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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

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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
- *Example*

<u>Risk Summary</u>

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

- *Example*

<u>Risk Summary</u>

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

Pregnancy 8.1

Risk Summary

The limited data with TRADENAME and drug name use in pregnant women are not sufficient to inform a TRADENAME -associated or drug name-use associated risk for major birth defects and miscarriage. Published studies with drug name 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)

Data

Human Data

Published data from post-marketing studies have not reported a clear association with drug name 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 drug-name-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

8.1 Pregnancy

Risk Summary

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

Example 2 (cont'd)

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

<u>Data</u>

Human Data (continued)

The second study examined 1970 women who received drug name prescription during pregnancy and reported no association between drug name 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)

<u>Data</u>

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 drug name 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 drug name 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 drug name 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

8.1 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)

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.

Example 3 (cont'd)

Data

Animal Data

In studies where drug name was administered to pregnant Cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), drug name crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of drug name in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

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

8.1 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)

<u>Data</u>

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 drug name 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 drug name-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)

<u>Data</u>

Human Data (continued)

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.

From Draft PLLR Guidance 2014

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

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of drug name in human milk at infant doses of 0.1% to 1% of the maternal serum level. There are no reports of adverse effects of drug name 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

8.2 Lactation

Risk Summary

Small amounts of drug name have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected drug name in breast milk at average steady state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of drug name 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)

Data

A pharmacokinetic study in ten lactating women, who were at least 12 weeks postpartum, evaluated the concentrations of drug name 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. Drug name was detected in breast milk at average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of drug name 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

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