

# **A White Paper**

Taken from the book:

**Pregnancy and the Pharmaceutical Industry:  
The Movement Towards Evidence-Based Pharmacotherapy  
for Pregnant Women**  
(Elsevier 2019)

and from the dissertation:

**The Inclusion of Pregnant Women in Clinical Research:  
Implications for the U.S. Pharmaceutical Industry**  
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## Introduction

The treatment of medical conditions complicating pregnancy is challenged by a serious lack of information about the safety and effectiveness of the medications used by pregnant women. To improve our knowledge of what constitutes the most effective therapeutic interventions, we conduct systematic research. Such research for pregnant women, however, is challenging.

In response, the U.S. Food and Drug Administration (FDA) released a draft guidance in April 2018 entitled, "Pregnant Women in Clinical Research: Scientific and Ethical Considerations"<sup>1</sup> and The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) released its report<sup>2</sup> in September 2019.

This white paper provides data from key informant interviews<sup>a</sup> conducted with industry clinicians, researchers and lawyers, Institutional Review Board (IRB) members, and representatives from FDA and PhRMA (Pharmaceutical Research and Manufacturers of America), to assist industry and its stakeholders prepare to adopt the recommendations from FDA and the Pregnancy and the Task Force on Research Specific to Pregnant Women and Lactating Women.

### EXCLUSION OF PREGNANT WOMEN FROM INDUSTRY-SPONSORED PHASE IV STUDIES

One recent study found that, of 367 Phase IV studies in which pregnant women could appropriately participate (the drugs were in FDA pregnancy categories A, B, or C and the conditions being studied could occur during pregnancy), 95% excluded pregnant women from enrollment.<sup>26</sup>

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<sup>a</sup> Key informant interviews, conducted in 2011-2, sought to isolate the opinions of industry research, regulatory, and safety staff from pharmaceutical (n=5) and biotech (n=3) companies, legal counsel from industry (n=2), an IRB (n=1) and PhRMA (n=1), and other representatives from PhRMA (n=1), IRBs (n=2), and FDA (n=1).

## Background

In the U.S., of the almost 4 million women who give birth each year,<sup>3</sup> 50,000 experience severe complications of pregnancy<sup>4</sup> and 700 die from pregnancy-related causes.<sup>5</sup> To treat the morbidity, prevent the mortality, and achieve optimal pregnancy outcomes, over 60 percent of pregnant women are prescribed one or more drugs.<sup>6,7</sup> Because pregnant women are largely excluded from participation in clinical research studies, the efficacy and safety of these medications when used during pregnancy are largely unknown.<sup>8</sup>

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### CASE STUDY:

The potential impact of a lack of data for drug efficacy during pregnancy is illustrated by the 2002 recommendation by the American College of Obstetricians and Gynecologists (ACOG) of the use of amoxicillin by pregnant women as one method of anthrax post-exposure prophylaxis. Subsequent study results, published in 2007, showed that the dosage regimen was ineffective for the treatment of pregnant and post-partum women.<sup>9</sup> No studies are available for ciprofloxacin or doxycycline, the alternative antibiotics.

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Women's health care providers lament that the "current evidence base for the care of pregnant women facing illness is widely regarded as deplorable."<sup>10</sup>

The exclusion of pregnant women from participation in drug studies is widely accepted as the right thing to do. Thalidomide casts a long shadow.<sup>b</sup> Unless you are a pregnant woman with an illness or her health care provider, the consequences of the lack of research results are largely invisible.

Interviews in 2012 with key informants in industry, IRBs, PhRMA, and FDA found that the exclusion of pregnant women from clinical research is primarily based on the ethical principle of beneficence - the desire to avoid causing harm to a fetus. Even when the negative consequences

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<sup>b</sup> In the late 1950s and 1960s, women around the world were prescribed thalidomide to prevent miscarriage, for hyperemesis, and for sedation. It took several years, and over 10,000 cases of severe limb defects and other anomalies before its teratogenic properties were recognized.

of exclusion are recognized, other motives may be difficult to overcome. These include the perceived risk of litigation, scientific validity issues, risks to drug approval and to company reputation, and the increased complexity of conducting such trials. The lack of advocacy for their inclusion, the lack of a regulatory requirement or recommendation, and historic precedent are other rationales.

The FDA,<sup>11</sup> the Institute of Medicine,<sup>12</sup> the Council for International Organizations of Medical Sciences (CIOMS),<sup>13</sup> and ACOG<sup>14</sup> recommend the inclusion of pregnant women in research when the benefits outweigh the risks. These recommendations and an increase in requests to review clinical protocols that included pregnant women, spurred FDA's development of the guidance document. "Pregnant Women in Clinical Research: Scientific and Ethical Considerations"<sup>15</sup> was released in April 2018. It challenges the industry to increase its inclusion of pregnant women in clinical research studies.

## **FDA guidance and PRGLAC recommendations**

### **Rationale:**

**Why** should pregnant women be included in clinical research?

- Controlled studies provide evidence-based guidance on treatment options for application in medically compromised pregnancies.
- The supervision of the patient and the quality of the data acquired in rigorously controlled studies is superior to that received in the post-marketing environment.
- Safety and efficacy information will be obtained sooner and with fewer pregnant women and fetuses exposed than if the drug information is obtained following its release on the market (recognizing, as with all drugs, that some objectives cannot be met until widespread use occurs).

**When** should pregnant women participate in clinical research?

- When their exclusion cannot be justified by scientific rationale
- When participation in a study provides therapeutic benefit and the anticipated benefits

exceed the anticipated risks

- When there is medical need to treat a particular pregnant woman or pregnant women in general and there is reliable information from animal testing or human experience on the teratogenic and developmental risks of the proposed treatment.

### **Recommendations:**

*Where* in drug development should research include pregnant women?

- Clinical environment:
  - Pharmacokinetic (PK) testing
  - End of Phase III studies designed to include pregnant women
- Post-marketing:
  - Phase IV clinical studies designed for pregnant women
  - Enhanced surveillance: pregnancy exposure registries for active surveillance, cohort and case control studies for signal evaluation

*What* pregnant women should be included in clinical research?

- Pregnant women in need of treatment (whether for pregnancy-related conditions or unrelated illness) can be enrolled:
  - in studies that potentially provide therapeutic benefit and whose potential benefits exceed the potential risks
  - in studies designed to evaluate safety and/or efficacy during pregnancy
  - in general clinical trials on a compassionate use basis after individual consideration of risk/benefit and consent
- Pregnant women already taking approved medications in the post-marketing environment
- Women who become pregnant during a clinical trial who desire to remain in the study after individual consideration of risk/benefit and re-consent
  - Factors for consideration include the risk to the pregnant woman and her fetus from continuation of therapy, discontinuation of therapy, and the effectiveness and risks of alternative therapies (including risk of fetal exposure to the experimental and the alternative therapy).

## Findings from Industry Stakeholder Interviews

Via key informant interviews (KIIs), individuals within pharmaceutical companies and IRBs, including their legal counsels, recognized the unintended adverse consequences of pregnant women's exclusion from clinical research. While understanding the need for change from the current practice of general exclusion, they cautioned that such change would be difficult and probably incremental. KIIs identified barriers to inclusion and provided potential solutions. These are presented in Table 1 and are further discussed below.

**Table 1. Concerns and Solutions identified for Industry Consideration**

Key Concerns	Key Potential Solutions
Safety	Study design; scientific advances in modeling and animal testing; end of Phase III and post-marketing studies
Efficacy	PK testing on small numbers; partnerships with OPRU* and obstetrical community, data from multiple sources
Business	Define market; conduct post-approval studies; devise incentives and protections

### Safety

- Acknowledging the need to be extremely cautious, it is important to note that the majority of drugs are not teratogenic, and all<sup>c</sup> of the drugs found to be teratogenic in humans to date are teratogenic in animals as well.<sup>16</sup> Advances in **drug modeling, Phase 0 testing, and advancements in animal testing** are innovations being made by pre-clinical scientists.
- **All** pregnancies that occur during clinical trials should be **followed to outcome**.
- Consider **retaining** women who inadvertently become pregnant during clinical trials following an individual benefit/risk assessment and re-consent. Consider the risk of the

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<sup>c</sup> With the possible exception of misoprostol whose teratogenicity in rats has yet to be replicated.

exposure vs. the benefit of the treatment, the risk of discontinuing treatment, and the efficacy and safety - including fetal exposure – of the alternative treatments.

- Once efficacy in non-pregnant subjects and PK parameters in pregnant women have been established, studies can be designed specifically for the enrollment of pregnant women in **late Phase III and Phase IV**.
- **Post-marketing safety surveillance** must continue for the lifetime of the product with pregnancy registries and epidemiologic studies providing supporting data and signal evaluation.
- Create an **internal women's health committee** composed of subject matter experts within the company to consult on pregnancy-related issues – in study design and planning, in policy making on inclusion and retention in trials, in post-approval activities and for Risk Evaluation and Mitigation Strategies.

## Efficacy

- Key informants recommended that a treatment's **efficacy should be confirmed** by completing clinical trials in men and non-pregnant women before initiating testing in pregnant women.
- Proper dosing for pregnant women can only be gained by conducting PK testing in pregnant women. Such testing can be done on small numbers of women, and could be done with pregnant **women who are already taking the approved medication** in post-approval studies.
- Since 2004, four Obstetric-Fetal Pharmacology Research Centers (OPRCs) have been receiving government funding to conduct pharmacology studies on pregnant women "to enhance understanding of obstetrical pharmacokinetics and pharmacodynamics, and improve appropriate therapeutics during pregnancy."<sup>17</sup> Pregnancy-induced changes in PK and PD have been documented.<sup>18</sup> Sponsors should **partner with the OPRCs** to conduct studies that determine correct dosing for pregnant women.



## Business concerns

KIIs raised valid business concerns that must be recognized and addressed before change can be considered. These include: the additional **time** and financial **costs** with little **return on investment**, potential **delays** and threats to product approval, and **litigation risks** – **both financial and reputational**.

- The attitude of **senior management** and regulatory agency guidance are recognized as factors that will influence the inclusion/exclusion decision.
- Business analyses would be helpful to define the **market** for pharmaceutical use in pregnant women.
- To avoid delayed initial approval and access to products with established therapeutic benefit for the general population, conduct **post-approval studies** in pregnant women.

## **Recommendations to FDA**

Change from the widespread practice of excluding pregnant women from clinical research studies will call for regulatory directives, financial incentives, and legal protections. Clinicians and their patients are advised to weigh the potential therapeutic benefit to the pregnant woman (and fetus) against the risk of exposure to the therapeutic intervention. At what point does the agency consider that the Sponsor has 'enough' pre-clinical and clinical data to perform this benefit/risk assessment? The establishment of best practices for data collection and evaluation can provide standardization, improved knowledge, and protection from litigation.

**Table 2. Industry Concerns and Solutions identified for FDA Consideration**

<b>Key Concerns</b>	<b>Key Potential Solutions</b>
Litigation	Guidance/regulation; best practices; informed consent; indemnification; improved awareness of issue in public domain
Regulatory	Guidance, communication between agency and sponsors, incentives and protections, international harmonization

### Litigation

- There is no evidence that suggests that designing clinical trials for pregnant women will increase the risk of litigation against the company (though experience is limited).
- There is evidence that discovering teratogenicity in the post-marketing period in therapies not evaluated during development raises the risk for litigation.<sup>19</sup>
- Sponsors should not be punished for following best practices to ascertain if a product is teratogenic. The financial and reputational costs of a product that has been inaccurately branded teratogenic, e.g., Bendectin,<sup>20,21</sup> can be substantial (see box). Therefore, best practices should be defined and standardized and company indemnification must be considered as protection against litigation. (See further discussion of indemnification in the Addendum.)

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#### **CASE STUDY:**

Bendectin, a combination of vitamin B6 and an antihistamine, which are both available over the counter as separate medications, was FDA approved and is effective for the treatment of nausea and vomiting during pregnancy. Despite having been extensively studied in animal, clinical, and epidemiologic studies with no findings of measureable risk to the developing fetus, the product was withdrawn from the market in 1983 due solely to the burdens of litigation. The product remains on the market in the UK and Canada where it is widely used.

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- The agency should consider a public awareness campaign to publicize the need for research that benefits pregnant women and their babies.
- The agency should provide guidance on the process of informed consent that will cover the inclusion of pregnant women in clinical research studies.

## Regulatory

- **Provide guidance:**
  - The ability for Sponsors to access FDA reviewers to discuss study design options and obtain agency advice was cited as an obstacle to drug development. Communication between FDA reviewers and company representatives needs to be substantially improved in order to facilitate the planning and conduct of studies in pregnant women. Without communication, the voluntary conduct of such studies will be negatively impacted.
- **Identify priority drugs and diseases**
  - Identify diseases and drug classes that are a priority for drug testing for pregnant women so that resources can be targeted efficiently.
- **Define when pregnant women should be included**
  - Define the conditions under which Sponsors should consider studies for pregnant women, e.g., prevalence of the condition in pregnancy, risk of no or delayed treatment, safety and efficacy data available for alternative treatments, etc.
  - Define the considerations that would support the inclusion of pregnant women in clinical studies, e.g., when the benefit outweighs the risk, when there is no evidence of teratogenicity in preclinical studies or human exposures, the condition commonly (define commonly) occurs in pregnant women and its treatment should not be postponed, etc.
- **Define when pregnant women should be excluded**
  - Provide a list of considerations that would rationally result in the exclusion of pregnant women, e.g. evidence of teratogenicity in preclinical studies or human exposures, conditions that would never or rarely occur in pregnant women, treatment that could usually be postponed until the conclusion of the pregnancy, etc.

- **Make determinations on an individual entity basis**
  - Develop an efficient process within the agency for individual review of New Drug Applications (NDAs) as to whether they should or should not include testing in pregnant women (i.e., do not recommend testing in pregnant women solely by indication and drug class).
- **Consider incentives and protections**
  - Identify potential company incentives for the design and implementation of studies that include pregnant women. Consider:
    - Provide fast track review for NDAs that include plans for studies in pregnancy
    - Implement financial incentives to offset costs (patent protections and transferable extensions, tax incentives, orphan drug status (the number of pregnant women needing treatment for many conditions may be <200,000), research subsidization, create new incentives
    - Partner with NIH, CDC, OPRCs, and others
  - Consider company indemnification. [See Addendum for commentary on indemnification.]
- **Include generic companies**
  - Recommend that generic companies, where applicable, participate in and contribute to the costs of research on marketed, off-patent products used by pregnant women.
- **Spearhead international harmonization**
  - Harmonize recommendations with CIOMS and the International Committee on Harmonization to assist global standardization in multinational research.

## **Recommendations to PhRMA/BIO**

Pharmaceutical companies have a responsibility to provide efficacy and safety information for products **intended for women of childbearing potential**. Consideration of the need for drug testing in pregnant women should be **part of routine drug development** for all new molecular entities. Prioritizing studies for pregnant women by those conditions and drug classes where the need is greatest may facilitate acceptance and target resources to where they are needed the most.

To assist in these efforts, PhRMA/BIO can:

- Sponsor the collection of additional data that would be helpful to industry to inform its response to the draft guidance including:
  - **Market analysis** – what are the expected financial returns – or lack thereof – for the approved or off-label use of a product during pregnancy? What are the expected costs of conducting additional clinical trials for pregnant women? While financial considerations may not be the deciding factors in the decision to conduct such studies, the associated costs must be factored into the total research costs of a product in development.
  - **Legal analysis** on the risk of increased litigation if pregnant women are:
    - retained in clinical trials in which they inadvertently became pregnant
    - included in clinical trials designed for testing in pregnancy during development (late Phase III) or in the post-marketing environment
  - **Legal opinion on potential protections** to prevent litigation in clinical and post-marketing environment, including indemnification.
- Produce a position paper for industry on the inclusion of pregnant women in clinical research.
- Convene a maternal health working group to consider recommendations for the expansion of the inclusion of pregnant women in clinical research.
- Host a pregnancy-specific data safety monitoring board that can provide oversight and decision-making functions for open trials, similar to other organ-specific DSMBs.

## Future Steps

### Dialogue and Communication

PRGLAC should consider sponsoring a **maternal health committee** with members from pharma and bio companies, FDA and other stakeholders series of workshops to bring together key stakeholders, including PhRMA, FDA, and Industry, the Second Wave Initiative,<sup>d,22</sup> professional associations like ACOG and the March of Dimes, women's health advocates, etc., to share concerns, discuss issues, and generate and evaluate potential solutions. Understanding each other's genuine concerns and the guidance's potential impacts will be key to finding

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<sup>d</sup> This initiative is driven by a group of physicians, scientists, and bioethicists working to advocate for the importance of advancing the evidence base for the treatment of pregnant women facing serious illness.

solutions. The realization of a comprehensive guidance document that addresses stakeholders' perceptions and concerns and results in acceptance of the outcome will rely upon dialogue, negotiation, and cooperation.

## **Evaluation**

The maternal health committee should monitor and evaluate the **impact of the inclusion of pregnant women in clinical research.**

- **Impact on inclusion:** indicated by the actual increase in proportion of clinical trials that a) do not exclude pregnant women and b) those that are designed specifically for enrollment of pregnant women.
- **Impact on labeling:** indicated by an increased proportion of drug labels that include evidence-based recommendations for use in pregnancy. Labeling changes would include information specific to use during pregnancy including: pregnancy indications, dosing changes in pregnancy, pharmacokinetic information, and new safety information.
- **Financial costs to industry:** the costs of conducting the trials, related infrastructure and administration, delays in approvals, experience with litigation, etc., – and costs offset by the financial impact of any implemented incentives.
- **Impact on pregnant women and their babies:** case reports, field studies, or surveys of practical experience in obstetrical practice and clinical research.

## **Benchmarking / Best Practices**

As the practice of including pregnant women in clinical studies will be new to the research community, benchmarking and sharing of best practices will be vital to the continuing improvement of clinical research practices involving pregnant women. Sharing lessons learned by experience would be facilitated by ongoing participation and monitoring by the proposed committee on maternal health.

## **Concerns**

Rarely occurring adverse effects, including birth defects, may not be identifiable until a large

number of people have taken the drug. Concern has been raised that it may not be possible to enroll enough pregnant women to achieve statistical significance. Because pregnant women have been routinely excluded from clinical studies we do not know to what extent they might volunteer to participate. Pregnant women could only be invited to participate if they are in need of treatment, if the study would potentially provide therapeutic benefit, and if the potential benefits exceeded the potential risks. In this way, their treatment in a research study would be similar to their treatment in clinical practice - with the added benefit of improved informed consent, enhanced pregnancy monitoring, and the knowledge that she has contributed her experience to the accumulated medical knowledge base to assist other pregnant women. Currently, evidence from pregnant women treated in clinical practice is rarely captured at all. Safety surveillance complements clinical research data and needs to continue throughout the life-cycle of all products.

## WILL PREGNANT WOMEN PARTICIPATE IN CLINICAL TRIALS?

One small study found that 95% of pregnant women interviewed said that they would participate "if there is a chance that participation in a clinical trial would help their pregnancy and improve their baby's health" (22). Further research is needed to confirm or refute this finding.

## Conclusion

Women's health advocates, medical experts, and key informants within industry and related organizations believe that pregnant women and their fetuses are at a higher risk of adverse medical consequences if they are not included in clinical trials than if they are included in clinical trials,<sup>1,2,9,11-13,23</sup> They believe that conducting trials on drug treatment for pregnant women, while ethically, legally, and operationally challenging, is morally required and will be advantageous to pregnant women and their fetuses, their health care providers and prescribers, and society in general. With the release of the FDA draft guidance on the inclusion of pregnant women in clinical research and the publication of the PRGLAC Taskforce Report, the pharmaceutical industry is challenged to confront assumptions and past practices and address the obstacles that prevent effective, evidence-based treatment for pregnant women.

**Note on the Author:**

Kristine Shields MSN, DrPH is an OB/GYN Nurse Practitioner with a doctorate in Public Health Administration. After years of clinical practice in women's health, she joined the pharmaceutical industry in 1998 where she developed and managed one of the earliest and most comprehensive pregnancy registry programs in the industry. Her book, Pregnancy and the Pharmaceutical Industry: The Movement Towards Evidence-Based Pharmacotherapy for Pregnant Women was published in 2019 by Elsevier Academic Press. She is currently a medical writer and consultant to pharma on pregnancy issues, based in the Philadelphia area.



## Addendum

### Company Indemnification

While many of the study participants were doubtful that indemnification was a real possibility, several of the pharmaceutical company and IRB participants recommended not dismissing company indemnification outright. They thought that the concept should be included when considering all the potential solutions to improving knowledge of pharmaceutical therapy for pregnant women.

Pharmaceutical industry concern about both the cost and the potential harm to a product and to a Company's reputation is a legitimate barrier to the implementation of efforts to increase the enrollment of pregnant women in clinical research. The following four points should be considered:

- **The President's Commission for the Study of Bioethical Issues'** recommendation of a national compensation system,<sup>24</sup> which states that "Because subjects harmed in the course of human research should not individually bear the costs of care required to treat harms resulting directly from that research, the federal government, through the Office of Science and Technology or the Department of Health and Human Services, should move expeditiously to study the issue of research-related injuries to determine if there is a need for a **national system of compensation or treatment for research-related injuries.**"
- One of the conclusions of the 2000 University of Texas Medical Branch conference held "to address the national problem of underrepresentation of pregnant women in clinical trials" was that "[t]here should be a **nationally supported mechanism to protect private sponsors and industry** from excessive or inordinate liability claims and to develop incentives to promote industry-supported research on this population."<sup>25</sup>
- The success of the **Vaccine Injury Compensation Program**, and
- The potential for **industry-sponsored group insurance**.

For FDA and PhRMA consideration: Consider an agency-industry-legal working group to explore the feasibility of indemnification. The adoption of the practice of designing and conducting studies for pregnant women may rest on the outcome of this question. Jury awards for children with birth defects and developmental disabilities – rightly or wrongly attributed to drug exposure – can be severe. Litigation costs can remove effective products from the market (e.g., Bendectin). Potential break-through medications are removed in early development due to this concern. Improvement in maternal health and positive pregnancy outcomes relies upon accurate knowledge of the safety and efficacy of treatment options during pregnancy. Systematic research is required to obtain this knowledge but litigation may prevent it.

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