

# Two Years In: Lessons Learned with the Pregnancy and Lactation Labeling Rule- Approaches to Human Data

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# Overview



- Introduction
- Review of Draft PLLR Guidance Regarding Human Data
- Current Approaches to Inclusion of Human Data in Labeling
- Conclusion

# Introduction



# The Information Gap



- Human data about medical product safety in pregnancy at the 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 to have accurate and up-to-date labeling recommendations which reflect the post-approval experience

# Human Data Sources for Pregnancy



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

# Draft PLLR Guidance regarding inclusion of Human Data in Subsection 8.1, Pregnancy



# 8.1 Pregnancy-Data, Human Data

- Must include the following elements:
  - Data source (e.g., controlled clinical trials, ongoing or completed pregnancy exposure registries, other epidemiological or surveillance studies, case series)
  - Number of subjects
  - Study duration
  - Exposure information (timing, duration, and dose of exposure)
- Limitations of the data, including potential confounders and biases, if known
- If available, data from the comparator or control group, and data confidence intervals and power calculations should also be included

From Draft PLLR Guidance 2014.



# 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

# Current Approach to the Inclusion of Human Data in Subsection 8.1



# Key Considerations



- Quantity of Data
  - none, limited, extensive
- Quality of Data
  - Relevant and detailed information available
  - Study design: case reports/series, observational studies
- Consistency/pattern of outcomes
- Impact
  - None
    - Risk Summary risk statement only
    - Do not report under Human Data
  - Triggers potential change in safety message
    - Report under Human Data

# No Data-No Impact



Often NMEs or New BLAs

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no available data on TRADENAME use in pregnant women to inform a drug-associated risk of adverse developmental outcomes.

# Some Data-No Impact



- Case reports only, with sparse details from clinical development program
- Moderate number of case reports with no patterns or consistency of outcomes
- NMEs or New BLAs, rare disease drugs, newly marketed drug

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Limited available data with TRADENAME use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.

# More Data - No Impact – No Consistency



- Data from large epidemiologic studies reporting no clear association of adverse outcomes with drug use; no consistency or pattern
- Does not necessarily establish or exclude absence of a risk
- Detailed description of every study is not the goal; however, a conclusion about the safety message from this data is most valuable
- This situation may only include simple statements in Risk Summary and Data. Any further description of data must be balanced and present meaningful information to the prescriber.

# Example 1



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

The limited data with TRADENAME and drug name use in pregnant women are not sufficient to inform a TRADENAME-associated or drugname-associated risk for major birth defects and miscarriage. Published studies with drugname use during pregnancy have not reported a clear association with drug name and major birth defect or miscarriage risk [see *Data*].

# Example 1 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

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



# Quality Data - Potential Impact- 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
- Report details under Human Data

# Example 2:

## Human Data Sources



- Two large retrospective cohort studies
  - One with no increase of congenital malformations
  - Second found association with congenital cardiac malformations
- One case-control study
  - Finding of isolated cleft palate
- Several smaller observational studies
  - No findings of adverse outcomes, but other limitations
  - Too small to detect anything but a major teratogenic effect

# Example 2



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Available data do not reliably inform the association of TRADENAME and adverse fetal outcomes. Published epidemiological studies on the association between drugname and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation *[see Data]*. ...

# Example 2 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### 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 drugname in pregnancy. Two large retrospective cohort studies of drugname use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of drugname or received drugname 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 drugname 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)]).

# Example 2 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

The second study examined 1970 women who received drugname prescription during pregnancy and reported no association between drugname 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.

# Example 2 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of drugname 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 drugname exposure *in utero* in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th 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 drugname exposure in early pregnancy can cause cleft palate.

# Quality Data – Clearly Identified Safety Finding

- Case reports/series with quality information to reasonably determine a risk; especially when a rare finding occurs at increased frequency with drug use
- Pregnancy registries or other quality epidemiologic studies report a specific increased risk
- Report details under Human Data

# Example 3

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

TRADENAME can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of TRADENAME 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.



# Example 3 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

In post-marketing reports, use of TRADENAME 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 TRADENAME either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after TRADENAME was stopped. In one case, TRADENAME therapy resumed after amniotic index improved, and oligohydramnios recurred.



# Pregnancy Exposure Registries

- May be required by FDA to collect more information on risk of adverse events in pregnancies exposed to specific drugs
- Usually designed to assess risk of any adverse pregnancy outcome

From Lockwood Taylor presentation, Teratology Society meeting, June 28, 2016

# Example 4



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Limited clinical data are available from the TRADENAME Pregnancy Registry. Excluding lost-to follow-up, data from the registry reports a rate of 5.6% for major birth defects with first trimester use of drug name in pregnant women with rheumatoid arthritis (RA), and a rate of 7.8% and 5.5% for major birth defects in the disease-matched and non-diseased comparison groups [see *Data*].

# Example 4 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

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

# Example 4 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

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#### Data

##### *Human Data*

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

# Regulation and Draft PLLR Guidance: Inclusion of Data in Subsection 8.2-Lactation



## 8.2 Lactation-Data



- When relevant human and/or animal lactation data are available, the Risk Summary must include a cross-reference to the Data portion of the **Lactation** subsection where the details of the data are presented (§ 201.57(c)(9)(ii)(A)).
- Data may come from a clinical lactation study(s) or from other sources (e.g., published literature, lactation databases).
- Applicants should evaluate the quality and quantity of data available with respect to what information warrants inclusion in labeling.

## 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



# 8.2 Lactation-Data



- Data - Include only when information are available
  - Description of clinical lactation study/data
  - Description of animal lactation study (only if there are no human data)
- Note: If considered meaningful for information on concentration in breast milk or adverse reactions in infants, information from case reports may be reflected briefly under the Risk Summary or Data headings

# Example 1



## 8 USE IN SPECIFIC POPULATIONS

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### 8.2 Lactation

#### Risk Summary

Limited data from case reports in the published literature describe the presence of drugname in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of drugname on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME, and any potential adverse effects on the breastfed child from TRADENAME, or from the underlying maternal condition.

# Example 2



## 8 USE IN SPECIFIC POPULATIONS

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### 8.2 Lactation

#### Risk Summary

Small amounts of drugname have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected drugname in breast milk at average steady state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of drugname from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose [see *Data*]. The study did not evaluate the effects of TRADENAME on milk production or the effects of TRADENAME on the breastfed infant...

# Example 2 (cont'd)



## 8 USE IN SPECIFIC POPULATIONS

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### 8.2 Lactation

...

#### Data

A pharmacokinetic study in ten lactating women, who were at least 12 weeks postpartum, evaluated the concentrations of drugname in plasma and breast milk. TRADENAME 150 mg oral capsule was given every 12 hours (300 mg daily dose) for a total of four doses. Drugname was detected in breast milk at average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of drugname from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose. The study did not evaluate the effects of TRADENAME on milk production. Infants did not receive breast milk obtained during the dosing period, therefore, the effects of TRADENAME on the breast fed infant were not evaluated.

# Conclusion



- The goal of PLLR is to accurately communicate known information about the risks with prescription drug use in pregnant and lactating women
- PLLR format improves presentation of currently available data, but does not help when there are poor quality or sparse data
- Determination of adequate data is based on clinical review
- It is important to have the applicant's input on the available data and rationale for updates to safety messaging in the labeling
- The FDA continues to think about how to include human data into labeling that is both accurate and meaningful to the prescriber

