Fulfilling the Intent of PLLR: Current Approaches and Challenges

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Objectives

- Data sources
- Challenges: How to get from data to labeling
- Examples

Where do the human data come from?

- Pregnant women are mostly excluded from drug development trials
- Data on safety in pregnancy are collected in the post marketing phase

Data Sources : Pregnancy Registries

- Pregnancy Registries
  - Prospective observational cohort study
  - Most common type of pregnancy study required by FDA
- Advantages
  - Prospective design, detailed patient level data
- Disadvantages
  - Small sample size
  - Selection bias

Data Sources : Retrospective Cohort Studies

- Retrospective cohort studies
  - Based on administrative claims or electronic health data
- Advantages
  - Large sample size
- Disadvantages
  - Exposure misclassification-based on pharmacy dispensing
  - Outcome misclassification-based on diagnosis codes
  - Non-live birth outcomes not typically assessed

Data Sources : Case control Studies

- Case control studies
  - Often conducted by surveillance networks
- Advantages
  - Large sample size; sufficient power to assess specific rare birth defects
- Disadvantages
  - Recall bias
  - Chance findings

Data Sources : Pharmacovigilance Data

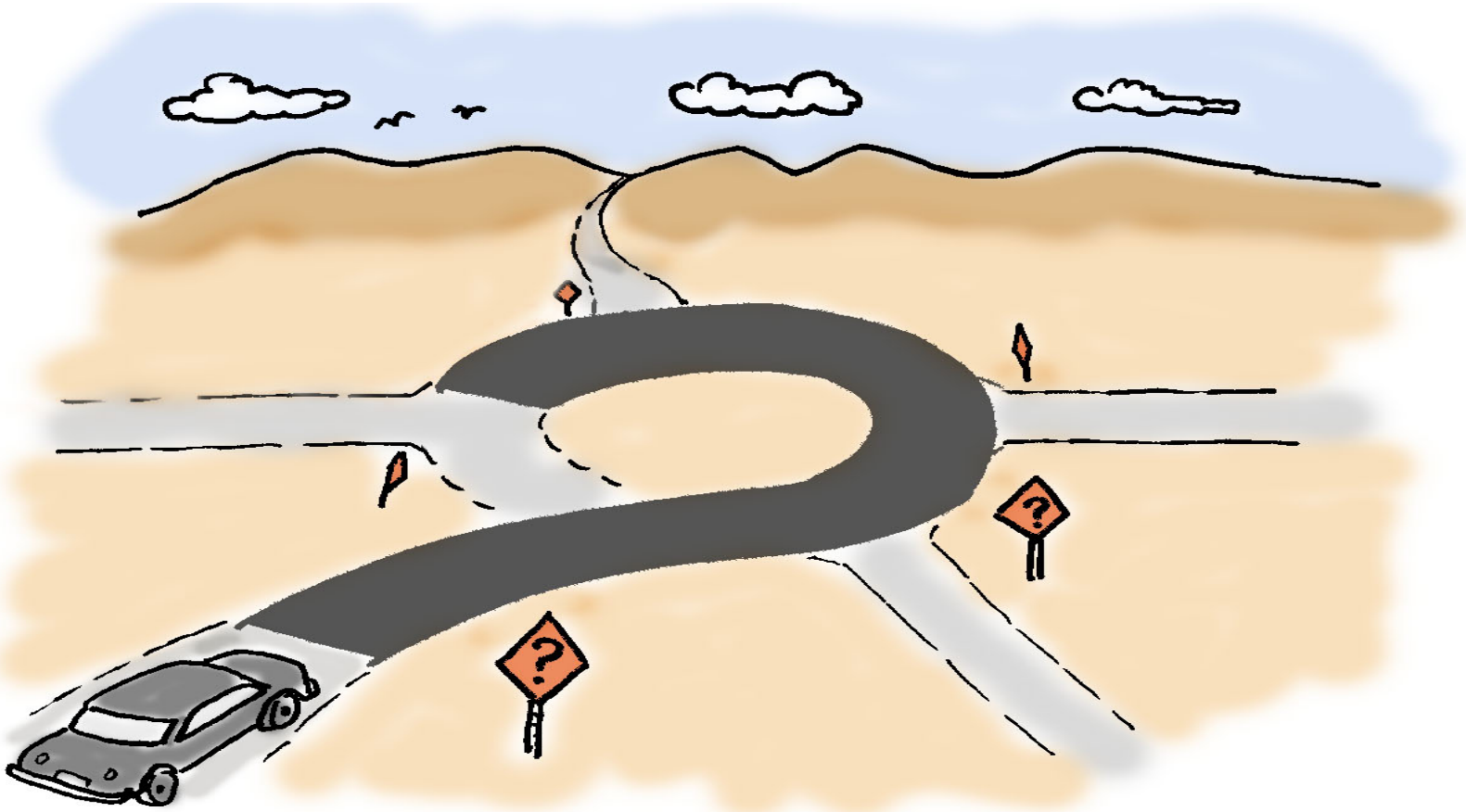
- Pharmacovigilance data
  - "Spontaneous" reports
- Advantages
  - May facilitate early signal detection
- Disadvantages
  - Unknown denominator
  - Important information often missing
  - Reporting bias

How Data Are Assessed

- Multi-disciplinary review that involves epidemiologists, medical officers, and statisticians
- Factors that affect the ability to draw conclusions
  - Quality of individual studies
  - Consistency of findings across studies, especially in studies that use different methodology/design
  - Sample size of studies; cumulative exposures
  - Power considerations
  - Comparators and assessment of confounding due to the underlying disease
  - Confounders/biases
  - Timing of exposure, dose information
  - Biological plausibility

Challenges with Interpreting the Data

- Limitations of individual studies
  - Methodologic issues: differences in exposed cohort vs. comparator cohort/adjustment for confounders
  - Small sample sizes; insufficient power to show a difference
  - Differences in outcomes assessed-difficult to make comparisons across studies
- Conflicting study results


THE INTERSECTION OF SCIENCE, REGULATIONS AND COMMUNICATION

Labeling Example 1 – Only Animal Data

Xenazine (tetrabenazine)-Page 18 of Backgrounder

Risk Summary

There are no adequate data on the developmental risk associated with the use of XENAZINE in pregnant women. Administration of tetrabenazine to rats throughout pregnancy and lactation resulted in an increase in stillbirths and postnatal offspring mortality. Administration of a major human metabolite of tetrabenazine to rats during pregnancy or during pregnancy and lactation produced adverse effects on the developing fetus and offspring (increased mortality, decreased growth, and neurobehavioral and reproductive impairment). The adverse developmental effects of tetrabenazine and a major human metabolite of tetrabenazine in rats occurred at clinically relevant doses *[see Data]*.

Labeling Example 1 –Xenazine (tetrabenazine)

Animal Data (excerpt)

Tetrabenazine had no clear effects on embryofetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m2 basis). Tetrabenazine had no effects on embryofetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m^2 basis).

When tetrabenazine (5, 15, and 30 mg/kg/day) was orally administered to pregnant rats from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. A no-effect dose for pre- and postnatal developmental toxicity in rats was not identified. The lowest dose tested (5 mg/kg/day) was less than the MRHD on a mg/m^2 basis.

Labeling Example 2-Inconsistent Study Findings

Zofran (ondansentron) 10-2016

- Two large retrospective cohort studies
  - One with no increase in 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

Labeling Example 2-Inconsistent Study Findings

Zofran (ondansentron)-Page 22 of Backgrounder

Risk Summary

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

Labeling Example 2-Zofran

Human Data

Methodological limitations of the epidemiology studies *preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.* Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron 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 ondansetron 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)]).

Labeling Example 2-Zofran

Human Data (continued)

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

Labeling Example 2-Zofran

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 ondansetron 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 ondansetron 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 ondansetron exposure in early pregnancy can cause cleft palate.

Labeling Example 3-Lack of a Consistent Safety Finding

Enbrel (etanercept) 11-2017

- Data from a pregnancy registry and a retrospective cohort study showed a higher birth defect rate compared to unexposed women with the disease, but no pattern of birth defects

Labeling Example 3-Lack of a Consistent Safety Finding-Enbrel (etanercept) Page 24 of Backgrounder

Risk Summary

Available studies with use of etanercept during pregnancy *do not reliably support an association between etanercept and major birth defects*. Clinical data are available from the Organization of Teratology Information Specialists (OTIS) Enbrel Pregnancy Registry in women with rheumatic diseases or psoriasis and a Scandinavian study in pregnant women with chronic inflammatory disease. Both the OTIS Registry and the Scandinavian study showed the proportion of liveborn infants with major birth defects was higher for women exposed to etanercept compared to diseased etanercept unexposed women. However, the lack of pattern of major birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects (*see Data).*

Labeling Example 3-Lack of a Consistent Safety Finding-Enbrel

Data

Human Data

A prospective cohort pregnancy registry conducted by OTIS in the US and Canada between 2000 and 2012 compared the risk of major birth defects in liveborn infants of women with rheumatic diseases or psoriasis exposed to etanercept in the first trimester. *The proportion of major birth defects among liveborn infants in the etanercept-exposed (N = 319) and diseased etanercept unexposed cohorts (N = 144) was 9.4% and 3.5%, respectively*. The findings showed no statistically significant increased risk of minor birth defects and no pattern of major or minor birth defects.

Labeling Example 3-Lack of a Consistent Safety Finding-Enbrel

Data

Human Data (continued)

A Scandinavian study compared the risk of major birth defects in liveborn infants of women with chronic inflammatory disease (CID) exposed to TNF-inhibitors during early pregnancy. Women were identified from the Danish (2004-2012) and Swedish (2006-2012) population based health registers. *The proportion of major birth defects among liveborn infants in the etanercept-exposed (N=344) and CID etanercept unexposed cohorts (N = 21,549) was 7.0% and 4.7%, respectively.*

Overall, while both the OTIS Registry and Scandinavian study show a higher proportion of major birth defects in etanercept-exposed patients compared to diseased etanercept unexposed patients, the lack of pattern of birth defects is reassuring and differences between exposure groups (e.g. disease severity) may have impacted the occurrence of birth defects.

Goal of Labeling

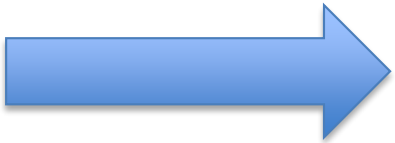
- Provide information in a clear and concise manner to facilitate prescribing decisions
- Balanced messaging
  - In the context of the background risk
  - In the context of treatment benefit
  - Public health impact

Concern for potential unintended consequences

- Confusing message
- Incorrect message
  - If risk perception is worse than actuality,

    unnecessary discontinuation or switching of treatment, pregnancy termination
  - If risk perception is better than actuality,

    false reassurance

Challenges

- The data in many cases are absent
- The quantity of data are often limited
- The data often have limitations
- Data to support definitive risk statements are usually lacking
- Risk statements that are “less than definitive” are difficult to communicate

Summary

- Clear and balanced messaging is the goal
- Messaging needs to balance risk with benefit
- Messaging is challenging in the presence of imperfect data.

Questions