

Federal Updates on Maternal Health Activities: FDA

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Disclosure Statement

- I have no financial relationships to disclose relating to this presentation
- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

FDA Offices with Focus on Maternal Health



- Office of the Commissioner: Office of Women's Health
- Center for Drug Evaluation and Research:
 - Division of Pediatric and Maternal Health
 - Division of Bone, Reproductive, and Urologic Products
- OB FDA
 - Initiated in 2018
 - Centralized group of experts to discuss and advise on issues related to the unique population of pregnant women
 - Allows efficient, consistent, and expert consideration of science related to pregnancy and lactation
 - Includes membership across FDA and multiple disciplines (e.g., medical statistics, epidemiology, pharmacology, toxicology)
 - Meets quarterly

FDA Activities in Maternal Health

- Promoting clear communication to prescribers and pregnant women
- Increasing the availability of quality data to evaluate the safety of drugs used during pregnancy and lactation
 - Fund and conduct research to support regulatory decision-making
- Collaborating with outside stakeholders to advance maternal health

Promoting Clear Communication

Pregnancy Categories

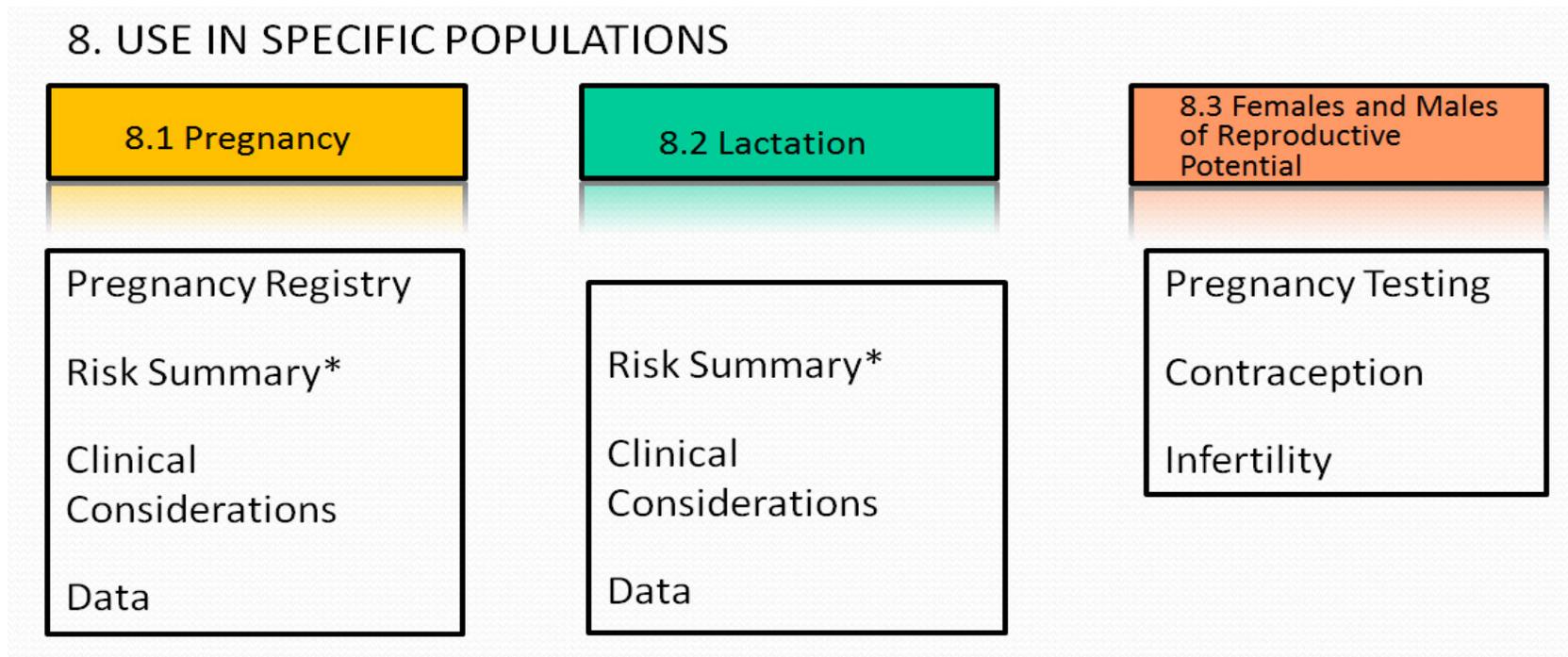
| | |
|----------|---|
| A | Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). |
| B | Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk, and AWC studies in pregnant women during the first trimester have not confirmed risk (and there is no evidence of risk in later trimesters). |
| C | Animal reproduction studies have shown an adverse effect on the fetus and there are no AWC studies in humans, BUT the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, OR studies in women and animal are not available. |
| D | There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective). |
| X | Studies in animals or humans have demonstrated fetal abnormalities, OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available). |

The Problem with Letters

- Pregnancy letter category system was overly simplistic
- Misinterpreted as a grading system
- Pregnancy Category C
 - Animal reproduction studies have shown an adverse effect on the fetus, and there are no AWC studies in humans, BUT the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
 - Studies in pregnant women and animals are not available
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information

Pregnancy and Lactation Labeling Rule (PLLR)

- Published on December 4, 2014
- ALL prescription drugs are required to remove pregnancy letter categories
- Replaced with new format that emphasizes description of risk when used during pregnancy and lactation



Risk Communication Advisory Committee



- Held on March 5-6, 2018
- Discussed the impact of pregnancy and lactation labeling information in prescription drug and biological products as modified under the Pregnancy and Lactation Labeling Rule
 - How information in PLLR labeling is being perceived and used by health care providers and other stakeholders
 - Factors that are critical to health care providers' interpretation of the data and counseling of pregnant women on the risks and benefits of a medication, and
 - How to convey risk information to health care providers to accurately and adequately inform risk-benefit considerations for medication use during pregnancy.
- Recordings and other materials available at:
 - <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/RiskCommunicationAdvisoryCommittee/ucm594576.htm>

Practitioner Survey

- American Academy of Allergy, Asthma and Immunology
- Email invitation to participate in electronic survey
- 126 allergists responded
 - The majority of responders did not know of the new PLLR changes (56%)
 - Most responders were reverting back to letter categories when counseling patients (76%)
 - Most of the responders found the risk information included in labeling to be helpful (73%)
 - More than half of responders felt that the new labeling did not bring more meaningful information to them or their patients and that compared with past letter categories, it was unhelpful

Communicating Risk

- Pregnant women often tend to overestimate the magnitude of teratogenic risk.
- Health providers also may have distorted perceptions of risk, even in the presence of evidence-based facts.
- Teratogen (and other medical) data may be limited and contradictory.
 - Data are rarely adequate on all aspects of reproductive toxicity (e.g. adverse behavioral outcomes).
- Situations where there are no data or inadequate data predispose to inaccurate and extreme interpretation:
 - No data...assume huge risk vs. no data...assume no risk



Highlights of RCAC Recommendations

- Ensure that the benefit is stated clearly, including the potential risks of NOT taking the drug
- Presentation/format of information should allow for quick review
- Use plain language and consistent terminology
- Improve on organization and presentation of information
- Consider a tabular summary of the evidence, including the strength and quality of the evidence of animal data; strength of evidence of human data; time on market
- Improve on information provided about relationship of animal data to human data
- Improve on certain terminology and phrases that are confusing (e.g., adverse developmental outcomes)
- Test messaging for comprehension

“Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials”

- Published April 9, 2018
- There is need for data to inform safe and effective treatment during pregnancy, such that clinicians and patients do not have to undertake a risk-benefit analysis for the use of drugs and biological products in pregnant women with limited human safety information
- In certain situations, it is ethically and scientifically appropriate to collect data in pregnant women in clinical trials conducted during drug development
- Ethical Considerations
 - FDA regulations do not contain a section similar to 45 CFR part 46, subpart B; however, FDA recommends that these requirements be satisfied for FDA-regulated clinical research.
 - Mirror the same 10 requirements under 45 CFR 46 Subpart B

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM603873.pdf>

Increasing Availability of Quality Data



Office of Women's Health

- The FDA Office of Women's Health (OWH) awards intramural research grants to support FDA regulatory decision-making and advance the science of women's health, including research related to pregnancy
- Examples of projects funded in 2018:
 - Development of an artificially intelligent virtual pregnant woman modeling suite to support regulatory decisions
 - Evaluation of women-targeted dietary supplements for labeling compliance and potential contamination, containing live microbes in the U.S. market with special emphasis on pregnant and lactating women and infants
 - Utilizing model-informed drug development to facilitate antimalaria dosing in pregnant women

National Center for Toxicological Research (NCTR)



- Non-regulatory component of FDA established to conduct integrated toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health
- Conducts scientific research to generate data for FDA decision-making
- NCTR spearheaded the formation of the Perinatal Health Center of Excellence
 - Advance regulatory science to improve the characterization of safety, efficacy, or potential toxicity of FDA-regulated products.
 - PHCE awarded grants totaling \$1,898,095 for 14 proposals to investigators representing CBER, CDER, CDRH, CFSAN, and NCTR—all with either internal or external collaborators including NIH, universities, OC, and ORA

Collaborate with Outside Stakeholders

Research Specific to Pregnant Women and Lactating Women (PRGLAC)



- HHS task force established under the 21st Century Cures Act
- Advise HHS Secretary on gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women
- Report and recommendations published in August 2018
[Final Report: https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf](https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf)
- Task force charter reviewed for another 2 years to continue work

Other Areas of Collaboration

- Collaborate with other Federal partners
 - Obstetric-Fetal Pharmacology Research Centers (OPRC) Network
 - NIH Best Pharmaceuticals for Children Act (BPCA) Program
 - CDC Division of Reproductive Health
- Collaborate with other organizations
 - American College of Obstetricians and Gynecologists
 - Society for Maternal-Fetal Medicine
 - Coalition to Advance Maternal Therapeutics
 - International Society for Pharmacoepidemiology

Coming Attractions

- FDA plans to publish draft guidances
- Have begun discussions with other regulatory authorities about increasing collaborations to increase coordination of activities related to maternal health
- Complete implementation of PLLR by 2021 as scheduled
- Advance research in pregnancy and lactation
- Continue collaborations with internal and external stakeholders



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Thank You