in pregnant women. Explicitly states study findings of developmental toxicity that were found in animal studies.
    - **Animal reproductive studies show increased incidence of fetal structural abnormalities, skeletal malformations, retarded ossification, decreased fetal body weight in offspring of rats and rabbits given pregabalin orally during organogenesis at doses 16x human exposure at 600 mg/day**
  - Data: Provides study results of information summarized in Risk Summary subsection, giving doses used for studies in pregnant rats and female rabbits during organogenesis and the developmental toxicities associated with the doses given

Source: Pregabalin [product information]. 2018.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **PREGABALIN**

PREGABALIN

- **8.2 Lactation**
  - Risk Summary: States that small amounts of pregabalin have been detected in milk of lactating women
    - **Provides pharmacokinetic study in lactating women that detected pregabalin in breast milk at average steady state concentrations approximately 76% of those in maternal plasma**
    - Provides summary of animal data: **there is potential risk of tumorigenicity with exposure of pregabalin to breastfed infant through breast milk and therefore, breastfeeding while taking pregabalin is not recommended.**
  - Data: Provides more information on pharmacokinetic study done in lactating women and the dose and frequency given

Source: Pregabalin [product information]. 2018.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **PREGABALIN**

PREGABALIN

- **8.3 Females and Males of Reproductive Potential**
  - Infertility: Provides information on Males and effects on spermatogenesis
    - Summarizes randomized-controlled, non-inferiority trial assessing effects of pregabalin on sperm characteristics
    - **9% of pregabalin group (6/65) and 3% in placebo group (2/62) had ≥ 50% reduction in mean sperm concentrations from baseline at week 26**
    - Difference between pregabalin and placebo was within the pre-specified non-inferiority margin of 20%

Source: Pregabalin [product information]. 2018.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **TIOTROPIUM**

TIOTROPIUM

- **8.1 Pregnancy**
  - Risk Summary: States there is limited human data animal available but animal reproductive studies are published
    - **Studied in pregnant rats and rabbits showed no structural abnormalities were observed when tiotropium was administered during the period of organogenesis at maximum recommended human daily inhalation dose**
  - Data: Provides additional data regarding animal studies summarized in Risk Summary subsection
    - Includes data from two separate embryo-fetal developmental animal studies
    - Provides data on outcomes when given in higher doses in pregnant rats and rabbits

Source: Pregabalin [product information]. 2018.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **TIOTROPIUM**

TIOTROPIUM

- **8.2 Lactation**
  - Risk Summary:
    - **States there is NO data on the presence of tiotropium in human milk, the effects of the breastfed infant, or effects on milk production**
    - Provides a statement that clinical relevance is unclear due to species-specific differences in lactation physiology
  - Data:
    - Describes data from information summarized in Risk Summary subsection
    - Provides information on dose used in lactation animal study: **tiotropium bromide 10 mg/kg single intravenous dose to lactating rats showed tiotropium or its metabolites in milk at concentrations above those in plasma**

Source: Tiotropium [product information]. 2018.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **IBANDRONATE**

IBANDRONATE

- **8.1 Pregnancy**
  - Risk Summary: States there are **no** data with ibandronate studied in pregnant women
    - Provides information on reproductive toxicity studies in rats
    - **Ibandronate resulted in obstruction of labor, maternal periparturient mortality, and pup loss**
    - **Pregnant rats administered with ibandronate also gave birth to offspring that experienced kidney development toxicity from doses greater than 47x human exposure**
    - **Pregnant rabbits administered with ibandronate with doses 19x the human recommended dose resulted in maternal mortality and decreased fetal weight**
  - Data: Describes animal studies summarized in Risk Summary

Source: Ibandronate [product information]. 2016.

EXAMPLES OF CATEGORIES → ADDITIONAL DATA PROVIDED IN PLLR: **IBANDRONATE**

IBANDRONATE

- **8.2 Lactation**
  - Risk Summary: There is **no** information on presence of ibandronate in human milk, breastfed infant or milk production
    - Summarized animal studies that showed ibandronate in presence of rat milk
    - Clinical relevance unknown
  - Data:
    - Describes data from information summarized in Risk Summary subsection
    - Provides information on dose used in lactation animal study: **ibandronate 0.08 mg/kg administered in lactating rats resulted in presence of ibandronate in breast milk at 8.1 – 0.4 ng/mL concentrations from 2-24 hours after dose administration**

Source: Ibandronate [product information]. 2016.

SUMMARY OF EXAMPLES

- Pregabalin, tiotropium and ibandronate are all categorized as category C medications
  - All three medications clearly state there is no human data regarding studies in pregnant women
  - Pregabalin and ibandronate labeling contain descriptive animal studies with doses and corresponding structural deformities, pregnancy, lactation, and reproductive potential risk
  - Tiotropium labeling states no risk shown in animal studies

Source: Pregabalin [product information]. 2016.

ASSESSMENT QUESTION 5

The new Pregnancy and Lactation Labeling Rule now consists of:

A. Pregnancy, Labor & Delivery, Nursing Mothers
B. Pregnancy, Lactation, Labor & Delivery
C. Pregnancy, Lactation, Reproductive Potential
D. Pregnancy, Labor & Delivery, Reproductive Potential

QUESTION 5 RESPONSE

The new Pregnancy and Lactation Labeling Rule now consists of:

A. Pregnancy, Labor & Delivery, Nursing Mothers
B. Pregnancy, Lactation, Labor & Delivery
C. Pregnancy, Lactation, Reproductive Potential
D. Pregnancy, Labor & Delivery, Reproductive Potential

WHERE IS THE DATA COMING FROM?

	Strengths	Limitations
Retrospective cohort studies	Large sample size	Exposure misclassification-based on pharmacy dispensing – Outcome misclassification-based on diagnosis codes – Non-live birth outcomes not typically assessed
Case control studies	Large sample size Sufficient power to assess specific rare birth defects	Recall bias Chance findings
Pharmacovigilance data	May facilitate early signal detection	Unknown denominator Important information often missing Reporting bias

Source: U. S. Food and Drug Administration, 2018.

PHARMACISTS ROLE

- Various types of healthcare providers (HCPs) and patients will rely on pharmacists to provide information about risks of medications administered during pregnancy
- Studies have shown that 90 percent of pharmacists will directly refer their patients to their physician without providing patients proper information
  - Only 14 percent referred to the literature to dispense evidence-based information
- With a proper understanding of the current FDA labeling rule and access to the literature, pharmacists should be equipped to offer more to patients and HCPs

Source: Chamber C. 2019.

CONCLUSION

- The PLLR provides a more descriptive and structured approach to medication labeling to provide available data that can be utilized in complex risk/benefit discussions
- It will be clearly stated when data are not available
- With more information on available data, both human and animal, it will assist prescribers with critical decision-making when treating pregnant/lactating women instead of assessing pregnancy risk with oversimplified categories

REFERENCES

- U. S. Food and Drug Administration/Center for Drug Evaluation and Research. (2014). *Pregnant? Breastfeeding? Better Drug Information is Coming*. Washing, DC.
- Brucker MC, King TL. The 2015 US Food and Drug Administration Pregnancy and Lactation Labeling Rule. J Midwifery Women's Health. 2017;62(3):308-316.
- U. S. Food and Drug Administration/Center for Drug Evaluation and Research. (2016). *The Pregnancy and Lactation Labeling Rule (PLLR)*. Washing, DC: Dinitale, M.
- Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist. 2014;79(233):72063-103.
- Wood, W. FDA pregnancy categories: Help or hindrance? *Mental Health Clinician*. 2013;3(2):78-80.
- Pregabalin [product information]. Pfizer, Inc. New York, NY. May 2018.
- Tiotropium [product information]. Boehringer Ingelheim Pharmaceuticals Inc. Ridgefield, CT. Feb 2018.
- Ibandronate [product information]. Genentech, Inc. South San Francisco, CA. Dec 2016.
- U. S. Food and Drug Administration/Center for Drug Evaluation and Research. (2018). *Fulfilling the Intent of PLLR: Current Approaches and Challenges*. Washing, DC: Sahin, L.
- Chambers C, Namazy JA. Clinicians perspective of the new pregnancy and lactation labeling rule (PLLR): results from a FDA/AAAAI survey [abstract]. In: J Allergy Clin Immunol; 2019 Feb. Abstract nr 674.

THANK YOU!

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