Generating Meaningful Information for Use in Pregnant Women During Program Development

Christina Bucci-Rechtweg, MD
Global Head, Pediatric & Maternal Health Policy
Novartis Pharmaceuticals
ASCPT – Session 21/Sub-session 342
11 Mar 2016

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

- The views and opinions expressed in the following PowerPoint slides are those of Christina Bucci-Rechtweg and should not be attributed to Novartis Pharmaceuticals nor the American Society for Clinical Pharmacology and Therapeutics (ASCPT), its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.

- These PowerPoint slides are the intellectual property of Christina Bucci-Rechtweg and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved.

- All trademarks are the property of their respective owners.
In drug regulatory science, who “is” a pregnant woman?

- Pregnant women are **not** a separate and distinct population, except, when a drug treats a condition unique to pregnancy.

- Pregnant women are a dynamic subset of the adult and adolescent female population who use drugs and biologics.

- It should be **routine** to consider whether, when, and how to study pregnant women in the drug development process.
The Current Imbalance

- Most medicines are not indicated for use in pregnancy\(^1\)
- 90% of pregnant women use on average 3 or 4 medicines during pregnancy\(^2\)

Historical Triggers

- **Diethylstilbestrol (DES)**
  - Highlighted need for strong independent regulatory authority

- **Thalidomide**
  - (1962) Kefauver-Harris Drug Amendments Act requiring manufacturers to prove medicines are both safe and effective for consumption
Consequences

- Risk of harm & for liability in the post-DES/thalidomide era
  1. Exclusion of pregnant women from clinical trials
  2. Study participants who become pregnant while on study dropped from trial per-protocol
  3. Pregnancy treated as (S)AE

- Which has led to:
  - General lack of research
  - Insufficient data capture to inform on safe and effective use even when known pregnancies occur
“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.”

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

We are failing patients and providers.

- UTI, Pyelonephritis, Bladder infection
- Malignancies
- Group B strep infection
- Iron deficiency
- Rheumatoid arthritis
- DVT
- Pre-eclampsia
- Diabetes – Type I or II
- Depression, Schizophrenia
- Asthma
- Epilepsy, seizure disorders
- Hypertension
- HIV
- Migraine
- Sexually transmitted diseases
- Thyroid disease
- Migraine headaches
- Bacterial vaginosis
- Cytomegalovirus, Toxoplasmosis
### Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry

**DRAFT GUIDANCE**

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Drug Evaluation and Research (HFA-305), Food and Drug Administration, 5600 Fishers Lane, rm. 1051, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes the *Federal Register*.

For questions regarding this draft document contact Rosemary Addy (CBER), at 301-796-2200, or Office of Communication, Outreach and Development (CBER) at 240-402-7800.

---

**Pregnancy, Lactation, and Reproductive Potential**

**Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry**

**Pregnancy**

The final rule requires that the labeling include certain information about drug use during pregnancy. This information includes:

1. The results of any studies performed to determine the safety and efficacy of the drug during pregnancy.
2. The presence or absence of information in the drug's package inserts regarding its known or potential effects on pregnancy.
3. The known or potential effects of the drug on pregnancy and fetal development.
4. Whether the drug should be used during pregnancy.
5. The risks and benefits of using the drug during pregnancy compared to the potential benefits of not using the drug.
6. The potential consequences of discontinuing therapy during pregnancy.
7. The need for closely monitoring the fetus during pregnancy.
8. The need for close monitoring during delivery and postpartum follow-up.

**Lactation**

The final rule requires that the labeling include certain information about drug use during lactation. This information includes:

1. The results of any studies performed to determine the safety and efficacy of the drug during lactation.
2. The presence or absence of information in the drug's package inserts regarding its known or potential effects on lactation.
3. The known or potential effects of the drug on lactation.
4. Whether the drug should be used during lactation.
5. The risks and benefits of using the drug during lactation compared to the potential benefits of not using the drug.
6. The potential consequences of discontinuing therapy during lactation.
7. The need for closely monitoring the mother during lactation.
8. The need for close monitoring during delivery and postpartum follow-up.

**Reproductive Potential**

The final rule requires that the labeling include certain information about drug use during reproduction. This information includes:

1. The results of any studies performed to determine the safety and efficacy of the drug during reproduction.
2. The presence or absence of information in the drug's package inserts regarding its known or potential effects on reproduction.
3. The known or potential effects of the drug on reproduction.
4. Whether the drug should be used during reproduction.
5. The risks and benefits of using the drug during reproduction compared to the potential benefits of not using the drug.
6. The potential consequences of discontinuing therapy during reproduction.
7. The need for closely monitoring the patient during reproduction.
8. The need for close monitoring during delivery and postpartum follow-up.

**Content and Format**

The final rule requires that the labeling include certain information in a specific format. This information includes:

1. A statement of the potential risks and benefits of using the drug during pregnancy, lactation, and reproduction.
2. A statement of the potential risks and benefits of using the drug during pregnancy.
3. A statement of the potential risks and benefits of using the drug during lactation.
4. A statement of the potential risks and benefits of using the drug during reproduction.

**Guidance for Industry**

This guidance document is being distributed for comment purposes only.
The new PLLR is intended to

- Prominent listing of contact information for pregnancy exposure registries for the drug

- Narrative presentation of information related to use of a drug during pregnancy including a Risk Summary, clinical considerations for use, and the supporting data

- A lactation subsection that provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant

- A subsection on females and males of reproductive potential with information about the need for pregnancy testing, contraception, and information about infertility as it relates to the drug
In order to generate meaningful information for use in pregnant women during a clinical development program (pre-market) ...

**Plan ahead** using one of two potential scenarios:

1. Design clinical trials that prospectively plan to enroll pregnant women for whom the study drug offers potential direct benefit

2. Female trial participants who become pregnant while in the study
Is it ethical to enroll pregnant women in clinical trials?

- Pregnant women with a medical condition requiring treatment may be involved in clinical trials in the pre-market drug development setting if:
  - **Access to drug holds the prospect of direct benefit to the pregnant woman that is not otherwise available to her**
    - Pregnant women have not clinically responded to other available therapies
    - Alternative therapies are not safe in pregnant women or developing fetuses
  - **The risk to the fetus is not greater than minimal and important knowledge is required** (which cannot be obtained by other means)
  - The intended indication is expected to **address a therapeutic condition associated with pregnancy**
Program considerations

Clinical drug development (PoC to Phase III)

- Are effective alternative therapies with better documented developmental toxicity profiles available? Within class? across the classes?
- Does an established safety database exist in non-pregnant WOCBP?
- Are nonclinical developmental and reproductive toxicity studies complete and adequate? Are there positive findings of developmental toxicity in animals?
- What are the risk/benefit considerations for mother and fetus with regard to the drug and the condition it is intended to treat?
Subpopulation differences

Pregnant women vs. non-pregnant women

- Drug dose (and safety) cannot be entirely extrapolated from non-pregnant women to pregnant women

- The pregnant state can have an effect on pharmacology
  - Changes in total body weight and body fat composition
  - Expansion of plasma volume
  - Increase cardiac output
  - Changes in regional blood flow
  - Increase in GFR
  - Altered GI motility
  - Decrease in Albumin
  - Changes in hepatic enzyme activity and drug metabolism by CYP450 system
When to conduct a pharmacokinetic (PK) study in pregnant women

✓ The drug is anticipated to be used in pregnant women and females of reproductive potential

✓ Use is expected to be rare, but the consequences of under- or over-dosing are great (e.g., narrow therapeutic range drugs, cancer chemotherapeutics)

✓ Drugs that are:
  • Primarily cleared via the kidney
  • Known substrates of CYP450 isoenzymes
  • Undergoes phase 2 metabolic pathways (e.g., N-acetyltransferase and glucoronidation)
Considerations for collecting PK data in pregnant women

- Pregnant healthy volunteers should **not** be used to obtain PK data
  - Maternal and fetal exposure to the drug **does not hold the prospect of direct benefit to either mother or fetus** but does confer unnecessary research-related risks

- Two ethically appropriate ways to collect PK data in pregnant women
  - Identify pregnant women using the drug therapeutically and obtain serum levels of drug (post-market)
  - Collect blood samples for PK assessments from pregnant women taking a drug for therapy or prophylaxis in a clinical trial or observational cohort study setting

  - Using these approaches, the **drug holds the prospect of direct benefit to the mother and/or the fetus**
Considerations for confirmatory trial designs

Prospective planning to include pregnant women

- Placebo control or active control with established therapy?
  - What is the known/unknown developmental and reproductive toxicity of the active control?

- Are there/can there be planned PK assessments early in the study to ensure adequate systemic exposure to achieve efficacy (e.g., nested PK study in Phase 3 clinical trial)?

- Pre-identified efficacy outcomes and safety endpoints that are specific to the pregnant condition and/or fetal outcomes?
Women who become pregnant while enrolled in clinical trials

- Drug development research protocols typically require “discontinuation from study”

- Raises its own host of ethical challenges

- Consider when a woman who becomes pregnant while enrolled in a clinical trial can/should be allowed to continue on study drug?

- If the potential benefits of continued treatment outweigh
  - The potential risks of ongoing fetal exposure to study drug
  - The risks of discontinuing maternal therapy, and/or risks of exposing the fetus to additional drugs if the mother is placed on an alternative therapy
Considerations for the informed consent process in females of reproductive potential

- **Consented and randomized non-pregnant females**
  - Contraceptive counseling based on known/unknown risks to developing fetus
  - Potential embryo-fetal toxicity counseling

- **Consented and randomized females who become pregnant while on study drug**
  - Re-consent as pregnant study subject
  - Discuss
    - Alternative treatment options & comparative therapeutic risk : benefit
    - Risk of fetal exposure (continued fetal exposure) to study drug vs. risk of fetal exposure to the study drug and the new alternative therapy
    - Risk of untreated maternal disease
  - Referral pathway for pregnancy counseling & management
Additional protocol considerations

- Collect clinical efficacy data, don’t restrict focus to safety
- Collect clinical pharmacology data, don’t restrict focus to safety data
- When collecting data, ensure data collection mechanisms capture maternal, fetal, and neonatal outcomes of interest including (but not limited to)
  - Gestational timing and duration of drug exposure
  - Collection of ultrasound reports and results of other prenatal testing
  - Records of maternal complications
  - Pregnancy outcomes
    - Gestational age at delivery
    - Delivery complications
    - Condition of the neonate and complications in the neonatal period
Next Steps

DIA Expert Panel convened in Fall 2013 to discuss ‘Clinical Data for Informed Medication Use in Pregnancy’

### Table 3. Data generation and collection workstream objectives.

<table>
<thead>
<tr>
<th>Develop Standards</th>
<th>Compile Existing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Define core research parameters that are harmonized; establish standards and related protocols for data collection (include women, fetus, infant)</td>
<td>- Map out data already available, noting strengths and limitations</td>
</tr>
<tr>
<td>- Define what acceptable level of evidence is needed to allow for approval of using a drug in pregnancy</td>
<td>- Create comprehensive directory of ongoing efforts, and identify opportunities for collaboration</td>
</tr>
<tr>
<td>- Define what constitutes a well-documented case of pregnancy and pregnancy outcome; define constructs for follow-up of patient and offspring</td>
<td>- Gather, combine, and analyze existing data to build benefit-risk assessments and identify gaps</td>
</tr>
<tr>
<td>- Establish guidelines for data capture in the preconception, conception, and postconception periods, including pharmacokinetics/pharmacodynamics, safety, clinical outcome, and pregnancy outcome data (standardize data collection)</td>
<td>- Engage existing registry owners to combine efforts; develop platform to make this work effectively</td>
</tr>
<tr>
<td>- Standardize data assessment methods and harmonize around accepted statistical concepts; include how to capture more subtle effects on development</td>
<td>- Compile existing guidance (eg, regulatory, professional association, advocacy)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Develop Data Capture Tools</th>
<th>Capture New Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Identify and create data capture and analysis tools for inclusion of existing and new data across data types with a focus on patient and provider usability</td>
<td>- Develop a central public database, and pool data (existing and new) across companies and organizations</td>
</tr>
<tr>
<td>- Develop prospective data tools that utilize health care social application technologies</td>
<td>- Collect and address data for subpopulations (eg, age, disease, race); engage patients and collect pharmacokinetic and effect-of-pregnancy data</td>
</tr>
<tr>
<td>- Investigate alternative data collection collaborations</td>
<td>- As appropriate, include pregnant women in random controlled trials</td>
</tr>
<tr>
<td>- Apply continuous health care learning system concepts</td>
<td>- Collect self-reported data from pregnant mothers</td>
</tr>
</tbody>
</table>

Closing Thoughts

- 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

Source: www.Wildbox.com
Thank You

Christina Bucci-Rechtweg
Global Head, Pediatric & Maternal Health Policy
Novartis Pharmaceuticals

Christina.buccirechtweg@novartis.com