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Assessing U.S. Food and Drug Administration Authorities, Guidance, and Policies for Prescription Drug, Biological Product, and Medical Device Development and Commercialization for Use by Pregnant and Lactating Women

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INTRODUCTION

While many pregnant and lactating women may require at least one medication or device intervention during these phases of life, there is often little information available about the appropriate use and overall safety of these interventions in pregnant and lactating women. In particular, the U.S. Food and Drug Administration (FDA) has acknowledged that development of therapeutics for use in pregnant and lactating women has trailed behind the development of therapeutics for other populations. In this paper, we have summarized FDA authorities, guidance, and policies relating to drug, biological product, and medical device development and commercialization that are specific to pregnant and lactating women. We provide an overview of how FDA reviews and authorizes testing and marketing of prescription drugs, biological products, and medical devices, with a specific focus on requirements that are specific to obtaining safety and efficacy information for use of such interventions in pregnant and lactating women.

METHODS

Throughout this paper, we use a number of defined terms. We have focused our review of FDA's authorities, guidance, and policies on prescription products. When we refer to "prescription products," we are including (1) drugs approved by FDA pursuant to a New Drug Application (NDA); (2) biological products approved by FDA pursuant to a Biologics License Application (BLA); and (3) medical devices that have come to market through FDA's premarket approval, de novo authorization, or premarket notification pathways. For medical devices subject to these pathways for market entry, we collectively use the term *approval* when referring to the regulatory process for obtaining market entry. This paper does not summarize FDA authorities, guidance, or policy relating to over-the-counter drugs or devices. When we refer to a product as *investigational*, we mean a drug, biological product, and/or medical device that is not yet authorized by FDA for marketing or commercial distribution in the United States and is subject to the requirements of FDA's Investigational New Drug (IND) Application, in the case of drugs and biologics, or investigational device exemption (IDE), in the case of medical devices. When an FDA authority, guidance, or policy is specific to a particular product type (i.e., drugs, biological products, and/or medical devices), such term(s) are used in a distinct manner to signify the specific requirements for the particular product type.

We reviewed FDA's authorities, guidance (with a primary focus on those currently in effect, whether draft or final), and policies requiring or recommending that sponsors obtain information to inform the safe and effective use of prescription products (irrespective of the indication(s) for use) by pregnant and lactating women, as well as those authorities that authorize FDA to require or mandate labeling changes for approved interventions when new information becomes available. Where applicable, we reviewed the *Federal Register* docket for draft FDA regulations and guidance, including public comments submitted to the applicable FDA dockets. We also reviewed FDA's responses relating to potential incentives or disincentives for sponsors to obtaining information to inform the safe and effective use of prescription products for use by pregnant and lactating women. Our review of public comments and FDA's responses focused in particular on health care professionals, medical societies and associations, and industry members and industry associations.

We also reviewed other FDA public resources, such as FDA workshop and public meeting transcripts, action plans, and FDA reports related to the inclusion of pregnant and lactating women in clinical research to support prescription product use in these populations. We also researched relevant FDA statistics, as well as FDA's databases, relating to approved or currently marketed prescription products with respect to their labeling content, postmarketing commitments (PMCs) and postmarketing

requirements (PMRs), and supportive clinical data in pregnant and lactating women. We also searched ClinicalTrials.gov for a sampling of industry-sponsored clinical trials involving investigational products that are or were conducted in the United States and that proactively enrolled pregnant and/or lactating women.

RESULTS

The mission of FDA is to protect the U.S. public health by ensuring the safety and efficacy of prescription products prior to public availability. Drugs and medical devices are subject to regulation under the Federal Food, Drug, and Cosmetic Act (the FD&C Act), and biological products are subject to regulation under the FD&C Act and the Public Health Service Act (the PHS Act), as well as other federal, state, and local statutes and regulations. Both the FD&C Act and the PHS Act and their implementing regulations (as applicable) govern, among other things, the preclinical testing, clinical trials, labeling, safety and efficacy, packaging, manufacturing, distribution, advertising and promotion, and post-approval studies and surveillance of drugs, biological products, and medical devices. For purposes of this summary, we focused on preclinical testing, clinical trials, approval, labeling, and postapproval studies and surveillance requirements enumerated in statutes and regulations, as well as recommendations described in FDA guidance documents or FDA policies (neither of which establish legally enforceable responsibilities). We identified numerous relevant FDA authorities related to drugs and biological products but not medical devices. Given that medical devices are generally used for procedures and have a specific intended use based on their FDA classification, this was not unexpected and, as such, our findings primarily relate to requirements and recommendations for sponsors of drugs and biological products.

Our review concluded that FDA has demonstrated a commitment to protecting and advancing the public health of pregnant and lactating women in the following ways: (1) requiring certain preclinical testing to uncover potential developmental and/or fetal toxicities, (2) recommending the inclusion of pregnant women in clinical trials, and (3) requiring the presentation of pregnancy and lactation risk information and clinical considerations in drug and biological product labeling to support informed prescribing decisions in these populations. However, we also observed that FDA maintains no single database of prescription drugs, biological products, or medical devices that are indicated for use by pregnant and lactating women. While sponsors are required to list and post results for certain clinical trials evaluating drugs, biological products, and medical devices on ClinicalTrials.gov, our search of the platform did not easily identify interventional clinical trials that enrolled or are currently enrolling pregnant and lactating women.

We also observed that as of 2021, FDA has only approved nine drugs specifically for nononcology obstetrical indications, and to date there have been numerous devices authorized for obstetrical and gynecological use. It is unclear whether FDA has approved any prescription products specifically for a stipulated use in lactating women, and the authorized prescription devices for the lactating population appear to be limited to breast pumps. As of December 2018, FDA has withdrawn three prescription products from the market that were related to pregnancy and lactation: (1) diethylstilbestrol, (2) bromocriptine mesylate, and (3) Makena (hydroxyprogesterone caproate). There are also 13 prescription products that are subject to a risk evaluation and mitigation strategy (REMS) program to minimize embryo-fetal toxicities in pregnant or lactating patients. Additionally, of the approximately 2,300 PMRs and PMCs listed in FDA's database, around 2.6 percent involved preclinical developmental and reproductive toxicity (DART) studies, around 0.2 percent involved clinical trials in pregnant individuals, around 1.2 percent involved clinical lactation studies, and approximately 8 percent involved a pregnancy registry or other prospective and/or retrospective observational study in pregnant and lactating individuals. Based on our review of FDA's authorities, guidance, and policies on prescription products that specifically relate to pregnancy and lactation, we provide a list of discrete considerations and opportunities that may support regulatory initiatives relating to the development and commercialization of prescription products for use by pregnant and lactating women.

Preclinical Testing

Overview

Before testing any prescription drug or biological product in humans, FDA requires that the product undergo preclinical (also referred to as *nonclinical*) testing, which includes laboratory evaluations of the product's characteristics, chemistry, toxicity, and formulation, as well as animal studies to assess the potential safety and activity of the product to support use of the product in clinical trials. The results of these preclinical studies aid in determining an initial starting dose, dose titration, and the highest safe dose for human clinical trials, while also initially characterizing potential adverse effects that might occur in humans (ICH, 2020).

As a part of an IND application to initiate a clinical trial for an investigational drug and biological product, FDA requires inclusion of:

[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of

animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. . . As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety. (21 CFR § 312.23(a)(8))

Developmental and Reproductive Toxicity (DART) Studies

Generally, when adult men and women are to be enrolled in clinical trials, preclinical DART studies are conducted to reveal any effect of the drug or biological product on mammalian reproduction that may be relevant for human risk assessment. FDA's guidance documents relating to preclinical DART studies primarily include ICH S5(R3) "Detection of Reproductive and Human Developmental Toxicity for Human Pharmaceuticals" and ICH M3(R2) "Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals," which have been adopted by FDA and were issued to industry as final guidance in 2021 and 2010, respectively (ICH, 2020; ICH, 2009a). However, ICH S5(R3) states "No guidance can provide sufficient information to cover all possible cases, and flexibility in testing strategy is warranted" (ICH, 2020).

The following six stages of reproduction are generally assessed in DART studies:

- Stage 1: pre mating to conception
- Stage 2: conception to implantation
- Stage 3: implantation to closure of the hard palate
- Stage 4: closure of the hard palate to the end of pregnancy
- Stage 5: birth to weaning
- Stage 6: weaning to sexual maturity (ICH, 2020)

The above stages have typically been evaluated using three in vivo study types:

- fertility and early embryonic development (FEED) studies, which assess stages 1 and 2;
- embryo–fetal development (EFD) studies in two species, which assess stages 3 and 4; and
- pre- and postnatal development (PPND) studies, which assess stages 3 through 6 (ICH, 2020).

FEED studies aim to test for adverse effects of new drugs and biologics on both male and female fertility, as well as implantation and

development of the embryo. These studies are typically conducted in rodents, with treatment of the investigational product beginning before mating and continuing until after implantation of the embryo. EFD studies aim to detect adverse effects on the pregnant animal and survival and the development of the embryo and fetus following treatment of the investigational product upon embryo implantation until just prior to birth. These studies are typically conducted in both rodent and nonrodent species. PPND studies aim to detect adverse effects following exposure of the pregnant animal from implantation of the embryo through weaning in order to evaluate effects on the pregnant or lactating female and development of the offspring (ICH, 2020).

According to ICH, the risks to all stages (considered one complete life cycle—from conception in one generation through conception in the following generation) should be assessed unless the stage is not relevant to the intended population. The stages assessed in individual studies are at the discretion of the sponsor, but the timing of studies within the product development process is dependent on the intended study populations and phase of development. According to ICH, there are several key factors sponsors should consider when developing an overall integrated testing strategy to evaluate effects on reproduction and development. ICH notes sponsors should consider the target patient population and therapeutic indication for their investigational product, which may influence whether DART studies evaluating all stages of reproduction and development are warranted (see “Preventive and Therapeutic Vaccines for Infectious Diseases and Oncology Products” section below). Additionally, ICH further notes the timing for conducting specific DART assessments “should take into consideration the need for these data to support the safe use of the pharmaceutical in clinical trials or the intended patient population” (ICH, 2020).

The ICH M3(R2) “Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” further elaborates on the timing and conduct of DART studies based on the target patient population for a planned or proposed clinical trial, noting the following:

- Men can be included in Phase I and Phase II clinical trials before the conduct of a preclinical male fertility study since an evaluation of the male reproductive organs is performed as part of another preclinical toxicity study, called the repeated-dose toxicity study, which is required to initiate clinical trials of an investigational drug or biological product in humans. A preclinical male fertility study should be completed before initiation of large-scale or long-duration clinical trials (ICH, 2009a).
- Women not of childbearing potential can be included in clinical trials without DART studies if the relevant preclinical repeated-dose toxicity

studies, which include an evaluation of the female reproductive organs, have been conducted (ICH, 2009a).

- For women of childbearing potential (WOCBP), it is important to characterize and minimize the risk of unintentional exposure of the embryo or fetus, which can be achieved by conducting DART studies to characterize the risk of the drug and take appropriate precautions during exposure of WOCBP in clinical trials, or limit the risk by taking precautions to prevent pregnancy during clinical trials (ICH, 2009a).
 - In all ICH regions, including the United States, the European Union (EU), and Japan, WOCBP can be included in early clinical trials without DART studies in certain circumstances. Two examples of such circumstances provided in the guidance include intensive control of pregnancy risk over short duration (e.g., 2 weeks) clinical trials, and where there is a predominance of the disease in women and the objectives of the trial cannot be effectively met without the inclusion of WOCBP and there are sufficient precautions to prevent pregnancy during the trial (ICH, 2009a). Where appropriate preliminary DART data are available from two species and where precautions to prevent pregnancy in clinical trials are used:

inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing. This is based on the very low rate of pregnancy in controlled clinical trials of this size and duration, and the ability of adequately designed preliminary studies to detect most developmental toxicity findings that could raise concern for enrollment of WOCBP in clinical trials. The number of WOCBP and the duration of the study can be influenced by characteristics of the population that alter pregnancy rates (e.g., age, disease) (ICH, 2009a).
 - In the United States EFD studies can be deferred until the initiation of Phase III trials, the final phase of clinical research prior to submitting marketing applications, for WOCBP where there are precautions to prevent pregnancy in the trial. In the EU and Japan, for example, other than in the circumstances described above, definitive DART studies should be completed before exposure of WOCBP. In all ICH regions, WOCBP can be included in repeated-dose Phase I and Phase II trials before the conduct of a preclinical female fertility study where a preclinical repeated-dose toxicity study is performed. Nonclinical studies that specifically address female fertility should be completed to support inclusion of WOCBP in large-scale or long-duration clinical trials (ICH, 2009a).

- In all ICH regions, including the United States, the PPND study should be submitted for marketing approval (ICH, 2009a).
- Lastly, all preclinical female reproduction toxicity studies and standard genotoxicity tests should be completed before the inclusion of WOCBP not using highly effective birth control in any clinical trial (ICH, 2009a).
- Pregnant women should only be included in clinical trials after all preclinical female reproduction toxicity studies and standard genotoxicity studies have been conducted. Additionally, any safety data from previous human exposure should be evaluated prior to inclusion (ICH, 2009a).

In June 2023, FDA issued a final guidance entitled, “Nonclinical Evaluation of Immunotoxic Potential of Pharmaceuticals,” which is intended to assist sponsors in the nonclinical evaluation of the immunotoxic potential of drugs and biological products and provides expanded guidance to sponsors for approaches for assessing the effects of immunotoxicants on pregnancy and developmental immunotoxicity. The final guidance states that for pharmaceuticals that are not intended to affect the immune system, the risk for adverse effects on the maternal immune system that can affect implantation and gestation would typically be identified in nonclinical FEED and EFD studies and such studies would be considered adequate for assessing such risk. For pharmaceuticals that are intended to affect the immune system, FEED and EFD studies may be useful in characterizing similar risks; however, if the mechanism of action of the pharmaceutical is known to be incompatible with fertility or maintenance of pregnancy, it may be appropriate to assess the risk to implantation and pregnancy based on a weight-of-evidence approach. The final guidance also notes that FEED and EFD studies are not generally warranted for pharmaceuticals intended to treat patients with advanced cancer (FDA, 2023a).

Product-Specific Guidance—Preventive and Therapeutic Vaccines for Infectious Diseases

In February 2006, FDA published a final guidance, “Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications,” which sets forth recommendations for the assessment of developmental toxicity of preventive and therapeutic vaccines for infectious disease indicated for females of childbearing potential and pregnant individuals. In this guidance, FDA states the target population for vaccines often includes females of childbearing potential who may become pregnant during the vaccination period, and “Unless the vaccine is specifically indicated for maternal immunization, no studies are

conducted prior to product licensure to determine the vaccine’s safety in pregnant women” (FDA, 2006a). FDA goes on to further state:

Because pregnant women are usually excluded from clinical trials, data from developmental toxicity studies in animal models offer one approach to screen for potential developmental hazards. Studies in animal models may frequently present the only information available to draw conclusions regarding developmental risk to be included in the product labeling required under section 201.57(f)(6) in Title 21 Code of Federal Regulations. (§ 201.57(f)(6)) (FDA, 2006a)

FDA recommends sponsors consider conducting preclinical developmental toxicity studies for vaccines that are indicated or may have the potential to be indicated for immunization of pregnant women, as well as for vaccines indicated for adolescents and adults (FDA, 2006a). The final guidance describes the recommended timing for conducting preclinical developmental toxicity studies to support the inclusion of either pregnant individuals or WOCBP in clinical trials based on the vaccine’s intended indicated population as follows:

- **Maternal immunization:** For vaccines indicated specifically for immunization of pregnant women, sponsors should have nonclinical developmental toxicity study data available prior to the initiation of any clinical trial enrolling pregnant women (FDA, 2006a).
- **WOCBP:** For vaccines indicated for WOCBP, sponsors may include such subjects in clinical trials without having conducted nonclinical developmental toxicity studies prior to initiation, provided that appropriate precautions are taken by subjects enrolled in these trials to avoid vaccination during pregnancy (e.g., pregnancy testing, birth control). Developmental toxicity study data should be included with the BLA for the product regardless of whether such information was previously submitted with the IND (FDA, 2006a).
- **Males:** Males may be included in clinical trials in the absence of nonclinical male fertility studies, but such studies may be recommended for certain products in the future (FDA, 2006a).

FDA notes “The decision whether a developmental toxicity study needs to be performed should be made on a case-by-case basis taking into consideration historical use, product features, intended target population, and intended use” (FDA, 2006a).

Product-Specific Guidance—Oncology Products

In October 2019, FDA issued a final guidance, “Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations,”

which describes less stringent preclinical DART study considerations for most anticancer agents than for other diseases. Specifically, the final guidance states that while an EFD toxicity assessment is needed to support marketing applications for the treatment of patients with advanced malignancies, fertility and PPND studies are generally not warranted, but for pharmaceuticals used in certain adjuvant or neoadjuvant indications, fertility and PPND studies may be needed on a case-by-case basis and results could be submitted after approval (FDA, 2019a). ICH S9 “Nonclinical Evaluation for Anticancer Pharmaceuticals,” which was adopted by FDA as final guidance in 2010), expands on this principle and states that a fertility and early embryonic development study is not warranted to support clinical trials or a marketing application of pharmaceuticals intended for the treatment of patients with advanced cancer (ICH, 2009b).

Clinical Trials

Overview

FDA-regulated clinical trials involve the administration of an investigational prescription drug, biological product, or medical device to human subjects under an FDA-authorized IND for investigational drugs and biological products or an IDE application for medical devices and are conducted to assess the safety and efficacy of the new therapeutic or device for the treatment, prevention, or mitigation of a particular disease (21 CFR § 312.20; 21 CFR § 812.20). Such clinical trials must be conducted in accordance with good clinical practice requirements, which include the requirement that all trial subjects provide their informed consent in writing for their participation in any clinical trial as well as obtaining and maintaining institutional review board (IRB) approval for the clinical trial until completion (21 CFR Part 50; 21 CFR Part 56).

In the last 2 decades, FDA has issued a number of guidance documents related to the inclusion of pregnant and lactating women in clinical trials. FDA has been active in this area, repeatedly updating and refining its guidance for industry and approach since its initial 1977 guidance advising that nonpregnant WOCBP should be excluded from Phase I and early Phase II studies (FDA, 1977). This 1977 guidance was lifted in 1993 with the implementation of FDA’s final guidance, “Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” which recommended that analyses be performed to assess differences in drug action attributable to gender in controlled clinical trials and emphasized that, where appropriate, WOCBP should use contraception or abstinence while participating in early clinical trials (FDA, 1993).

Shortly thereafter, in 2000, FDA issued a final rule amending its “Clinical Hold Regulations for Products Intended for Life-Threatening Disease” promulgated at 21 CFR § 312.42 to allow FDA to place a clinical hold on clinical trials for the treatment of a serious or life-threatening disease if “women with reproductive potential” (or men) with the disease or condition being studied were excluded from a clinical trial solely because of risk or potential risk of reproductive or developmental toxicity from use of the investigational drug or biological product (FDA, 2000a). One comment to the proposed rule was received, stating that “pregnant women have the same right to make informed decisions about their own treatment as other women with reproductive potential” and concluded by recommending that the proposed regulation also apply if pregnant women are excluded from clinical trials for life-threatening diseases. FDA responded that it did not intend the phrase “women with reproductive potential” to include pregnant women (and this clarity was added to the regulations), and that it did not question pregnant women’s ability to provide informed consent. However, FDA noted there is “increased complexity in conducting clinical trials with pregnant women because of their changing physiology. FDA will continue to explore this issue in other forums” (FDA, 2000b).

Inclusion of Pregnant Women in Clinical Trials

FDA-regulated clinical trials that include pregnant women must conform to all applicable FDA regulations, including those related to human subject protections (21 CFR Part 50 [informed consent]; 21 CFR Part 56 [IRBs]). In addition, if the trial is supported or conducted by the U.S. Department of Health and Human Services (HHS), then the federal regulations found in 45 CFR Part 46 may also apply, which would include compliance with subpart B, “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.” FDA regulations do not contain a section similar to 45 CFR Part 46, subpart B; however, FDA recommends that these requirements be satisfied and has referred to the requirements of subpart B in certain of its own guidance documents for FDA-regulated clinical trials (outlined below) (FDA, 2018a).

Where appropriate, such as when sponsors may enroll WOCBP in clinical trials evaluating their investigational products, FDA requires a statement in the informed consent form that the investigational product or procedure may involve risks to the study subject, or to the embryo or fetus, which are currently unforeseeable (21 CFR § 50.25(b)(1)). Under FDA’s final guidance issued in August 2023, “Informed Consent Guidance for IRBs, Clinical Investigators, and Sponsors,” FDA explains that if long-term preclinical safety studies are not completed, the informed consent process should explain that researchers have not completed such studies

that may identify potential unforeseeable risks (e.g., carcinogenicity or teratogenicity studies), including risks to the embryo or fetus if the study subject is or becomes pregnant (FDA, 2023b).

For sponsors planning on including pregnant women in clinical trials of their investigational prescription drug, biological product, or medical device, FDA recommends that sponsors be prepared to discuss such plans with the appropriate FDA review division early in the development phase, and such discussions should involve FDA experts in bioethics and maternal health (FDA, 2018a, 2013a).

FDA's 2004 final guidance, "Pharmacokinetics in Pregnancy, Study Design, Data Analysis, and Impact on Dosing and Labeling," provides specific recommendations for designing and conducting pharmacokinetic studies (PK) and pharmacodynamic (PD) studies in pregnant women and lays out a framework to stimulate further study and research to assist in rational therapeutics for pregnant patients. Acknowledging that (1) pregnant women are "actively excluded" from clinical trials, (2) data in product labels regarding PK and dose adjustments during pregnancy rarely provide information for appropriate prescribing in pregnancy, and (3) there has been a significant amount of pharmacological research conducted to improve the quality and quantity of data available for other altered physiologic states (e.g., patients with renal and hepatic disease) and subpopulations (e.g., pediatric patients), FDA states "The need for PK/PD studies in pregnancy is no less than for these populations, nor is the need for the development of therapeutic treatments for pregnant women" (FDA, 2004). This guidance specifies that pregnant women may be involved in PK studies if the following conditions are met (45 CFR subpart B, § 46.204):

1. Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and
2. The risk to the fetus is not greater than minimal, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means (FDA, 2004).

Additionally, FDA's final guidance recommends that PK studies be conducted in pregnant women in any of the following situations:

1. The drug is known to be prescribed in or used by pregnant women (especially in the second and third trimesters) (FDA, 2004).
2. It is a new drug or indication, if there is anticipated or actual use of the drug in pregnancy (FDA, 2004).

3. Use is expected to be rare, but the consequences of uninformed dosages are great (e.g., narrow therapeutic range drugs, cancer chemotherapy) (FDA, 2004).
4. Pregnancy is likely to alter significantly the PK of a drug (e.g., renally excreted drug) and any of the above apply (FDA, 2004).

FDA guidance provides that PK studies in pregnant women are not recommended if the drug is not used in pregnant women or the drug has known or highly suspect fetal risk. FDA further states in this guidance:

Although PK studies in pregnancy can be considered in Phase III development programs depending on anticipated use in pregnancy and the results of reproductive toxicity studies, FDA anticipates that most PK studies in pregnant women will occur in the postmarketing period and will be conducted using pregnant women who have already been prescribed the drug as therapy by their own physician. (FDA, 2004)

FDA's draft guidance, "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials," provides the most expansive current guidance to industry on how and when to include pregnant women in clinical trials for drugs and biological products. This guidance discusses both the scientific and ethical issues that sponsors should address when considering the inclusion of pregnant women in clinical trials (FDA, 2018a).

FDA recommends sponsors consider including an ethicist in planning their drug development programs because of the complex ethical issues involved when including pregnant women in their clinical trials. If an IRB regularly reviews research involving pregnant women, the IRB must consider including one or more individuals who are knowledgeable about and experienced in working with such subjects (21 CFR § 56.107(a)), and IRBs are required to determine that additional safeguards are included in the trial to protect the rights and welfare of subjects who are pregnant (21 CFR § 56.111(b)) (FDA, 2018a). FDA does not appear to have expanded on, either through regulation or guidance, what these "additional safeguards" may be in the context of research involving pregnant women.

This 2018 guidance provides that pregnant women may be enrolled in clinical trials that involve greater than minimal risk to the fetuses. When a trial offers the potential for direct clinical benefit to the enrolled pregnant women and/or their fetuses, it can be acceptable to expose a fetus to greater than minimal risk. FDA provides examples of when such exposure would be acceptable, which include when a trial offers a needed but otherwise unavailable therapy or when a drug or biological product being studied reduces the risk of acquiring a serious health condition (FDA, 2018a).

Importantly, FDA explicitly states in this 2018 guidance that FDA considers it ethically justifiable to include pregnant women with a disease

or medical condition requiring treatment in clinical trials under the following circumstances:

- For FDA-approved drugs being studied in the postmarketing setting, it is justifiable to include pregnant women with the disease or medical condition when: (1) adequate nonclinical studies (including DART studies) have been completed, (2) there is an established safety database in nonpregnant women from clinical trials or preliminary safety data from the medical literature and/or other sources regarding use in pregnant women, and (3) either efficacy cannot be extrapolated and/or safety cannot be assessed by other study methods (FDA, 2018a).
- For investigational drugs and biological products (regardless of the indication), it is justifiable to include pregnant women with the disease or medical condition when: (1) there have been adequate nonclinical studies completed, and (2) the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or the fetus that is not otherwise available outside of the research setting or cannot be obtained by any other means (FDA, 2018a).
- For a woman who becomes pregnant while already enrolled in a clinical trial, her continued inclusion and treatment with the investigational therapy is justified when the risks and benefits have been evaluated post unblinding and counseling and the pregnant participant completes a second informed consent process that includes the additional risk–benefit considerations given the pregnancy. If a woman becomes pregnant while enrolled in a clinical trial and fetal exposure to the investigational therapy has already occurred, the woman should be allowed to continue on the investigational therapy if the potential benefits of continued treatment for the woman outweigh the risks of ongoing fetal exposure to the investigational therapy, the risks of discontinuing maternal therapy, and/or the risks of exposing the fetus to additional drugs if placed on an alternative therapy. Regardless of whether the woman continues in the trial, FDA states that it is important to collect and report the pregnancy outcome (FDA, 2018a).

According to FDA’s draft guidance for drug developers, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products,” pre-IND and later clinical-stage meetings between FDA and sponsors can include discussion of trial populations as well as design plans (FDA, 2017). Additionally, for developers of medical device products, FDA’s final guidance, “Requests for Feedback and Meetings for Medical

Device Submissions: The Q-Submission Program,” provides a similar opportunity for interaction between sponsors and FDA on matters involving study design and population plans (FDA, 2023c). However, FDA notes in its medical device draft guidance:

Resource constraints do not permit FDA to prepare or design particular study plans. If a submitter would like FDA’s feedback on a protocol, they should submit a proposed outline, with a rationale for the chosen approach.

For more productive feedback, we recommend that the submitter include specific questions about their protocol. Without directed questions, FDA’s feedback may be more general in nature and not provide adequate specifics on the area of interest. (FDA, 2023c)

As such, in both cases, the nature of information exchange from FDA to the sponsor is generally framed for sponsors as reactive feedback on what a sponsor submits to or asks of FDA rather than a proactive inquiry by FDA of the sponsor to help proactively recommend to sponsors the best design for a particular clinical trial program. As a result, the possibility for a proactive recommendation by FDA to include pregnant women in clinical trials may be limited to occasions where a sponsor has directly placed a question or trial design before FDA that outlines plans to include pregnant women in a clinical trial. However, other than FDA’s resource constraints, we are not aware of any reason FDA would be prohibited under its current authorities from proactively discussing the inclusion of pregnant women in clinical trial programs that sponsors submit for FDA review and feedback.

When pregnant women are enrolled in a clinical trial, FDA’s draft guidance, “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials,” provides that data collection elements should include (at a minimum): (1) gestational age at enrollment; (2) gestational timing and duration of drug exposure; and (3) pregnancy outcomes including adverse maternal, fetal and neonatal events. Further, the draft guidance states while all clinical trials require monitoring, clinical trials that involve pregnant women should include a data monitoring plan that includes members with relative specialty and perinatal expertise to permit ongoing recognition and evaluation of safety concerns that arise during the course of the trial (FDA, 2018a).

The draft guidance also states that there may be situations where it would be appropriate to stop a randomized, controlled clinical trial that is enrolling pregnant women, such as when an appropriately planned interim analysis demonstrates superior efficacy of the control or active comparator arm, or when there are documented serious maternal or fetal adverse events that can be reasonably attributed to drug exposure and are

deemed to exceed the potential benefits of drug treatment (FDA, 2018a). We did not identify any analyses or other reports, either by FDA or third parties, evaluating the effect of FDA's 2018 guidance on industry's inclusion of pregnant women in clinical trials.

In 2019, FDA updated its draft guidance, "Clinical Lactation Studies: Considerations for Study Design," which provides recommendations for sponsors conducting pre- or postmarketing clinical lactation studies. The draft guidance clarifies that while FDA has required lactation studies under section 505(o)(3) of the FD&C Act under certain circumstances to inform breastfeeding with drug use recommendations included in the "Lactation" subsection of labeling, the draft guidance states that FDA "is considering additional circumstances in which lactation studies may be required" (FDA, 2019b).

FDA's clinical lactation studies guidance encourages sponsors to consider conducting clinical lactation studies even when not required, such as when a drug under review for approval is expected to be used by women of reproductive age, use of a drug in lactating women becomes evident after approval, the sponsor is seeking a new indication for an approved drug that provides evidence of use or anticipated use of the drug by lactating women, and when marketed medications are commonly used by women of reproductive age (FDA, 2019b).

Inclusion of Lactating Women in Clinical Trials

Similar to clinical trials involving pregnant women, FDA-regulated clinical trials involving lactating women must conform to all applicable FDA regulations. However, FDA has recommended, through its draft guidance on clinical lactation studies, that sponsors should consider the following additional ethical considerations for clinical lactation studies:

- In the postapproval setting, it is ethically acceptable to enroll a woman in a clinical trial of an approved drug where the woman has already made a decision to take the drug (as a part of her standard of care) while breastfeeding and allow the woman to continue breastfeeding while taking the drug in the clinical trial (FDA, 2019b).
- In the research setting, FDA's draft guidance states:

Where a woman who is currently breastfeeding starts an investigational drug [or biological product] for a disorder or condition, breastfeeding must be discontinued for the duration of the study because the risks of the exposure to the drug [or biological product] in the breastfeeding infant may outweigh the benefits. The potential drug exposure of a breastfeeding infant must be considered a research risk (and offers no clinical benefit to the infant). (FDA, 2019b)

However, it is acceptable to enroll breastfeeding women who are participating in a clinical trial of an investigational drug or biological product in clinical lactation studies if the breastfeeding woman agrees to temporarily pump and discard milk to avoid exposing the infant to the investigational product. The length of time that the milk will need to be discarded should be specified in the clinical trial protocol and will vary depending on factors such as the half-life of the investigational product (FDA, 2019b).

- In a research setting “where a healthy woman who is currently breastfeeding volunteers for a clinical lactation study, breastfeeding must be discontinued for the duration of the study so that an infant is not exposed to the investigational drug [or biological product]” (FDA, 2019b).

As noted above with respect to the inclusion of pregnant women in clinical trials, the same FDA guidances on formal meetings between the sponsors and FDA are relevant in providing an opportunity for FDA feedback on the inclusion of lactating women in clinical trials of prescription products. As noted above, because formal meetings are generally structured for FDA to provide reactive feedback in response to information and questions that a sponsor submits, the possibility for FDA feedback on the inclusion of lactating women in clinical trials may be limited to instances where a sponsor has directly sought such feedback in the questions it has submitted to FDA or where feedback is sought from FDA on the study population that includes lactating women. Again, other than FDA’s resource constraints, we are not aware of any reason FDA would be prohibited under its current authorities from proactively discussing the inclusion of lactating women in clinical trial programs that sponsors submit for FDA review and feedback.

Recent Efforts Relating to Increasing Diversity in Clinical Trials

FDA’s most recent efforts in this space relate to increasing diversity in clinical trials. In 2020, FDA issued a final guidance, “Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs,” which provides recommended approaches that sponsors of clinical trials intended to support an NDA or a BLA can take to increase enrollment of underrepresented populations in clinical trials. This guidance encourages sponsors to consider various trial designs and methodologies to help facilitate the enrollment of a broader population in the clinical trial, but FDA recognizes that certain exclusions are appropriate when necessary to help protect individuals, such as pregnant and lactating women who are “frequently excluded from clinical trials when there is inadequate information to assess the risk to the fetus or

infant” (FDA, 2020a). The final guidance includes several recommendations for increasing diversity in clinical trials, but the only recommendation relating to the inclusion of pregnant and lactating women is for sponsors to consider including PK sampling to establish dosing for women who become pregnant during a trial “when it is possible for continued participation with sufficient assurances of safety, and if the risks to the participant and fetus of continued trial participation are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be expected to result.” Over time, this may provide important information on drug metabolism during pregnancy and across trimesters (FDA, 2020a).

In 2022, FDA published its draft guidance, “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials,” which builds on its 2020 final guidance and advises sponsors to seek diversity in clinical trial enrollment beyond populations defined by race and ethnicity, and to include pregnancy and lactation status as underrepresented populations. This guidance further states “Some individuals from these groups have often been underrepresented in medical product development, and FDA considers their representation in clinical trials and studies to be a priority,” (referring to enrollment of women, and pregnant or lactating women) (FDA, 2022a). FDA encourages sponsors to submit race and ethnicity diversity plans for their clinical trials that ensure adequate participation of these underrepresented populations to provide important information pertaining to medical product safety and effectiveness for product labeling (FDA, 2022a).

Under the Food and Drug Omnibus Reform Act of 2022 (FDORA), sponsors of prescription investigational drugs, biological products, and medical devices will be required, unless waived by FDA, to submit a diversity action plan for all Phase III clinical trials, or as appropriate, another pivotal study conducted under an IND or IDE, in support of a marketing application. Under FDORA, these plans must be submitted no later than when sponsors submit their Phase III or other pivotal trial protocol, and FDA has the authority to modify the plan or waive the requirement for the plan in certain circumstances (such as if conducting the trial in accordance with a diversity action plan would otherwise be impracticable). FDORA requires FDA to issue new draft guidance or update existing draft guidance within 12 months of enactment of FDORA (FDORA, 2022).

Building on FDA’s 2022 draft diversity guidance, FDA published a draft guidance in August 2023 titled, “Postmarketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products.” The draft guidance reemphasizes the

importance of including patient populations in clinical trials that are historically underrepresented in clinical research (e.g., populations based on race, ethnicity, sex, and age), and FDA notes that efforts should be made, both in the pre- and postmarket settings, to include other underrepresented populations, including those based on pregnancy status and lactation status (FDA, 2023d).

Congress, through Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), created ClinicalTrials.gov to “increase the availability of information to the public” and to “communicate the risks and benefits of drugs [and devices]” in order to “help patients, providers, and investigators learn new information and make more informed health care decisions” (FDAAA, 2007). Using ClinicalTrials.gov, we attempted to evaluate current uptake by industry of FDA’s recommendations and the effect of required diversity action plans by researching the number of clinical trials that have enrolled or are currently enrolling adult pregnant and lactating women. Our research results on ClinicalTrials.gov identified 719 clinical trials that were initiated between January 1, 2022, and August 1, 2023, that were interventional (i.e., involved a drug, biological product, or device), funded by industry (as opposed to a U.S. federal agency, individual, or university), enrolled or were enrolling adult female participants (including healthy volunteers), and were early Phase I, II, III, or IV trials that had trial sites in the United States. Owing to the limitations of the search functionality, any search of *pregnant* or *lactating* (or variations of these terms) under the eligibility criteria section of ClinicalTrials.gov identified clinical trials where *pregnant* or *lactating* (or variations of these terms) were listed as *either* an inclusion or exclusion criteria. Additionally, owing to the variability of terms used by sponsors in describing the eligibility criteria for their clinical trials (as there are no enforced formatting rules or guidelines), the search results on ClinicalTrials.gov could not be refined to those clinical trials that affirmatively enrolled or were enrolling pregnant and lactating women. As a result, there is currently no effective research tool or database we are aware of to measure the effect of FDA’s recommendations and required diversity action plans on increasing research enrollment opportunities for pregnant and lactating women.

Review and Approval

Overview

Following completion of the necessary preclinical tests and clinical trials, the results of the preclinical tests and clinical trials, together with detailed information relating to the product’s chemistry, manufacturing, controls, and proposed labeling, among other things, are submitted to

FDA as part of an NDA, in the case of drugs, and a BLA, in the case of biological products, requesting approval to market the product for one or more indications.

In September 2011, FDA issued a final guidance titled, “Reproductive and Developmental Toxicities—Integrating Study Results to Assess Concerns,” which is intended to describe an approach for applicants of NDAs and BLAs to estimating possible human developmental or reproductive risks associated with drug or biological product exposure when a non-clinical finding of toxicity has been identified but definitive human data are unavailable to help ensure a consistent review by FDA review staff. FDA notes that the approach presented in the final guidance is used when there is a toxicity finding and involves the integration and consideration of a variety of nonclinical information, including reproductive toxicology, general toxicology, and toxicokinetic and PK information; however, “Available clinical information to evaluate a drug’s potential to increase the risk of an adverse developmental or reproductive outcome in humans should be evaluated separately and, when definitive, can supersede any nonclinical findings” (FDA, 2011a).

The final guidance defines two broad toxicity categories—reproductive (i.e., structural and functional alterations that affect reproductive competence in sexually mature male and females) and developmental (i.e., adverse effects on the developing organism that result from exposure prior to conception, during the prenatal period, or postnatally up to the time of sexual maturity)—and further categorizes eight classes of possible effects that may be considered during the nonclinical data integration and assessment:

- Classes of reproductive toxicity:
 - a. Male fertility
 - b. Female fertility
 - c. Parturition (toxicities affecting labor and delivery)
 - d. Lactation
- Classes of developmental toxicity:
 - a. Mortality
 - b. Dysmorphogenesis (structural abnormalities)
 - c. Alterations to growth
 - d. Functional impairment (FDA, 2011a)

The final guidance goes on to describe a data integration process that is divided into three components: (1) all nonclinical toxicology and pharmacokinetic datasets; (2) nonclinical datasets without evidence of reproductive or developmental toxicity; and (3) nonclinical datasets with positive indications of reproductive or developmental toxicity (FDA,

2011a). See Appendix E-1 for FDA's schematics on these data integration approaches.

FDA states in the final guidance that recommendations for wording in labeling should be based on the results of the integration and assessment process and specific considerations leading to a risk conclusion should be provided, which may later be helpful in discussions between FDA reviewers and NDA and BLA applicants (FDA, 2011a).

According to a 2021 article published by members of FDA's Division of Urology, Obstetrics & Gynecology within FDA's Center for Drug Evaluation and Research in the *American Journal of Obstetrics and Gynecology*, there are three recognized categories of prescription product use by pregnant and lactating women:

1. The prescription product is approved specifically for an obstetrical or lactation-specific indication(s);
2. The prescription product is prescribed for an approved indication(s) in adults, which includes pregnant and lactating women (unless specifically contraindicated or there are warnings against such use), but the indication is not specific to an obstetrical, gynecological, or lactation-specific condition; and
3. The prescription product is prescribed during pregnancy or lactation off-label, where even if used for an approved indication(s), the product labeling expressly disallows or warns of product risks if administered during pregnancy or lactation and/or recommends against such use (Wesley et al., 2021). Note that under FDA's labeling regulations for prescription drug and biological products, FDA may require addition of a "specific warning" to a product's label "if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard" (21 CFR § 201.57(c)(6)(i)).

Prescription Products Approved Specifically for Obstetrical, Gynecological, and Lactation Indications

As of 2021, according to Wesley et al., there are only nine drugs that have been approved by FDA for marketing in the United States specifically for obstetrical indications, noting that this list does not appear to include products approved for all postpartum conditions, such as postpartum depression (Wesley et al., 2021).

1. Methergine (methylergonovine maleate) was approved in 1946 for use following delivery of the placenta, for routine management of uterine atony, hemorrhage, and subinvolution of the uterus,

- and for control of uterine hemorrhage during the second stage of labor following the delivery of the anterior shoulder. Methergine's current labeling states it is used for the prevention and control of postpartum hemorrhage (Edison Therapeutics LLC, 2012).
2. Syntocinon (oxytocin nasal spray) is a supplemental NDA approved in 1968 for "initial milk let-down." Syntocinon has been discontinued from marketing (Wesley et al., 2021).
 3. Pitocin (oxytocin for intramuscular or intravenous administration) was approved in 1980 for the "initiation or improvement of uterine contractions and to control postpartum bleeding" (Par Sterile Products, 2021).
 4. Yutopar (ritodrine) was approved in 1980 to control premature labor. Yutopar has since been discontinued from marketing (Wesley et al., 2021).
 5. Prepidil (dinoprostone) was approved in 1992 "for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction" (Pfizer, 2017).
 6. Cervidil (dinoprostone) was approved in 1995 "for the initiation and/or continuation of cervical ripening in patients at or near term in whom there is a medical or obstetrical indication for the induction of labor" (Ferring Pharmaceuticals, Inc., 2020).
 7. Magnesium sulfate was approved in 1995 for the "prevention and control of seizures in preeclampsia and eclampsia, respectively" (Hospira, Inc., 2019).
 8. Makena (hydroxyprogesterone caproate) was granted accelerated approval in 2011 "to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth." FDA withdrew the approval of Makena in April 2023 after the sponsor's postmarketing confirmatory study failed to verify clinical benefit (further discussed below) (Amag Pharmaceuticals, 2018).
 9. Diclegis (doxylamine succinate and pyridoxine hydrochloride) was approved in 2014 "for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management" (Duchesnay Inc., 2022). The combination of doxylamine and pyridoxine had been marketed as Bendectin in the 1950s and approved for the same indication until its discontinuation in 1983 (Wesley et al., 2021).

FDA maintains a list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness, and this list was last amended on December 11, 2018 (21 CFR § 216.24). Of the products on this list, diethylstilbestrol had been prescribed to pregnant

women between 1940 and 1971 to prevent miscarriage, premature labor, and related complications of pregnancy, and was later used to stop lactation, but approval of the product was withdrawn based on its carcinogenic risks (NIH, 2015). Bromocriptine mesylate had been approved for preventing postpartum lactation, but FDA withdrew approval after concluding that “bromocriptine mesylate’s risks of hypertension, seizures, and cardiovascular accidents outweighed the product’s marginal benefit in preventing postpartum lactation, which can be suppressed without risk by using more conservative, nonpharmacological treatments” (FDA, 2018b).

More recently, on April 6, 2023, FDA announced the withdrawal of its approval of Makena (hydroxyprogesterone caproate injection) (FDA, 2023e). The product had been approved under the accelerated approval pathway to reduce the risk of preterm birth in women pregnant with one baby who had a history of spontaneous preterm birth. As a condition of accelerated approval, Makena’s sponsor was required to conduct a confirmatory clinical trial to verify the predicted clinical benefit. However, this trial did not show improvement to the health of infants born to mothers treated with Makena and did not show that Makena reduced the risk of preterm birth, leading ultimately to its withdrawal from the market. There are known risks associated with Makena, and FDA determined that, given that effectiveness had not been shown, no level of risk was justified (FDA, 2023f).

A sponsor may elect to withdraw its own approved product from the U.S. market for a number of reasons, including commercial viability considerations unrelated to safety or effectiveness. Although FDA regularly updates the database of Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) to reflect drug and biological products that have been discontinued, there is not a central repository of voluntarily withdrawn products that is searchable by indication (i.e., to determine the number of pregnancy-specific products that have been withdrawn).

For devices, FDA’s regulations at 21 CFR Part 884 set forth the classification of devices intended for obstetrical and gynecological use, including:

- Diagnostic devices used to evaluate the fetus: amniotic fluid sampler, fetal blood sampler and transabdominal amnioscope
- Devices used for monitoring pregnant patients: obstetric data analyzer, obstetric-gynecologic ultrasonic imager, fetal cardiac monitor, and fetal electroencephalographic monitor
- Obstetrical and gynecological prosthetic devices: cervical drain, vaginal pessary, fallopian tube prosthesis, and vaginal stent
- Obstetric, gynecological, and fetal surgical devices: obstetric forceps and fetal head elevator

- Obstetrical and gynecological therapeutic devices: abdominal decompression chamber and perineal heater
- Various assisted reproduction devices (21 CFR Part 884)

Devices classified under these regulations include Class I (general controls), Class II (special controls), and Class III (premarket approval) devices. Each regulation corresponds with a product code (or product codes) established by FDA, and there are numerous products listed under these codes in FDA's device premarket approval and premarket notification databases.

In our searches of FDA's labeling database, we did not identify any prescription drugs or biological products specifically indicated to treat lactating women; each of the labels returned in these searches with references to "lactation" or "lactating" referenced a contraindication, warning, or other safety information related to lactation.

With respect to prescription medical devices, FDA has regulations for nonpowered breast pumps (21 CFR § 884.5150), which are Class I devices, and powered breast pumps (21 CFR § 884.5160), which are Class II devices. There are 167 products listed in FDA's device database under the HGX product code for powered breast pumps.

Prescription Products Prescribed for Approved Indications in Adults

Where a prescription product is approved for use in adults, the product is also approved for use in pregnant or lactating women unless there is a clear contraindication or warnings against the product's use during pregnancy or lactation. This is because pregnant (and lactating) women are considered a subpopulation of the adult population and therefore, absent a contraindication or warnings against the product's use during pregnancy (or lactation), these women are not excluded from the approved population if a drug or biological product is approved for use in adults (FDA, 2018c). An example of such an approved product that is labeled to permit use during pregnancy or lactation with the opportunity to join a pregnancy exposure registry to monitor outcomes from use during pregnancy is Dupixent (dupilumab), which is indicated for several uses including asthma and moderate-to-severe atopic dermatitis (Regeneron Pharmaceuticals, Inc., 2023).

Prescription Products Prescribed for Unapproved Uses During Pregnancy or Lactation

When a prescription product is used in a manner not specified in FDA's approved labeling, such use is considered off-label. Although

manufacturers of prescription products are not permitted to promote their products for off-label uses, FDA has noted that “once FDA approves a drug, health care providers generally may prescribe the drug for an unapproved use when they judge that it is medically necessary for their patient” (FDA, 2018d). In the case of prescription products for use during pregnancy or lactation, a product would be considered as prescribed for an off-label use where the labeling of the product expressly contraindicates or warns against known risks of use during pregnancy or lactation. An example of such a drug would be Zocor (simvastatin), which is indicated for several uses including as an adjunct to diet to reduce low-density lipoprotein cholesterol (Organon LLC, 2023). The labeling for Zocor expressly warns of fetal harm and recommends against use during lactation.

Labeling

Overview

Labeling for prescription medicines is required for all FDA-approved prescription drugs and biological products and contains a summary of the essential scientific information needed for the safe and effective use of the medicine (21 USC § 355).

FDA’s Physician Labeling Rule (the PLR), effective June 30, 2006, established FDA’s first system for ensuring that product labeling identified the risks prescription drugs posed to pregnant women, fetuses, and breastfeeding infants (FDA, 2006b). The PLR established five pregnancy categories for sponsors to communicate the risks of adverse pregnancy outcomes posed by their products based on the information obtained during research and development:

1. Pregnancy category A was intended for products that had failed to demonstrate a risk to the fetus in the first trimester through adequate and well-controlled studies in pregnant women or animals (FDA, 2006b).
2. Pregnancy category B was intended for products in which animal reproduction studies had shown an adverse effect but further studies in pregnant women had failed to demonstrate a risk to the fetus within the first trimester (FDA, 2006b).
3. Pregnancy category C was reserved for products in which animal reproduction studies had shown an adverse effect on the fetus, without adequate and well-controlled studies in pregnant women, but where benefits from use of the product in pregnant women might be acceptable despite potential risks (FDA, 2006b).

4. Pregnancy category D was intended for products that had positive evidence of human fetal risk based on adverse reaction data but had a perceived positive benefit–risk ratio for pregnant women who used the product (FDA, 2006b).
5. Pregnancy category X was reserved for products with demonstrated fetal abnormalities or had exhibited positive evidence of fetal risk based on adverse event data from preclinical tests or clinical trials, and where the risk of product use by pregnant women clearly outweighed any perceived benefits (FDA, 2006b).

In addition to a “Pregnancy” section on a drug label, the PLR further required inclusion of information regarding labor and delivery and lactation. A “Labor and Delivery” section had to include information on the effects of the drug on the mother and the fetus, the duration of labor and delivery, and the effect of the drug on the future growth, development, and maturation of the child. For the “Lactation” section of the label there had to be a “Nursing Mothers” subsection that included information about the excretion of the drug in human milk and its effects on the nursing infant. Additionally, a description of any pertinent adverse effects observed in animal offspring had to be included in the labeling (FDA, 2006b).

In 2014, FDA amended its regulations through the finalization of its Pregnancy and Lactation Labeling Rule (the PLLR) (initially proposed in 2008), which created a consistent format for providing information about the risks and benefits of prescription drug and biological product use during pregnancy and lactation and by females and males of reproductive potential. For human prescription drug and biological products approved on or after June 30, 2001 (including products with labeling approved under the PLR), the PLLR required that the pregnancy categories A, B, C, D, and X be removed from the product labeling, and that the labeling be revised to include a summary of the risks of using a drug during pregnancy (Section 8.1 of the labeling), lactation (Section 8.2 of the labeling), and for females and males of reproductive potential (Section 8.3 of the labeling), a discussion of the data supporting that summary, and relevant information to provide health care providers and patients with the best available evidence to make informed decisions regarding the use of medications during pregnancy and lactation. Under the PLLR, all new prescription drugs and biological products approved by FDA after June 30, 2015, must comply with the PLLR (FDA, 2018e).

- Under the PLLR, Pregnancy Section 8.1 of a drug or biological product’s labeling must include summaries of the pertinent available evidence providing information about the safety and use of the drug in pregnancy. Information on pregnancy exposure

registries, if available, including how to enroll or to obtain more information must also be included. A risk summary is also required that provides, as a narrative summary, a statement of background risk if there are data demonstrating that the product is systemically absorbed. This includes a separate summary based on human data, animal data, and pharmacology data that describes the risk of adverse developmental outcomes if such data are available. The risk summary section should also include background information regarding the risk of major birth defects and miscarriage in the U.S. general population. A “Clinical Considerations” section must detail disease-associated maternal and/or embryo–fetal risk, relevant dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal and neonatal adverse reactions, and labor and delivery information. Lastly, a “Data” section must describe the information and data used for the “Risk Summary” and “Clinical Considerations” sections (FDA, 2018e).

- Under the PLLR, “Lactation” section 8.2 of a drug or biological product’s labeling must include a “Risk Summary” that summarizes the information about the presence of the drug or biological product in human milk, the effects of the drug or biological product and its active metabolite(s) on a breastfed child and the effects of the drug or biological product and its active metabolite(s) on milk production and excretion. In addition, there must be a risk–benefit statement that provides a framework for health care providers and lactating women to use when considering the benefits of breastfeeding to the mother and infant and the mother’s need for treatment and benefits versus potential risks to the infant. Additionally, the “Risk Summary” should provide a risk–benefit statement if data demonstrate the therapeutic agent is systemically absorbed unless breastfeeding is contraindicated. Similar to the “Pregnancy” section, a “Clinical Considerations” section must include specific clinical information regarding ways to minimize exposure to the breastfed child and available interventions for monitoring or mitigating adverse reactions. A “Data” section must also describe the data that are the basis for the “Risk Summary” and “Clinical Considerations” sections (FDA, 2018e).
- Under the PLLR, a “Females and Males of Reproductive Potential” section 8.3 is required to be included in a drug or biological product’s labeling when “pregnancy testing and/or contraception is required or recommended before, during, or after drug therapy and/or when there are human and/or animal data that suggest drug-associated fertility effects” (FDA, 2018e). Specific information about pregnancy testing, contraception, and infertility are also required, if applicable (FDA, 2018e).

Additionally, the PLLR requires statements acknowledging when data on any of the labeling requirements are not available or do not establish the presence or absence of drug- or vaccine-associated risk. Lastly, the PLLR requires the label to be updated to include clinically relevant information as it becomes available to prevent the label from becoming “inaccurate, false, or misleading” (FDA, 2018e).

FDA also issued draft guidance in December 2014, which it revised in July 2020, titled “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format,” which provides detailed information for preparing the respective “Pregnancy,” “Lactation,” and “Females and Males of Reproductive Potential” subsections under the “Use in Specific Populations” section of a prescription drug or biological product’s full prescribing information. The document provides general guidance on revising labeling and formatting as well as guidance for writing information within each specified PLLR subsection to help ensure that the narrative format provides meaningful information to health care providers. Under the PLLR, applicants must develop labeling to include the “Pregnancy,” “Lactation,” and “Females and Males of Reproductive Potential” sections, and if a particular section of the PLLR required labeling information is not applicable, an applicant must submit information to FDA providing the rationale and justification for omitting subsections, headings, subheadings, or specific information required under the PLLR. The draft guidance reiterates that applicants are expected to update labeling as new information becomes available, including whether other sections of the labeling need to be updated (FDA, 2020b).

A study published in the *Journal of the American Medical Association Network Open* in 2020 indicated that, in a cross-sectional labeling analysis of 290 newly FDA-approved medications from January 2010 to December 2019 (focusing the review on new molecular entities and therapeutic products):

All products submitted after June 20, 2015, were in compliance with the Pregnancy and Lactation Labeling Rule (PLLR); however, of those submitted between 2010 and 2015, 32.6 percent were not in PLLR format by the designated date of June 30, 2019. Human data on pregnancy and lactation were available in less than 20 percent of new product labeling. (Byrne et al., 2020)

Only 31 of the products included human data related to pregnancy, but 260 products had animal data associated with pregnancy. When examining data related to lactation, 141 of the products had no data regarding medication safety. Only 8 products had human data related to lactation, but 143 had animal data related to lactation. The study also found that not all labels of products approved prior to the PLLR implementation

date had been converted to the PLLR format (and over one-third of these submissions still needed to be converted), therefore limiting the initial intent of the PLLR conversion to provide pregnancy and lactation risk summaries from available animal studies and clinical trials to aid health care providers when making prescribing decisions for pregnant or lactating patients (Byrne et al., 2020).

We conducted a search of FDA's labeling database (FDALabel), which is a web-based application used to perform customizable searches of human prescription drug and biological products, over-the-counter, and animal drug labeling documents. The source of FDALabel's data is FDA's Structured Product Labeling archive, which stores labeling documents submitted by manufacturers. As of February 21, 2023, there were 53,188 human prescription drug and biological product labeling in the database (FDA, 2023g). We identified approximately 4,500 prescription drug and biological product labeling results that include a "Section 8.1 Pregnancy" section as required by the PLLR. Of those, we identified approximately 980 prescription drug and biological product labeling results that include the phrase "human data" in "Section 8.1 Pregnancy" of the product labeling. Under the requirements of the PLLR as described above, a separate summary of human data that describes the risk of adverse developmental outcomes must be included if such data are available. Of the approximately 980 prescription drug and biological product labeling results described above, approximately 50 of them include the phrase, "There are no human data on the use of [Product] in pregnant women." Approximately 25 prescription drug and biological product labeling results included the phrase "pharmacokinetic" in "Section 8.1 Pregnancy" of the product labeling. Approximately 530 prescription drug and biological product labeling results include the phrase "pregnancy registry" in "Section 8.1 Pregnancy" of the product labeling.

Notable Comments to the PLLR

Following the publication of the proposed PLLR in 2008, FDA received comments from industry requesting that FDA clarify its expectations for the process and timing of updating the "Pregnancy" and "Lactation" subsections of labeling after new data become available, and the quantity and quality of data that necessitates a labeling update. FDA responded with the following:

Because studies are not usually conducted in pregnant women prior to approval, most of the data regarding pregnancy and lactation will be collected in the postmarketing setting. Accordingly, in order that a drug product does not become misbranded, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading. Applicants are responsible for

following the medical literature and also for updating labeling as new published and unpublished data become available. (FDA, 2018e)

Some industry commentators were concerned about whether the PLLR was a way for FDA to impose mandates on sponsors to include pregnant women in research. For example, one industry commentator requested that FDA determine whether or not there would be a requirement for “additional activities from sponsors to collect such information [on pregnant women] and what tools [FDA] envision[ed] for such activities” (Novartis, 2008). The commentator noted:

Whenever possible, animal data should be placed in context through label statements that (a) address the general applicability of the data to humans and (b) assess the overall strength of the data for a drug based on a comparison of results between treated and control animals and (c) discuss the consistency, or lack thereof, in results across animal species. (Novartis, 2008)

In the commentator’s opinion, this would eliminate manufacturer liability in instances where only animal data is used in labeling (Novartis, 2008).

On the other hand, some commentators wanted FDA to use the PLLR as a vehicle to mandate inclusion of pregnant women in clinical trials. An industry commentator noted that there was currently no regulatory requirement for sponsors to conduct clinical trials in pregnant women during the clinical development phase. This commentator further noted that it was industry practice to exclude pregnant women from preapproval clinical studies. Additionally, as there was no requirement that sponsors create pregnancy registries for any approved products (unless mandated by FDA as a postmarketing requirement; see “Postapproval Studies and Surveillance” section below), the commentator made the suggestion that in order to “encourage companies to more voluntarily and proactively obtain such information, FDA could request authority to provide incentives to industry to perform these studies and to collect more human data for labeling purposes” (Amylin, 2008). One comment further expounded upon this idea by stating that sponsors are unlikely to pursue pregnancy studies on their own and FDA is the only agency that could make pre- or postapproval studies with pregnant women a more common element of the approval and labeling processes (Public Citizen, 2008). A nonprofit organization focused on reproductive health also suggested FDA should use the new labeling guidelines as a way to encourage prescription drug sponsors to conduct studies on pregnant women (RHTP, 2008).

Incentives for industry to conduct studies with pregnant women were provided in commentary by health care providers, who suggested a 2- to 3-year extension of the drug’s patent life span similar to pediatric labeling.

Their primary concern was that without an incentive, most labels would be written with the default statement that there was no human data on pregnancy and lactation and that animal studies would continue to be the standard (Manson and Kimmel, 2008).

Updates to Labeling Based on New Information

An application holder may submit a labeling supplement for FDA review at any time, but FDA has the authority to require (and, if necessary, order) labeling changes should it become aware of new safety information that FDA believes should be included in the product labeling (21 USC § 355(o)(4)). The term “new safety information” with respect to a drug, means:

information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 355(o)(3) of this title), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific information deemed appropriate by the Secretary about: (A) a serious risk or an unexpected serious risk associated with the use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the [REMS] was required, or since the last assessment of the approved [REMS] for the drug; or (B) the effectiveness of the approved [REMS] for the drug obtained since the last assessment of such strategy. (21 USC § 355-1(b)(3))

As such, FDA may learn of new safety information through submissions from an application holder or through FDA’s own monitoring activities. For example, new safety information may emerge through FDA’s routine monitoring of its adverse event reporting systems; safety-related data in NDA, BLA, or IND submissions; inspections and investigations; medical literature submitted by application holders or external stakeholders (or identified by FDA staff); periodic safety updates or postmarket data submission from application holders; communications with foreign regulatory authorities regarding their analysis of adverse events associated with drugs approved in their countries; and meta-analyses of safety information, or new analyses of previously submitted information (FDA, 2013b).

According to FDA’s final guidance titled, “Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act,” FDA:

expects that information that meets the standard of new safety information that should be included in labeling, thereby triggering safety labeling changes under section 505(o)(4), generally will include, but is

not limited to, information that would be described in new or revised language in the following sections of the prescribing information:

- Boxed warnings
- Contraindications
- Warnings and precautions
- Drug interactions
- Adverse reactions (FDA, 2013b)

Once FDA determines that new safety information should be included in product labeling, FDA can send a safety labeling change notification letter to the application holder, after which the application holder can either submit a supplement with proposed labeling changes to reflect the new safety information, or notify FDA that it does not believe the labeling change is warranted, and provide a rebuttal detailing why the applicant believes the changes are not necessary. FDA and the application holder can work to reach consensus on the proposed labeling, but if consensus cannot be reached, FDA can order the application holder to make the specified labeling changes (FDA, 2013b). If the application holder neither submits a supplement within 15 calendar days of the date of FDA's order, nor initiates dispute resolution within 5 calendar days of the date of FDA's order, the application holder will be in violation of section 505(o)(4) of the FD&C Act, which may result in enforcement actions (21 USC § 355(o)(4)(G); FDA, 2013b). Enforcement actions could include one or more of the following:

- Charges for introducing or delivering into interstate commerce a drug where the application holder is in violation of section 505(o)(1) of the FD&C Act (FDA, 2013b)
- Misbranding charges where the application holder for the drug violates safety labeling change requirements (FDA, 2013b; 21 USC § 352(z))
- Civil monetary penalties where the application holder violates safety labeling change requirements. These penalties increase if the violation continues more than 30 days after FDA notifies the application holder of the violation (FDA, 2013b; 21 USC § 333(f)(4)(A)).

Importantly, an application holder is expected to monitor the use of an approved product to facilitate submission of postmarket safety reports and required annual reports. For example, an annual report for an approved drug product should include (in addition to published clinical trials of a product in a given year), "reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant" (21 CFR § 314.81(b)(2)(vi)(a)). As noted above,

FDA may take this information into account when evaluating whether changes to a product's label are needed (FDA, 2013b).

In April 2005, FDA issued a final guidance titled, "Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies," which aims to help FDA staff evaluate human fetal outcome data generated after medical product exposures during pregnancies in order to develop product labeling that is useful to medical care providers who provide care to patients who are pregnant or planning pregnancy (see also "Labeling" section below). FDA acknowledges in this guidance that little may be known about a drug's or biological product's teratogenic potential at the time of submission of the application and that postmarketing surveillance of the product's use in pregnancy is critical to the detection of drug-induced fetal effects. Therefore, FDA states "It is important that FDA and sponsors routinely review all available data on drug exposure during pregnancy and work together to provide up-to-date product labeling that reflects what is known and not known about human fetal risk or lack of risk" (FDA, 2005).

In this reviewer guidance, FDA identifies seven factors for reviewers to consider when presented with human pregnancy data and faced with making a determination of whether and how the data should be included in product labeling:

- The first factor is background prevalence of adverse pregnancy outcomes. The final guidance states "a reviewer should consider whether there are enough exposures to demonstrate an increase in risk if such a risk exists. Any studies reporting no increase in the background rate of birth defects in exposed pregnancies can be viewed with skepticism unless the power of the study to detect or rule out a stated level of risk is also included" (FDA, 2005).
- The second factor is combined versus individual rates of birth defects, whereby reviewers should evaluate the overall rate of birth defects in the study population as well as rates of individual birth defects (FDA, 2005).
- The third factor is major versus minor birth defects (FDA, 2005).
- The fourth factor is timing of exposure, whereby reviewers should consider the timing and duration of exposure and their relationship to windows of developmental sensitivity as well as identify the frame of reference for the reported gestational age (i.e., time since conception) since:

Knowledge of the sensitive period for human target organ development facilitates optimal data interpretation. . . . However, as a

practical matter the sensitive period for exposure to a drug, if there is one, is usually unknown. In situations where no clear toxicity has been identified, it is common to globally assess risk from first trimester exposures because that is the time of organogenesis. (FDA, 2005)

The final guidance goes on to state that there are two potential sources of error in using this global approach:

(1) sensitive time periods for a particular problem may make up a small portion of the first trimester; and (2) drug-induced fetal toxicities may not be limited to the first trimester or may produce abnormalities during more than one exposure window. The final guidance also states that evaluating the time of exposure is also important when assessing the power of a study (FDA, 2005).

- The fifth factor is intensity of exposure, whereby reviewers should consider the ability of a drug to cross the placenta and reach the fetus, including which stage of gestation such exposure occurs (FDA, 2005).
- The sixth factor is variability of response, whereby reviewers should consider that people differ in their responses to specific medications, for example:

Exposures during a sensitive time period known to increase the incidence of adverse pregnancy outcomes may do so only in a fraction of those infants exposed. . . . Although the effects of known teratogens are generally predictable from a population perspective, the nature and extent of effects are not necessarily possible to predict in individual patients under similar conditions. . . . Because of [maternal and fetal genotypic] variability, assessment of a drug's potential teratogenesis ought to consider the full range of birth defects. It is important to remember that the concept of variability extends not only to toxic responses, but also to baseline attributes of populations. (FDA, 2005)

- The seventh factor is class effects, whereby:

Understanding the structure/activity relationships and pharmacological mode of action of a class of therapeutic agents in some circumstances can provide a prediction of the possible safety and efficacy of a new agent. However, such knowledge is generally not predictive of human teratogenesis. . . . While the introduction of a new product from a class of drugs with known human teratogenicity will solicit heightened scrutiny, it cannot be assumed that the product will also be teratogenic. Similar findings in the animal studies for the new product compared to the class would be cause for more concern, whereas clean animal data would lessen the concern. (FDA, 2005)

With regard to the sources of human data on gestational drug exposures that FDA reviewers may receive, the final guidance states that “[information] on human gestational exposures will emerge during the postmarketing phase for virtually all drug products” and will come from a variety of sources, but “[f]or the most part, data will not be derived from controlled clinical trials, but from observational studies” (FDA, 2005). Human pregnancy outcome data is sent to FDA either directly by voluntary reports or via the sponsors as required by federal regulation (see “Postapproval Studies and Surveillance” section below). The final guidance states

No single methodology can delineate the complete spectrum of adverse outcomes associated with prenatal exposure to a drug. Therefore, it is important to consider information from all available postmarketing surveillance sources to optimize detection and characterization of the reproductive effects of prenatal drug exposure. (FDA, 2005)

FDA acknowledges that the most common types of data on human gestational exposures will likely come from case reports and epidemiological studies, including prospective cohort studies and pregnancy exposure registries, and retrospective birth defect registries and case control studies (FDA, 2005).

When conducting an overall assessment of postmarketing human data to determine whether there is an association between a gestational drug exposure and adverse pregnancy outcome, the final guidance states reviewers should consider evidence from all sources, including human data from case reports, epidemiology studies, and animal data, to determine the strength of the relationship. FDA further identifies six commonly used assessments that may be helpful to reviewers to apply to any accumulated data to test the possibility that an association is causal:

1. Strength of the association,
2. Consistency of the association,
3. Specificity of the association,
4. Appropriate timing,
5. Dose–response relationship, and
6. Biological plausibility (FDA, 2005).

Postapproval Studies and Surveillance

Overview

Any prescription drugs, biological products or medical devices manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by FDA, including, among other things, requirements related to manufacturing, record-keeping, reporting of adverse

experiences, periodic reporting, product sampling and distribution, and complying with FDA promotion and advertising requirements, among others.

As a condition of approval of an NDA for a drug or a BLA for a biological product, FDA may impose PMCs, PMRs, and/or a REMS program on the sponsor. The goal of PMCs, PMRs, and REMS programs are to better inform a “product’s safety, efficacy, or optimal use” (FDA, 2016). PMCs involve preclinical studies or clinical trials that a sponsor agrees to conduct postapproval but are not legally required to be performed (FDA, 2016).

PMRs, however, are preclinical studies or clinical trials that a sponsor is required to conduct in order to comply with certain laws and/or regulations, or to assess a known serious risk related to the use of the drug, assess signals of serious risk related to the use of a drug, or identify an unexpected serious risk when available data indicate the potential for a serious risk (FDA, 2016). FDA may also impose PMRs on manufacturers of certain Class II or Class III medical devices that are approved by FDA. Examples of such requirements can include tracking systems; reporting of device malfunctions, serious injuries, or deaths; and registering the establishments where devices are produced or distributed (21 USC § 360i; FDA, 2022b).

As of July 28, 2023, there were approximately 2,300 PMRs and PMCs listed in FDA’s PMR and PMC database. Of these, around 2.6 percent involved preclinical developmental and reproductive toxicity (“DART”) studies, around 0.2 percent involved clinical trials in pregnant individuals, around 1.2 percent involved clinical lactation studies, and around 8 percent involved a pregnancy registry or other prospective and/or retrospective observational study in pregnant and lactating individuals (FDA, 2023h). On FDA’s public list of pregnancy exposure registries, which is a list of registries that are posted based on a sponsor or investigator’s *request* to list their registry, there are 169 pregnancy exposure registries listed (FDA, 2023i).

FDAAA created section 505-l of the FD&C Act, which established FDA’s REMS authority. REMS programs are designed to reinforce medication use behaviors and actions that support the safe use of medication and ensure that the benefits of a drug or biological product outweigh its risks. If a drug raises serious safety concerns, FDA has the authority to require a sponsor to participate in a REMS program, either as part of the product’s approval, or postapproval if the drug or biological product later raises a safety issue (FDAAA, 2007; 21 USC § 355-l).

Current REMS Programs Specific to the Use of the Product in Pregnant or Lactating Women

As of August 25, 2023, there are 67 approved active REMS programs, 13 of which contain goals that are intended to, among other things,

mitigate risk of embryo–fetal toxicities in pregnant or lactating patients (FDA, 2023j). These 13 REMS programs are listed below:

1. Ambrisentan Shared System REMS (“The goal of the Ambrisentan REMS Program is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan.”): Ambrisentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) (FDA, Ambrisentan Shared System REMS).
2. Bosentan Shared System REMS (“The goal of the Bosentan REMS Program is to mitigate the risk of hepatotoxicity and embryo–fetal toxicity associated with bosentan.”): Bosentan is an endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) (FDA, Bosentan Shared System REMS).
3. Filspari REMS (“The goal of the FILSPARI REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with FILSPARI.”): Filspari is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression, generally a urine protein-to-creatinine ratio ≥ 1.5 g/g (FDA, Filspari REMS).
4. Isotretinoin iPLEDGE Shared System REMS (“The goals of the isotretinoin risk evaluation and mitigation strategy are . . . to prevent fetal exposure to isotretinoin.”): Isotretinoin is a retinoid indicated for the treatment of severe recalcitrant nodular acne in nonpregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater (FDA, Isotretinoin iPLEDGE Shared System REMS).
5. Lenalidomide Shared System REMS (“The goals of the Lenalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to lenalidomide.”): Lenalidomide is a thalidomide analogue indicated for the treatment of adult patients with multiple myeloma (MM) in combination with dexamethasone; MM, as a maintenance following autologous hematopoietic stem cell transplantation; transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities; mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib; previously treated follicular lymphoma (FL) in combination with a rituximab product; and previously treated marginal zone lymphoma (MZL) in combination with a rituximab product (FDA, Lenalidomide Shared System REMS).

6. Macitentan Shared System REMS (“The goal of the Macitentan REMS Program is to mitigate the risk of embryo-fetal toxicity associated with macitentan.”): Macitentan is an endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) (FDA, Macitentan Shared System REMS).
7. Mycophenolate and PC-Mycophenolate Shared System REMS (“The goal of the Mycophenolate REMS is to mitigate the risk of embryo-fetal toxicity associated with use of mycophenolate during pregnancy.”): Mycophenolate is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart, or liver transplants, in combination with other immunosuppressants (FDA, Mycophenolate Shared System REMS; FDA, PC-Mycophenolate Shared System REMS).
8. Pomalidomide Shared System REMS (“The goals of the Pomalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to pomalidomide.”): Pomalidomide is a thalidomide analogue indicated for the treatment of adult patients: in combination with dexamethasone, for patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy; and with AIDS-related Kaposi sarcoma (KS) after failure of highly active antiretroviral therapy (HAART) or in patients with KS who are HIV-negative (FDA, Pomalidomide Shared System REMS).
9. Pomalyst REMS (“The goals of the POMALYST risk evaluation and mitigation strategy are as follows . . . to prevent the risk of embryo-fetal exposure to pomalyst.”): Pomalyst is a thalidomide analogue indicated for the treatment of adult patients: in combination with dexamethasone, for patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy; and with AIDS-related KS after failure of HAART or in patients with KS who are HIV-negative (FDA, Pomalyst REMS).
10. Qsymia REMS (“To inform certified pharmacies and patients of reproductive potential about: (1) the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy; (2) the importance of pregnancy prevention for patients of reproductive potential receiving Qsymia; (3) the need to discontinue Qsymia immediately if pregnancy occurs.”): Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release,

- an antiepileptic drug, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a certain initial body mass index (FDA, Qsymia REMS).
11. Riociguat Shared System REMS (“The goal of the Riociguat REMS Program is to mitigate the risk of embryo-fetal toxicity associated with riociguat.”): Riociguat is a guanylate cyclase stimulator indicated for the treatment of adults with: persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (“CTEPH”) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class; and PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening (FDA, Riociguat Shared System REMS).
 12. Thalidomide Shared System REMS (“The goals of the Thalidomide REMS are as follows . . . to prevent the risk of embryo-fetal exposure to thalidomide.”): Thalidomide is approved: in combination with dexamethasone for the treatment of patients with newly diagnosed MM; for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL); and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence (FDA, Thalidomide Shared System REMS).
 13. Thalomid REMS (“The goals of the THALOMID REMS are as follows . . . to prevent the risk of embryo-fetal exposure to thalomid.”): Thalomid is approved: in combination with dexamethasone for the treatment of patients with newly diagnosed MM; for the acute treatment of the cutaneous manifestations of moderate to severe ENL; and as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence (FDA, Thalomid REMS).

As noted above, these REMS programs are designed (in part) to prevent or mitigate embryo-fetal toxicities, but we note that other products that are subject to REMS *may* be used by pregnant and lactating patients. For example, the Brixadi (buprenorphine) REMS program is intended “to mitigate the risk of serious harm or death that could result from intravenous self-administration” of the product, but the product, which is indicated to treat moderate to severe opioid use disorder, may be used by pregnant patients (and the prescribing information includes information on the “[l]imited data from trials, observational studies, case series, and case reports” in pregnant patients) (FDA, Brixadi REMS).

Section 505(o)(3) of the FD&C Act, added by section 901 of FDAAA, provides FDA with broad authority to require postapproval studies or

clinical trials (FDAAA, 2007; 21 USC § 355(o)(3)). The FDAAA expanded upon what postmarketing studies and clinical trials FDA can require in order to: (1) assess a known serious risk related to the use of the drug; (2) assess signals of serious risk related to the use of the drug; and (3) identify an unexpected serious risk when available data indicate the potential for a serious risk (21 USC § 355(o)(3)(B)). FDA also has the authority to require postapproval studies or trials if FDA becomes aware of new safety information (21 USC § 355(o)(3)(E)(ii); FDA, 2011b). Such authority has been interpreted to include FDA's ability to set the parameters for a sponsor's postapproval study or trial, which may include instructions on how to design the protocol, what type of population should be included, and for what indication (FDA, 2011b).

Additionally, sponsors of approved products may voluntarily conduct postapproval studies to gain additional experience from the treatment of patients in the therapeutic indication.

Section 505(o)(3)(E)(ii) of the FD&C Act requires a sponsor to "periodically report," and in any event at least annually, on the status of preclinical studies or clinical trials, regardless of whether or not the sponsor was required to conduct a clinical trial or study as part of a PMR, or voluntarily chose to do so. A sponsor must report on the preclinical study or clinical trial's status to comply with this section (21 USC § 355(o)(3)(E)(ii)). The status report should include a timetable for completion of specific target goals, along with a status update of the study or trial (FDA, 2011b).

Postapproval Studies in Pregnant and Lactating Women

In FDA's 2011 Guidance, "Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act," FDA describes examples of PMRs and PMCs. PMRs may include "observational pharmacoepidemiologic studies designed to assess a serious risk associated with a drug exposure or to quantify risk or evaluate factors that affect the risk of serious toxicity, such as drug dose, timing of exposure, or patient characteristics" (FDA, 2011b). In general, such a study would involve a thoughtfully designed protocol and include a control cohort, although some studies may not include a control group if there is reason not to. Data for these types of studies may come from institutional electronic medical records, health insurance claim data, as well as registries. These observational studies may aid in (1) assessing the relative risk of a serious adverse event occurring with use of a particular drug or biologic; (2) identifying certain risk factors that make the occurrence of a serious adverse event among a particular patient population more likely; and (3) obtaining data over a significant period of time, which may help identify rare serious adverse events, among others.

In regard to pregnancy, such observational studies may aid in informing pregnancy or child outcomes following drug exposure, in comparison to a group that has not been exposed to the drug product. Other types of PMRs may include meta-analyses to evaluate a safety endpoint and clinical trials with a safety endpoint designed to analyze a serious risk raised by FDA under section 505(o)(3). Examples of PMCs may include drug and biologic quality studies, pharmacoepidemiologic studies reviewing the natural progression of a disease, surveillance and observational pharmacoepidemiologic studies, or clinical trials involving a primary endpoint that seeks to further evaluate a drug or biological product's efficacy (FDA, 2011b).

Pregnancy Registries

Pregnancy registries are a common study design that may be used to collect safety data in the postapproval setting and can help inform decision making among health care providers and their patients (FDA, 2019c). Pregnancy registries involve the prospective enrollment of women who have been exposed to a drug or biologic product and are usually followed through delivery and postpartum to evaluate the effects of exposure on the newborn. Such registries may be led by a sponsor, government, or institution; they may be product specific or cover multiple products, can involve multiple institutions and other collaborative stakeholders, and include more than one country. They are an important and potentially powerful safety tool to use owing to their ability to prospectively capture detailed patient data over a long period of time. Because of difficulties in enrollment and retention, however, pregnancy registry data often may not carry enough statistical power to assess safety of drug and biological products during pregnancy (FDA, 2019c).

In 2002, FDA released its final guidance, "Establishing Pregnancy Exposure Registries," that provided recommendations on how to design and implement a pregnancy registry in the postapproval setting (FDA, 2002). Although it has since been withdrawn with the release of FDA's 2019 draft guidance (discussed below), the 2002 guidance laid a foundation for sponsors to more seriously consider the regular use of well-designed pregnancy registries in the postapproval setting (FDA, 2019c).

In 2014, FDA held a 2-day public meeting that included experts studying birth defects from academia, professional organizations, industry, and patient advocacy groups to discuss the development, design, and conduct of pregnancy registries, along with other types of study designs (FDA, 2019d). FDA also performed a review of pregnancy registries, as well as assessed pregnancy registry design methods and issues related to recruitment and retention (Gelperin et al., 2017).

Additionally, the 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to address the unmet needs of pregnant and lactating women in research, and in its 2018 report outlined recommendations to the secretary of HHS and Congress. PRGLAC's report noted that, to date, one of the most commonly used methods for obtaining information on pregnant women was through registries. In its recommendations, it noted that in order to maximize registry potential, the creation of a "user-friendly website for registry listing, developing registry standards with common data elements, and facilitating transparency and access to the data" was needed (PRGLAC Task Force, 2018; NIH, 2022). The report also emphasized that the design of disease- or condition-focused registries, as opposed to product-specific registries, would provide for more streamlined data collection into a single registry, but acknowledged that this would "require substantial coordination, collaboration, and funding mechanisms" (PRGLAC Task Force, 2018).

In 2019, FDA issued its draft guidance, "Postapproval Pregnancy Safety Studies." This guidance describes three postapproval approaches (which can be addressed in any one or combination of approaches) to use in assessing drug safety in pregnant women who have been exposed to drug or biological products: (1) pharmacovigilance; (2) pregnancy registries; and (3) complementary data sources. Based on an approach's strengths and limitations and application to a particular drug or biological product, FDA may recommend or require a particular approach or combination of approaches to be used by a sponsor for such drug or biologic product (FDA, 2019c).

A pharmacovigilance approach includes a compilation of data on adverse pregnancy outcomes in order to detect a safety signal or signals. Exposure reports received by the sponsor and FDA, medical literature involving case studies, and other specific case reports may be used as sources. As noted in the draft guidance, factors to evaluate may include: (1) a detailed synopsis of the adverse pregnancy outcome; (2) a complete account of the exposure, inclusive of the medication, its dose, frequency, route of administration, and duration; (3) the gestational age at which the exposure likely occurred; (4) a comprehensive medical history of the mother, including use of concomitant medications, supplements, etc.; and (5) any exposures to known or suspected environmental teratogens. In general, however, pharmacovigilance may not allow for a "conclusive assessment," often because of underreporting and a lack of complete information from such exposure reports, which may only capture a specific point in time (FDA, 2019c).

A large portion of the draft guidance discusses recommendations for the design and implementation of pregnancy registries. Pregnant women who have been exposed to a drug or biological product may volunteer to

participate in a registry during their pregnancy and be followed through delivery. Because a pregnancy registry follows a pregnant woman over the course of her pregnancy and following the birth of her newborn, it may allow assessment of “maternal, obstetrical, fetal, and infant outcomes, including pregnancies that do not result in a live birth” (FDA, 2019c). Although the draft guidance points to a number of strengths in using pregnancy registries, it highlights some limitations for such registries: (1) analyses may result in insufficient statistical power in detecting associations for rare pregnancy outcomes; (2) registries may not address more specific or rare congenital malformations, congenital anomalies, and birth defects; (3) there may be significant challenges to recruitment and retention; and (4) the data from a registry alone may not be able to adequately assess the safety of a drug or biological product taken during pregnancy (FDA, 2019c).

FDA may also require that a lactation study to capture potential drug exposure data during breastfeeding be added to a pregnancy registry. Such lactation data is gathered to assess the safety of drugs and biological products that women may take while breastfeeding, which may or may not have been taken while pregnant (FDA, 2019c).

The draft guidance also provides detailed recommendations for registry design, as well as advice on how to address recruitment and retention challenges. Importantly, FDA notes that sponsors should collaborate with health care providers, as well as with other potential stakeholders, such as existing registries, patient advocacy groups, medical societies, and other relevant organizations to help promote pregnancy registry recruitment. FDA also notes that sponsors may wish to collaborate with other sponsors on multiproduct registries and find other ways to create collaborative registries that reduce the administrative burden and potential duplicity of information in such registries. Although FDA actively lists pregnancy registries on its Office of Women’s Health website, it does not “endorse any registry and is not responsible for the content of registries listed on [FDA’s] web page” (FDA, 2019c).

FDA also provides guidance on the potential duration of a pregnancy registry. FDA recommends that pregnancy registries collect data until there is sufficient information gathered to meet the registry’s scientific objective(s), or conversely, if the registry is not able to collect sufficient information to meet its objectives, it should consider discontinuing the registry. If other, more efficient methods become available that allow the sponsor to obtain the same information that was being gathered from the registry, FDA notes the sponsor should also consider disbanding the registry (FDA, 2019c).

Finally, FDA discusses complementary studies that may be used alongside pregnancy registries that may be conducted to address “specific effects”

of a drug or biological product during pregnancy. These studies may be retrospective in their design and use secondary data sources, such as electronic health records, population-based surveillance, and national registries or registers (FDA, 2019c).

Public comments to FDA's 2019 draft guidance from pharmaceutical industry organizations, women's health research societies and organizations, academia, and other stakeholders have generally commented that pregnancy registries were overly discussed in the 2019 draft guidance and did not provide enough guidance on alternative available methods. In particular, because pregnancy registries alone may not provide sufficient data, commentors noted that considerations for other study methods are equally important to address. In addition, some commentors asked that more specific recommendations on the data elements for pregnancy outcomes and common exposure information be implemented across publicly funded and privately sponsored pregnancy registries (PhRMA, 2019). One commentor also noted that the draft guidance was silent on paternal or male sexual partner exposure (Medications in Pregnancy and Lactation Special Interest Group, 2019). Another comment encouraged FDA to also consider premarket actions that could further include pregnant and lactating women in clinical trials, as opposed to being focused entirely on the postapproval setting (Society for Maternal-Fetal Medicine, 2019).

On September 18, 2023, FDA, together with the Duke-Margolis Center for Health Policy, hosted a public workshop titled, "Optimizing the Use of Postapproval Pregnancy Safety Studies," which included discussions of designs of postapproval pregnancy safety studies for drug and biological products and experiences with implementing such studies, as well as considerations for further development of a framework that describes how data from different types of postapproval pregnancy safety studies might optimally be used when it has been determined that such data should be collected (FDA, 2023k).

Other Initiatives

FDA's Sentinel Initiative, a multistakeholder and collaborative initiative that "aims to develop new ways to assess the safety of approved medical products" has also been assessing infant and maternal outcomes from use of drug and biologic products (FDA, 2023l). In 2019, FDA established the Sentinel Innovation Center and Community Building and Outreach Center that has sought to "find[] ways to extract and structure information from electronic health records," which may help address some of the concerns that commentors voiced to the 2019 draft guidance regarding difficulties in linking maternal and infant health records (FDA, 2023m). The Sentinel Initiative has a page dedicated to pregnancy on FDA's website, stating that "developing and refining methods to assess medical product utilization,

safety, and effectiveness during pregnancy is a focus of FDA’s Sentinel System” (FDA, 2023n). One such initiative is using a statistical data mining tool, known as TreeScan, to “assess maternal and infant outcomes, test signal identification methods in a pregnancy setting, and evaluate methods performance using older drugs with relatively well-characterized safety profiles” (FDA, 2023o). These research initiatives include mother–infant electronic health record linkage, validation of an algorithm to identify stillbirths, and an algorithm to identify the gestational age of live births, to name a few (FDA, 2023p,q,r).

In addition, FDA is continuing the development of the “FDA MyStudies App,” an open-source mobile application software designed to facilitate direct patient input of real-world data that can be linked to electronic health data, thereby supporting traditional clinical trials, observational studies, and registries (FDA, 2023s; FDA, 2018f). A pilot study was conducted by the Harvard Pilgrim Health Care Institute through the FDA Sentinel Initiative Catalyst program that used this app to help identify “medication exposures, other risk factors, and pregnancy outcomes” among women from the Kaiser Permanente Washington health system (FDA, 2023s; Wyner, et al., 2020).

As the Society for Women’s Health Research (SWHR) pointed out in its comment to the 2019 draft guidance, real-world evidence is another valuable method of data collection. The National Institutes of Health (NIH) created the PregSource research study, which was concluded on April 30, 2023, and will have data available by August 27, 2023 (NIH, 2023a). PregSource was a mobile app that allowed pregnant women to enter data, such as their weight, sleep, and mood (NIH, 2023b). SWHR noted in its comment that although this type of data may not evaluate medical treatments, collection of real-world evidence during pregnancy, which may include medications taken during pregnancy, is nevertheless important data to gather and should not be overlooked (SWHR, 2010).

CONSIDERATIONS AND OPPORTUNITIES FOR THE FUTURE

Based on our review of FDA’s authorities, guidance, and policies that are available on the development and commercialization of prescription products for use by pregnant and lactating women, we have identified the following discrete considerations and opportunities that, if implemented by FDA, may support regulatory initiatives relating to the development and commercialization of prescription products for use by pregnant and lactating women:

- Assess the effect of FDA’s 2018 draft guidance, “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials,”

which is intended to provide guidance to industry on how and when to include pregnant women in clinical trials for drugs and biological products.

- Continue to support inclusion of pregnant and lactating women in clinical trials through strengthened recommendations in new or updated clinical trial diversity-related guidances.
- Issue new or updated guidances relating to formal meetings with FDA to proactively inform sponsors that FDA meeting packages should address why pregnant and lactating women are either included or excluded in clinical trial design plans in order to support FDA meeting discussion or written feedback from FDA on sponsor inclusion or exclusion plans for these populations.
- Issue new or updated guidance or guidelines for IRBs reviewing and providing oversight for clinical trials involving pregnant and lactating women, specifically clarifying what is required by “additional safeguards” that must be included in clinical trials to protect the rights and welfare of subjects who are pregnant under 21 CFR § 56.111(b), which can be an impediment for sponsors, especially for those conducting multisite studies.
- Together with NIH, expand existing search result filtering functionalities within ClinicalTrials.gov, especially as it relates to eligibility criteria, to ensure pregnant and lactating women interested in identifying available clinical research opportunities that permit enrollment of pregnant and lactating women are able to efficiently locate such studies. Consideration should also be given to establishing a set of pregnancy- and lactation-specific terms that sponsors and investigators should use to describe their clinical trials, particularly with respect to the description of inclusion and exclusion criteria, when listing their clinical trials on ClinicalTrials.gov. For example, without a standardized set of descriptors (i.e., defining the eligible pregnancy population by gestational age or trimester), sponsors employ varying terms to describe the stage of pregnancy where such women are eligible, thereby making it challenging for pregnant women to identify clinical trials for which they may be eligible.
- Make publicly available statistics on PLLR compliance, including the percentage of approved prescription products with human clinical data supporting their PLLR-compliant product labeling.
- Issue new or updated safety labeling and/or PLLR labeling guidances to prospectively describe circumstances where the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of product labeling should be updated when new information becomes available where such failure could cause the labeling to become inaccurate, false, or misleading.

- Recommend, or by expansion of law, require that all sponsors or investigators who establish a pregnancy registry list such registry on FDA's List of Pregnancy Exposure Registries.
- By expansion of law, develop a new marketing exclusivity period that may be awarded to sponsors or application holders who obtain and submit human clinical data to FDA evaluating their prescription products in pregnant and lactating women.

REFERENCES

- 21 CFR Part 50, Protection of Human Subjects.
- 21 CFR § 50.25(b)(1), Elements of informed consent.
- 21 CFR Part 56, Institutional Review Boards.
- 21 CFR § 201.57(c)(6)(i), Specific requirements on content and format of labeling for human prescription drug and biological products.
- 21 CFR § 201.57(c)(9), Specific requirements on content and format of labeling for human prescription drug and biological products.
- 21 CFR § 216.24, Drug products withdrawn or removed from the market for reasons of safety or effectiveness.
- 21 CFR § 312.20, Requirements for an IND.
- 21 CFR § 312.23(a)(8), IND content and format.
- 21 CFR § 314.81(b)(2)(vi)(a), Other postmarketing reports.
- 21 CFR § 812.20, Applications.
- 21 CFR Part 884, Obstetrical and Gynecological Devices.
- 21 USC § 333(f)(4)(A), Violations related to devices.
- 21 USC § 352(z), Postmarket studies and clinical trials; new safety information in labeling.
- 21 USC § 355, New Drugs.
- 21 USC § 355(o)(3), Postmarket studies and clinical trials; labeling.
- 21 USC § 355(o)(3)(B), Postmarket studies and clinical trials; labeling.
- 21 USC § 355(o)(3)(E)(ii), Postmarket studies and clinical trials; labeling.
- 21 USC § 355(o)(4), Postmarket studies and clinical trials; labeling.
- 21 USC § 355(o)(4)(G), Postmarket studies and clinical trials; labeling.
- 21 USC § 355-1, Risk evaluation and mitigation strategies.
- 21 USC § 355-1(b)(3)), Risk evaluation and mitigation strategies.
- 21 USC § 360l, Postmarket surveillance.
- Amag Pharmaceuticals. 2018. *Makena (hydroxyprogesterone caproate) Package Insert*. www.accessdata.fda.gov/drugsatfda_docs/label/2018/021945s012lbl.pdf (accessed August 11, 2023).
- Amylin. 2008. *Amylin Pharmaceuticals Public Comment*. <https://www.regulations.gov/comment/FDA-2006-N-0515-0038> (accessed August 11, 2023).
- Byrne, J. J., A. M. Saucedo, and C. Y. Spong. 2020. Evaluation of drug labels following the 2015 pregnancy and lactation labeling rule. *JAMA Netw Open*. 3(8):e2015094. <https://doi.org/10.1001/jamanetworkopen.2020.15094>.
- Duchesnay Inc. 2022. *Diclegis (doxylamine succinate; pyridoxine hydrochloride) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021876s016lbl.pdf (accessed August 20, 2023).
- Edison Therapeutics LLC. 2012. *Methergine (methylethylergonovine maleate) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/006035s078lbl.pdf (accessed August 11, 2023).
- FDA (Food and Drug Administration). *Ambrisentan Shared Systems REMS*. <https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=ReMSDetails.page&REMS=396> (accessed August 11, 2023).

- FDA. *Bosentan Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=395> (accessed August 11, 2023).
- FDA. *Brixadi REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=418> (accessed August 11, 2023).
- FDA. *Filspari REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=416> (accessed August 11, 2023).
- FDA. *Isotretinoin iPLEDGE Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=24> (accessed August 11, 2023).
- FDA. *Lenalidomide Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=410> (accessed August 11, 2023).
- FDA. *Macitentan Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=407> (accessed August 11, 2023).
- FDA. *Mycophenolate Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=37> (accessed August 11, 2023).
- FDA. *PC-Mycophenolate Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=419> (accessed August 20, 2023).
- FDA. *Pomalidomide Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=404> (accessed August 11, 2023).
- FDA. *Pomalyst REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=41> (accessed August 11, 2023).
- FDA. *Qysmia REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=45> (accessed August 11, 2023).
- FDA. *Riociguat Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=414> (accessed August 11, 2023).
- FDA. *Thalidomide Shared System REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=417> (accessed August 11, 2023).
- FDA. *Thalomid REMS*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=58> (accessed August 11, 2023).
- FDA. 1977. Final guidance for industry on general considerations for the clinical evaluation of drugs.
- FDA. 1993. Final guidance on the study and evaluation of gender differences in the clinical evaluation of drugs.
- FDA. 2000a. Final rule on investigational new drug applications; amendment to clinical hold regulations for products for life-threatening diseases and conditions. *Federal Register* 65(106), 34963.
- FDA. 2000b. Final rule on investigational new drug applications; amendment to clinical hold regulations for products for life-threatening diseases and conditions. *Federal Register* 65(106), 34963, Comment 12 at 34965.
- FDA. 2002. Final guidance for industry on establishing pregnancy exposure registries.
- FDA. 2004. Draft guidance for industry on pharmacokinetics in pregnancy—Study design, data analysis, and impact on dosing and labeling.
- FDA. 2005. Final reviewer guidance for evaluating the risks of drug exposure in human pregnancies.
- FDA. 2006a. Final guidance for industry on considerations for developmental toxicity studies for preventive and therapeutic vaccines for infectious disease indications.
- FDA. 2006b. Final rule on requirements on content and format of labeling for human prescription drug and biological products. *Federal Register* 71(15), 3922.
- FDA. 2011a. Final guidance for industry on reproductive and developmental toxicities—Integrating study results to assess concerns.
- FDA. 2011b. Final guidance for industry on postmarketing studies and clinical trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act.

- FDA. 2013a. Final guidance for industry and FDA staff on design considerations for pivotal clinical investigations for medical devices.
- FDA. 2013b. Final guidance for industry on safety labeling changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act.
- FDA. 2016. *Postmarketing Requirements and Commitments: Introduction*. <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments> (accessed August 11, 2023).
- FDA. 2017. Draft guidance for industry on formal meetings between the FDA and sponsors or applicants of PDUFA products.
- FDA. 2018a. Draft guidance for industry on pregnant women: Scientific and ethical considerations for inclusion in clinical trials.
- FDA. 2018b. Final rule on list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. *Federal Register* 83(237), 63569.
- FDA. 2018c. *FDA Briefing Document for Risk Communication Advisory Committee Meeting March 5–6, 2018: Communicating Information about Risks in Pregnancy in Product Labeling for Patients and Providers to Make Informed Decisions about the Use of Drugs during Pregnancy*. <https://www.fda.gov/media/110905/download> (accessed August 18, 2023).
- FDA. 2018d. *Understanding Unapproved Use of Approved Drugs “Off Label.”* <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label> (accessed August 13, 2023).
- FDA. 2018e. Final rule on content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. *Federal Register* 79(233), 72063.
- FDA. 2018f. *The FDA MyStudies App: Patient Centered Outcomes Research Trust Fund Enabler for Distributed Clinical Trials and Real World Evidence Studies – Collection of Patient-provided Information Through a Mobile Device Application for Use in Comparative Effectiveness and Drug Safety Research*. <https://www.fda.gov/media/119835/download> (accessed August 24, 2023).
- FDA. 2019a. Final guidance for industry on oncology pharmaceuticals: Reproductive toxicity testing and labeling recommendations.
- FDA. 2019b. Draft guidance for industry on clinical lactation studies: Considerations for study design.
- FDA. 2019c. Draft guidance for industry on postapproval pregnancy safety studies.
- FDA. 2019d. Final rule on enrollment and re-certification of entities in the 340B drug pricing program. *Federal Register* 84(90), 20372.
- FDA. 2020a. Final guidance for industry on enhancing the diversity of clinical trial populations—Eligibility criteria, enrollment practices, and trial designs.
- FDA. 2020b. Draft guidance for industry pregnancy, lactation, and reproductive potential: Labeling for human prescription drug and biological products—Content and format.
- FDA. 2022a. Draft guidance for industry on diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials.
- FDA. 2022b. Final guidance for industry on postmarket surveillance under Section 522 of the federal Food, Drug, and Cosmetic Act.
- FDA. 2023a. Final guidance for industry on nonclinical evaluation of immunotoxicity potential of pharmaceuticals.
- FDA. 2023b. Final guidance for IRBs, clinical investigators, and sponsors on informed consent.
- FDA. 2023c. Final guidance for industry and FDA staff on requests for feedback and meetings for medical device submissions: The Q-submission program.
- FDA. 2023d. Draft guidance for industry on postmarketing approaches to obtain data on populations underrepresented in clinical trials for drugs and biological products.

- FDA. 2023e. *News and Events*. <https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena> (accessed August 11, 2023).
- FDA. 2023f. *Postmarket Drug Safety*. <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information> (accessed August 11, 2023).
- FDA. 2023g. *FDALabel: Full-Text Search of Drug Product Labeling*. <https://www.fda.gov/science-research/bioinformatics-tools/fdalabel-full-text-search-drug-product-labeling> (accessed August 24, 2023).
- FDA. 2023h. *Postmarketing Requirements and Commitments: Downloadable Database File*. <https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-downloadable-database-file> (accessed August 24, 2023).
- FDA. 2023i. *List of Pregnancy Exposure Registries*. <https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries> (accessed August 14, 2023).
- FDA. 2023j. *Approved Risk Evaluation and Mitigation Strategies (REMS)*. <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm> (accessed August 11, 2023).
- FDA. 2023k. Optimizing the use of postapproval pregnancy safety studies; public workshop; request for comments. *Federal Register* 88(158), 56025.
- FDA. 2023l. *About the FDA Sentinel Initiative*. <https://www.sentinelinitiative.org/about> (accessed August 14, 2023).
- FDA. 2023m. *History of the Sentinel Initiative*. <https://www.sentinelinitiative.org/about#history-of-the-sentinel-initiative> (accessed August 14, 2023).
- FDA. 2023n. *Pregnancy*. <https://www.sentinelinitiative.org/featured-topics/pregnancy> (accessed August 14, 2023).
- FDA. 2023o. *TreeScan Pregnancy*. <https://www.sentinelinitiative.org/methods-data-tools/methods/treescan-pregnancy> (accessed August 14, 2023).
- FDA. 2023p. *Methods, Data, & Tools; Pregnancy: Models*. <https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model/mother-infant-linkage-table> (accessed August 14, 2023).
- FDA. 2023q. *Methods, Data, & Tools; Pregnancy*. <https://www.sentinelinitiative.org/methods-data-tools/methods/identification-pregnant-women-sentinel-distributed-database-and> (accessed August 14, 2023).
- FDA. 2023r. *Methods, Data, & Tools; Pregnancy: Health Outcomes Interest*. <https://www.sentinelinitiative.org/methods-data-tools/health-outcomes-interest/validation-stillbirth-icd-10-cm> (accessed August 14, 2023).
- FDA. 2023s. *FDA Catalyst Projects*. <https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects/collection-patient-provided-information-through-mobile> (accessed August 14, 2023).
- FDAAA (Food and Drug Administration Amendments Act) of 2007, Public Law, 110th Cong., 1st sess. (September 27, 2007), 110-85.
- FDORA (Food and Drug Omnibus Reform Act), Public Law, 117th Cong., 2d sess. (December 29, 2022), 117-328.
- Ferring Pharmaceuticals, Inc. 2020. *Cervidil (dinoprostone) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020411Orig1s0311bl.pdf (accessed August 16, 2023).
- Gelperin, K., H. Hammad, K. Leishear, S. T. Bird, L. Taylor, C. Hampp, and L. Sahin. 2017. A systematic review of pregnancy exposure registries: Examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. *Pharmacoepidemiology & Drug Safety*, 26(2), 208–214. <https://doi.org/10.1002/pds.4150>.
- Hospira, Inc. 2019. *Magnesium Sulfate Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020488Orig1s0241bl.pdf (accessed August 16, 2023).

- ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). 2009a. M3(R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.
- ICH. 2009b. S9 Nonclinical evaluation for anticancer pharmaceuticals.
- ICH. 2020. S5(R3) Detection of reproductive and developmental toxicity for human pharmaceuticals.
- Manson, J. and C. Kimmel. 2008. *Drs. Jeanne Manson and Carole Kimmel Public Comment*. <https://www.regulations.gov/comment/FDA-2006-N-0515-0051> (accessed August 14, 2023).
- Medications in Pregnant and Lactation Special Interest Group. 2019. *Medications in Pregnancy and Lactation Special Interest Group Public Comment*. <https://www.regulations.gov/comment/FDA-2018-D-4693-0012> (accessed August 14, 2023).
- NIH (National Institutes of Health). 2015. *National Cancer Institute*. <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones> (accessed August 11, 2023).
- NIH. 2022. *PRGLAC*. <https://www.nichd.nih.gov/about/advisory/PRGLAC> (accessed August 14, 2023).
- NIH. 2023a. *PregSource*. <https://pregsource.nih.gov/index.html> (accessed August 14, 2023).
- NIH. 2023b. *PregSource*. <https://www.nichd.nih.gov/newsroom/news/121321-PregSource> (accessed August 14, 2023).
- Novartis. 2008. *Novartis Public Comment*. <https://www.regulations.gov/comment/FDA-2006-N-0515-0039> (accessed August 11, 2023).
- Organon LLC. 2023. *Zocor (simvastatin) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019766s1041bl.pdf (accessed August 24, 2023).
- Par Sterile Products. 2021. *Pitocin (oxytocin) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/018261Orig1s0411bl.pdf (accessed August 16, 2023).
- Pfizer Inc. 2017. *Prepidil (dinoprostone) Package Insert*. https://www.accessdata.fda.gov/drug_satfda_docs/label/2010/019617s0101bl.pdf (accessed August 16, 2023).
- PhRMA (Pharmaceutical Research and Manufacturers of America). 2019. *PhRMA Public Comment*. <https://www.regulations.gov/comment/FDA-2018-D-4693-0010> (accessed August 14, 2023).
- Public Citizen. 2008. *Public Citizen Comment*. <https://www.regulations.gov/comment/FDA-2006-N-0515-0055> (accessed August 11, 2023).
- Regeneron Pharmaceuticals, Inc. 2023. *Dupixent (dupilumab) Package Insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761055s0501bl.pdf (accessed August 24, 2023).
- RHTP (Reproductive Health Technologies Project). 2008. *Reproductive Health Technologies Project Public Comment*. <https://www.regulations.gov/comment/FDA-2006-N-0515-0066> (accessed August 11, 2023).
- Society for Maternal-Fetal Medicine. 2019. *Society for Maternal-Fetal Medicine Public Comment*. <https://www.regulations.gov/comment/FDA-2018-D-4693-0009> (accessed August 14, 2023).
- SWHR (Society for Women's Health Research). 2010. *SWHR Public Comment*. <https://www.regulations.gov/comment/FDA-2018-D-4693-0011> (accessed August 14, 2023).
- PRGLAC Task Force (Task Force on Research Specific to Pregnant Women and Lactating Women). 2018. Report to Secretary, Health and Human Services, Congress.
- Wesley, B. D., C. A. Sewell, C. Y. Chang, K. P. Hatfield, and C. P. Nguyen. 2021. Prescription medications for use in pregnancy-perspective from the US Food and Drug Administration. *American Journal of Obstetrics and Gynecology* 225(1):21–32. <https://doi.org/10.1016/j.jog.2021.02.032>.
- Wyner, Z., S. Dublin, C. Chambers, S. Deval, C. Herzig-Marx, S. Rao, A. Rauch, J. Reynolds, J. S. Brown, and D. Martin. 2020. The FDA MyStudies app: A reusable platform for distributed clinical trials and real-world evidence studies. *JAMIA Open* 3(4):500-505. <https://doi.org/10.1093/jamiaopen/ooaa061>.

APPENDIX D-1

Schematics of Complete Data Integration Processes from FDA's 2011 Final Guidance for Industry on Reproductive and Developmental Toxicities—Integrating Study Results to Assess Concerns

Figure A is applicable to all nonclinical toxicology and pharmacokinetic datasets and should be used for any of the endpoints of reproductive or developmental toxicity.

Figure A. Overall Decision Tree for Evaluation of Reproductive/Developmental Toxicities

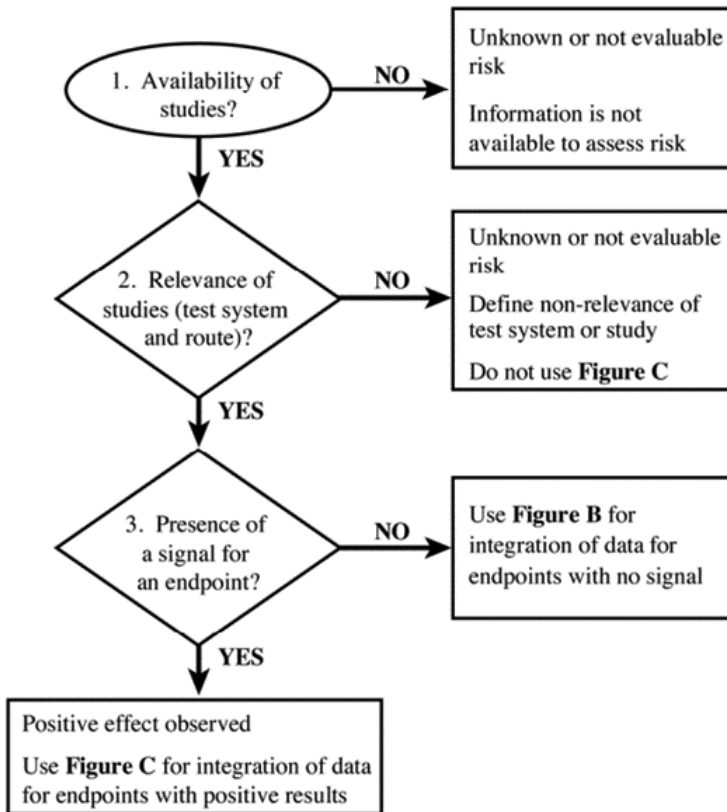


Figure B is applicable to nonclinical toxicology and pharmacokinetic datasets where there is no positive signal for an endpoint of reproductive or developmental toxicity.

Figure B. Decision Tree for Endpoints with No Signal

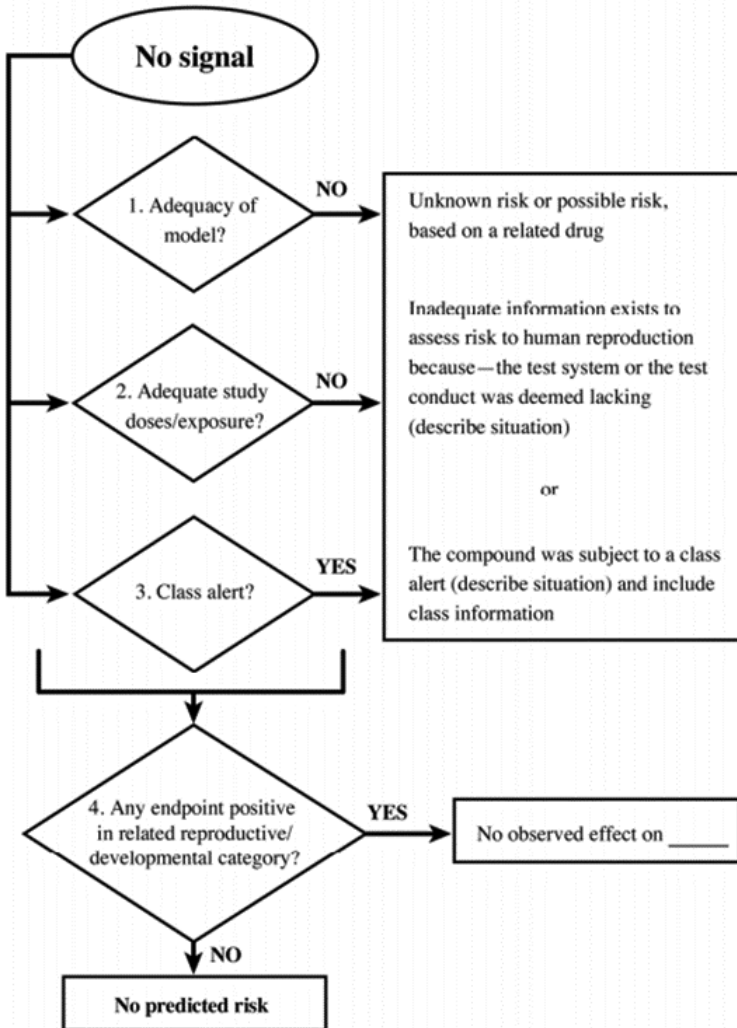


Figure C is applicable to nonclinical toxicology and pharmacokinetic datasets with positive indications of reproductive or developmental toxicity.

Figure C. Integration of Reproductive or Developmental Toxicities with a Positive Signal

