Incorporating Human Data

Christina Bucci-Rechtweg, MD

Global Head, Pediatric & Maternal Health Policy, Novartis Pharmaceuticals

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The old USPI pregnancy classification system

- Failed to advise prescribers and patients of the potential harm from with-holding a medication in pregnancy
- Inaccurately thought of as a grading system where risk increased from lowest (Category A) to highest (Category X)
- Led to incorrect assumptions that drugs in a particular category carry a similar risk
  - Most approved drugs are old Category C
  - Includes drugs with adverse animal data or no animal data at all (significance of adverse animal data may vary)

The Pregnancy, Lactation & Labeling Rule (PLLR) better addresses how to communicate important information

Photo credit: http://www.sheknows.com/pregnancy-and-baby/day/271

- **Pregnant women and females of reproductive potential**

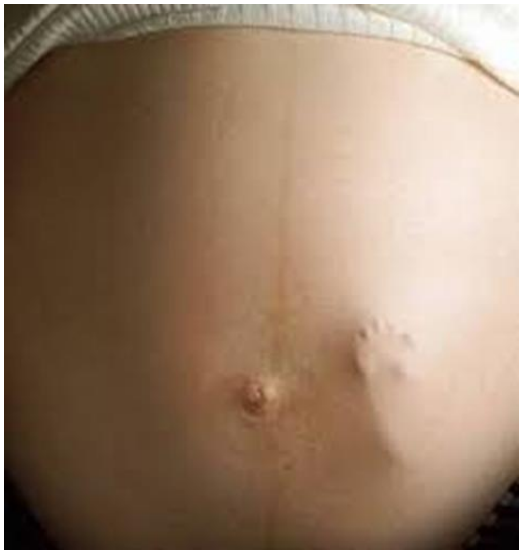

Photo credit: www.Wildbox.com

- **Developing fetuses and nursing infants**

Photo credit: www.bryanterril.com

- **Men with female partners of reproductive potential**

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PLLR Draft Guidance Regarding Human Data

- *IV. Specific Subsections*

  A. 8.1 Pregnancy

  a. Risk statement based on human data

  4. Data (a. Human data)

- "... describes the **data supporting any risk statement(s)** in the Risk Summary and the information under Clinical Considerations that is based on human data."

4. Data

Under the subheading Data, labeling must describe the data that provide the scientific basis for the information presented in the Risk Summary and Clinical Considerations (§ 201.57(c)(9)(i)(D)(1)). This subheading is required, as are the headings Human Data and Animal Data, to the extent information is available. Human data and animal data must be presented separately, and human data must be presented first (§ 201.57(c)(9)(i)(D)(2)).

a. Human data

This portion of labeling describes the data supporting any risk statement(s) in the Risk Summary and the information under Clinical Considerations that is based on human data. Both positive and negative study findings must be included (§ 201.57(c)(9)(i)(D)(3)). Applicants must update labeling as new data become available (§ 201.56(a)(2)). Applicants should evaluate the quality and quantity of data available with respect to what information warrants inclusion in labeling.[18] This portion of labeling must describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, and 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

[18] See FDA's reviewer guidance, *Evaluating the Risks of Drug Exposure in Human Pregnancies*.

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Contains Nonbinding Recommendations

Draft — Not for Implementation

- Study duration
- Exposure information (timing, duration, and dose of exposure)
- Limitations of the data, including potential confounders and biases, if known

Individual case reports are rarely sufficient to characterize risk and therefore ordinarily should not be included in this section.

If available, data from the comparator or control group, and data confidence intervals and power calculations should also be included.

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PLLR Draft Guidance: "...(human) data supporting any risk statement(s)..."

- ✓ Include Positive & Negative findings (if absent human data – no heading required)
- ✓ Update label as new data become available
- ✓ Evaluate both quality and quantity of data for inclusion in label
- ✓ Describe adverse developmental outcomes, adverse reactions, other adverse effects, including:
  - ❑ Data source (RCT, pregnancy exposure registry, epidemiologic or surveillance studies, case series)
  - ❑ Number of subjects
  - ❑ Study duration
  - ❑ Exposure information (timing, duration, and exposure dose)
  - ❑ Data limitations (biases & potential confounders)
- ✓ Include data from comparator/control, data CIs & power calculations

What is the hierarchy of evidence to support inclusion in Human Data subsection?

- Systematic reviews and meta-analyses
- Randomized control trials (RCTs) with definitive results
  - ✓ CIs do not overlap, clinically significant threshold effects
- RCTs without definitive results
  - ✓ point estimates suggest clinically significant effect, CIs overlap
- Cohort studies
- Case-control studies
- Survey based research (questionnaires, polls)
- Case series (*rarely sufficient to characterize risk*)
- Patient Registries

Meta-analyses

- Designed to evaluate a safety endpoint by statistical analysis of data from completed studies or clinical trials
- By combining studies, a meta-analysis increases the sample size and power to study effects of interest
- These studies should use:
  1. Prospectively designed study protocols and analysis plans
  2. Comprehensive selection of relevant studies or clinical trials
  3. Appropriate statistical methodology

Advantages

- ✓ Greater statistical power
- ✓ Confirmatory data analysis
- ✓ Greater ability to extrapolate to general population affected
- ✓ Considered an evidence-based resource

Disadvantages

- ✓ Difficult and time consuming to identify appropriate studies
- ✓ Not all studies provide adequate data for inclusion and analysis
- ✓ Requires advanced statistical techniques
- ✓ Heterogeneity of study populations

Observational pharmacoepidemiologic studies

- Pharmacoepidemiology applies the methods of epidemiology to assess the effects of drugs on large populations of pregnant women
- Generally designed to:
  - Assess a serious risk associated with a drug exposure, or,
  - Quantify risk, or,
  - Evaluate factors that affect the risk of serious toxicity (e.g., drug dose, timing of exposure, patient characteristics)
- Ideally, should always:
  - ✓ Have a protocol
  - ✓ Test pre-specified hypothesis
  - ✓ Include a control group
- Provide a 'real-world' perspective on potential beneficial and adverse effects of medication treatment

Sponsorship of observational pharmacoepidemiologic studies

- Data sources include
  - ✓ Administrative healthcare claims data
  - ✓ Electronic Medical Records (EMR)
  - ✓ Registries
  - ✓ Prospectively collected observational data
  - ✓ Other sources of observational information

- To successfully develop and execute studies, industry must collaborate with key stakeholders

- Sponsorship of hypothesis, analytical review, and resource should be a collaborative effort of:
  1. Investigators
  2. Advocacy/patient groups
  3. Governmental agencies
  4. Academic groups
  5. Professional societies
  6. Industry

Comparative cohort studies

- One or more samples (cohorts) are followed prospectively
- Subsequent assessments of the condition or disease are conducted to determine exposure characteristics (risk factors) for study participants'

Advantages

- ✓ Easier and cheaper than a randomized controlled trial
- ✓ Subjects in cohorts can be matched (limits confounding)
- ✓ Standardization of criteria/outcome is possible

Disadvantages

- ✓ Outcome of interest could take time to occur
- ✓ Cohorts can be difficult to identify due to confounding variables
- ✓ No randomization
- ✓ Blinding is difficult

Case-control studies

- Compares patients who have a disease or outcome of interest (cases) with patients who do not have the disease or outcome (controls)
- Looks retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease
- Designed to estimate odds

Advantages

- ✓ Good for studying rare conditions
- ✓ Less time needed to conduct the study because the condition has already occurred
- ✓ Allows for a simultaneous look at multiple risk factors
- ✓ Useful as initial studies to establish an association

Disadvantages

- ✓ Retrospective studies have problems with data quality because they rely on memory (recall bias)
- ✓ It can be difficult to find a suitable control group

Case series

- A report that describes and interprets an individual case(s), often written in the form of a detailed story
- First line of evidence because they are where new issues and ideas emerge
- If multiple case reports show something similar, the next step might be a case-control study to determine if there is a relationship between the relevant variables

Advantages

- ✓ May help in the identification of new trends or diseases or to detect new drug side effects and potential uses
- ✓ Identifies rare manifestations of a disease

Disadvantages

- ✓ Cases may not be generalizable
- ✓ Typically not based on systematic studies
- ✓ Causes or associations may have other explanations
- ✓ May contain misleading elements

Patient Registries (1)

- Come in several forms - can parallel many different study designs
- An observational study method on the *continuum from passive to active surveillance*
- Optimally, conducted with the rigor of a cohort study, including:
  - Recruitment, comparison group(s), exposure/outcome ascertainment, individual patient follow-up
- Drug-specific pregnancy exposure registries (PERs) the most common type of post-approval commitment study in pregnant women

❖ Advantages

✓ Provide real-world data related to safety, effectiveness and drug use patterns

❖ Disadvantages

✓ Often fail to provide useful information due to low enrollment, retrospective data acquisition, low prevalence of disease in pregnant women, awareness of PERs by HCPs and/or patients

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Patient registries (2)

Drug-focused vs. disease-focused

Drug-focused

Advantages

- ✓ Focused study population
- ✓ Cost / budget efficient
- ✓ Often clear safety objectives, defined stopping rules
- ✓ Often short timeline to meet Health Authority request, quicker to start than disease registry
- ✓ Voluntary participation may offer flexibility

Disadvantages

- ✓ Less generalizability – narrower study population, fragmented picture of entire disease spectrum
- ✓ Less scientific interest by academia/patients– could limit recruitment and/or bias selection
- ✓ No comparator treatment group
- ✓ Voluntary participation may present selection bias

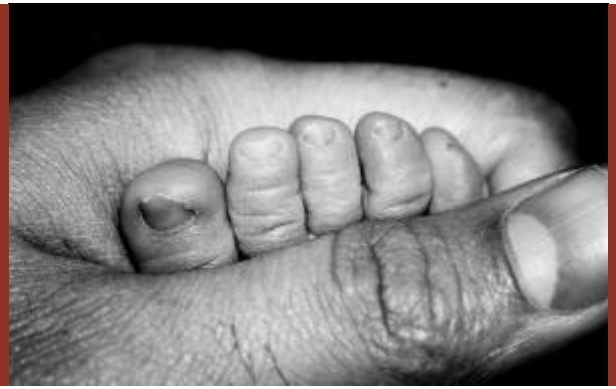
Disease-focused

Advantages

- ✓ Broad study population – enhances generalizability
- ✓ Often scientific objectives beyond safety
- ✓ Broad stakeholders (including academic interest)
- ✓ Quicker recruitment (Voluntary, larger pool)
- ✓ Real-world (e.g. LT outcomes)
- ✓ Rare disease population when little is known or published - creates datasets for LT future use
- ✓ May offer comparator treatment groups

Disadvantages

- ✓ Small patient populations may require many centers, many countries – all with different requirements and logistics
- ✓ May be more costly if larger in scope
- ✓ For small patient populations and stopping rules, statistical precision around an estimate may not be realistic
- ✓ Recruitment bias if multiple PERs competing for same sites/patients



Final Thoughts

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"Prediction is very difficult, especially if it's about the future."

Niels Bohr

Nobel laureate in Physics, 1922

Credit: *Nobelprize.org*

- “Prescribing in pregnancy can be challenging for providers facing insufficient information about drug safety, overestimation of the risk of medications by both the patient and the care provider, and increasing litigation costs.”[1]

- Pregnant women face the difficult choice between taking untested drugs or foregoing necessary treatment during pregnancy

[1] Mehta N, Chen K, Powrie R. Prescribing for the pregnant patient. Cleveland Clinic Jn of Med (2014). 81 (6). 367-372.

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Considering the pregnant patient during the design of a clinical development program

- *Primum non nocere* (First, do no harm)
  - Treating the pregnant mother is often best for the developing fetus
  - Are we using science to inform 'the' default research position to exclude pregnant women from clinical research?
- Protecting pregnant women and females of reproductive potential through research
  - Ethico-legal challenges
  - Requires thoughtful clinical trial methodologies
- Physiologic changes of pregnancy affect the pharmacokinetics of medications
  - Opportunity for application of pharmacometric approaches?

Will the Final Rule address the issues?

- It has laid the groundwork for more informed communication regarding important information when pregnancy is a consideration between
  - ✓ Companies and prescribers
  - ✓ Prescribers and their patients

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Thank You!

Christina Bucci-Rechtweg

Global Head, Pediatric & Maternal Health Policy

Novartis Pharmaceuticals

Christina.buccirechtweg@novartis.com

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