Generating Meaningful Information for Use in Pregnant Women During Program Development

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

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In drug regulatory science, who “is” a pregnant women?

- 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]

Photo credit: www.babycentre.co.uk

[1] Sachdeva P, Patel BG, Patel BK. Drug use in pregnancy: a point to ponder! Indian J Pharm Sci. 2009;71:1-7.; [2] Dewulf L. Medicines in pregnancy: women and children first? Therapeutic Innovation & Regulatory Science. 2013;47:528-532.

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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

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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

Where Are we Today?

- "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
- We are failing patients and providers

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

- 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

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Dec 2014 Publication of the PLLR/'Final Rule'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. FDA–2006–N–0515 (formerly Docket No. 2006N–0467)]

RIN 0910–AF11

Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling. For human prescription drug and biological products subject to the Agency's 2006 Physician Labeling Rule, the final rule requires that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. The final rule eliminates the "Labor and delivery" subsection because information about labor and delivery is included in the "Pregnancy" subsection. The final rule requires that the labeling include relevant information about pregnancy testing, contraception, and infertility for health care providers prescribing for females and males of reproductive potential. The final rule creates a consistent format for providing information about the risks and benefits of prescription drug and/or biological product use during pregnancy and lactation and by females and males of reproductive potential. These revisions will facilitate prescriber counseling for these populations.

DATES: This rule is effective June 30, 2015. See section IV of this document for the implementation dates of this final rule.

FOR FURTHER INFORMATION CONTACT: Kathy Schreier, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6246, Silver Spring, MD 20993–0002, 301–796–3432; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911.

SUPPLEMENTARY INFORMATION:

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Executive Summary

Purpose of the Regulatory Action

FDA is amending its regulations governing the content and format of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section (under § 201.57 (21 CFR 201.57)) and the "Precautions" section (under § 201.80 (21 CFR 201.80)) of the labeling for human prescription drug and biological products (both referred to as "drugs" or "drug products" in this final rule). In this rulemaking, the Agency is finalizing many of the provisions in the proposed rule issued on May 29, 2008 (73 FR 30831).

This rulemaking is part of a broad effort by the Agency to improve the content and format of prescription drug labeling. The final rule creates a consistent format for providing information about the risks and benefits of drug use during pregnancy and lactation and by females and males of reproductive potential. FDA's revisions to the content and format requirements for prescription drug and biological product labeling are authorized by the Federal Food, Drug, and Cosmetic Act (the FD&C Act) and by the Public Health Service Act (PHS Act).

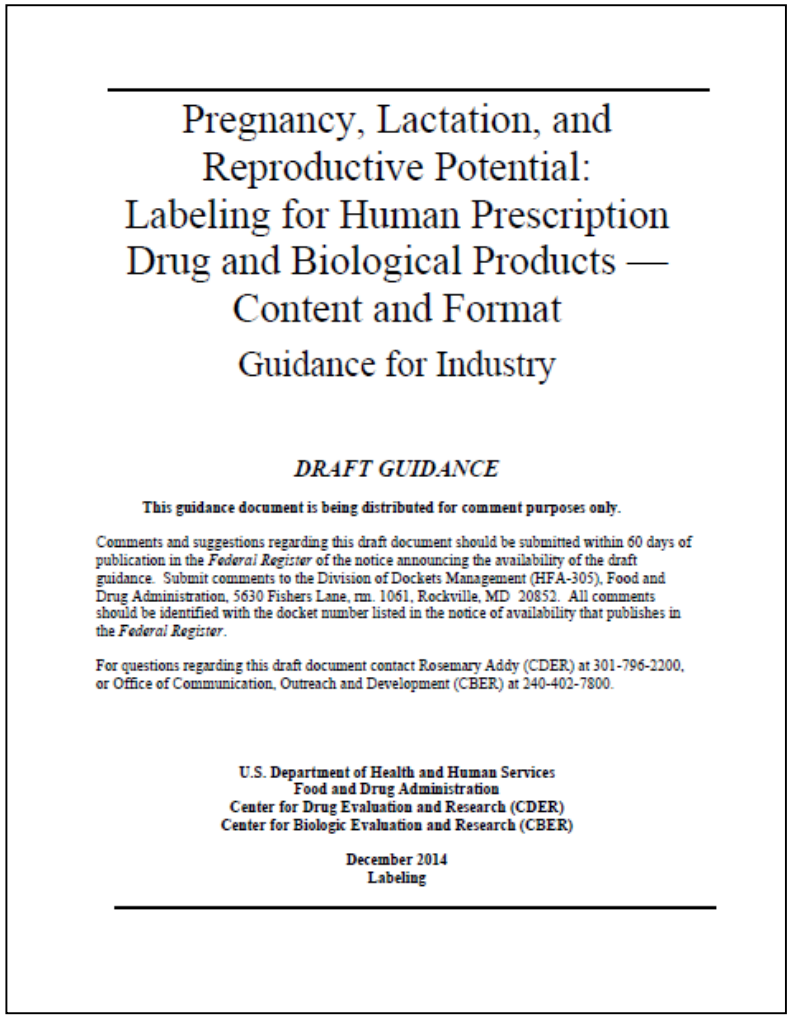
Summary of the Major Provisions of the Regulatory Action in Question

The final rule requires that for the labeling of certain drug products (as described in the "Implementation" section of this document), the subsections "Pregnancy," "Nursing mothers," and "Labor and delivery" be replaced by three subsections entitled "Pregnancy," "Lactation," and "Females and Males of Reproductive Potential." The final rule also requires the removal of the pregnancy categories A, B, C, D, and X from all drug product labeling.

"Pregnancy"

The final rule merges the current "Pregnancy" and "Labor and delivery" subsections into a single "Pregnancy" subsection of labeling. If there is a scientifically acceptable pregnancy exposure registry for the drug, the "Pregnancy" subsection must contain a specified statement about the existence of the registry, followed by contact information needed to enroll or to obtain information about the registry. The Agency has concluded that including information about pregnancy exposure registries in prescription drug labeling will encourage participation in registries, thereby improving data collection in pregnant women. Under "Pregnancy," the final rule also requires that the labeling include a summary of the risks of using a drug during pregnancy. If data demonstrate that a drug is not absorbed systemically, the "Risk Summary" must contain only a specified statement regarding this fact. If data demonstrate that the drug is absorbed systemically, the "Risk Summary" must include risk statements based on data from all relevant sources (human, animal, and/or pharmacologic), that describe, for the drug, the risk of adverse developmental outcomes.

The labeling must also contain relevant information, if it is available, to help health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy; this could include information on disease-associated maternal and/or embryo/fetal risk, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal/neonatal adverse reactions, and/or the effect of the drug on labor or delivery. FDA believes that including such information supports



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 Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologic Evaluation and Research (CBER)

December 2014
Labeling

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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

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- 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:

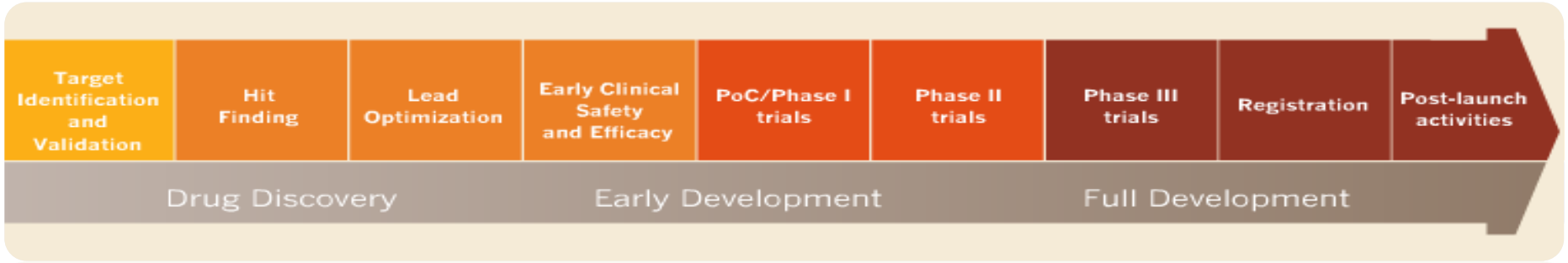
1. Design clinical trials that prospectively plan to enroll pregnant women for whom the study drug offers potential direct benefit

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?

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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 it 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'

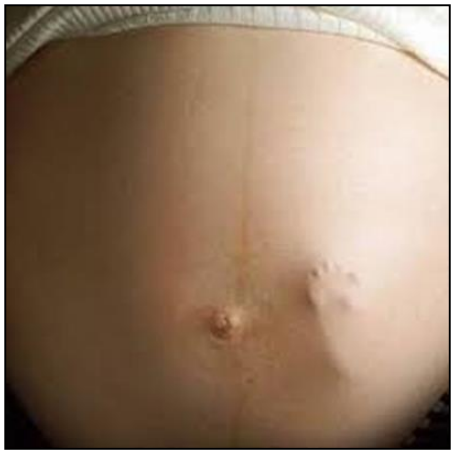
Table 3. Data generation and collection workstream objectives.

Develop Standards	Compile Existing Data
• Define core research parameters that are harmonized; establish standards and related protocols for data collection (include women, fetus, infant) • Define what acceptable level of evidence is needed to allow for approval of using a drug in pregnancy • Define what constitutes a well-documented case of pregnancy and pregnancy outcome; define constructs for follow-up of patient and offspring • 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) • Standardize data assessment methods and harmonize around accepted statistical concepts; include how to capture more subtle effects on development	• Map out data already available, noting strengths and limitations • Create comprehensive directory of ongoing efforts, and identify opportunities for collaboration • Gather, combine, and analyze existing data to build benefit-risk assessments and identify gaps • Engage existing registry owners to combine efforts; develop platform to make this work effectively • Compile existing guidance (eg, regulatory, professional association, advocacy)
Develop Data Capture Tools	**Capture New Data**
• 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 • Develop prospective data tools that utilize health care social application technologies • Investigate alternative data collection collaborations • Apply continuous health care learning system concepts	• Develop a central public database, and pool data (existing and new) across companies and organizations • Collect and address data for subpopulations (eg, age, disease, race); engage patients and collect pharmacokinetic and effect-of-pregnancy data • As appropriate, include pregnant women in random controlled trials • Collect self-reported data from pregnant mothers

Clemow et al. *A Proposed Framework to Address Needs of Clinical Data for Informed Medication Use in Pregnancy*. TIRS (2014). 48(2): 145 - 154.

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

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Thank You

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