Prescription medications for use in pregnancy—perspective from the US Food and Drug Administration

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Obstetrical healthcare providers frequently field questions about the safety of medications recommended or prescribed to their pregnant patients. Most women use as least 1 medication during pregnancy; however, there is little information about the safety or appropriate dosing of many medications during this phase of life. In addition, the development of drugs for use in pregnant women trails behind the development of drugs intended for other sectors of the population. Our goal is to inform the obstetrics community about the US Food and Drug Administration authority and their role in approving drugs for marketing. We begin with the statutes that led to the creation of the Food and Drug Administration and its current organization. We then cover drug development and the Food and Drug Administration review process, including the role of the advisory committee. The different types of drug approvals are discussed, with some specific examples. Finally, we enumerate the drugs specifically approved for use in obstetrics and contrast them with drugs commonly used by pregnant women and drugs used "off-label" during pregnancy. The Food and Drug Administration is committed to protecting and advancing the public health of pregnant women by guiding the development and ensuring the availability of effective and safe therapeutics for obstetrical indications and for medical conditions during pregnancy. We hope this review will inspire more research addressing drug use during pregnancy.

Key words: 17-hydroxyprogesterone caproate, Cervidil, Diclegis, dinoprostone, doxylamine, drug approval in pregnancy, drugs approved for use in pregnancy, FDA, FDA guidance, FDA regulations, FDA review of drugs, Makena, magnesium sulfate, Methergine, methylergonovine maleate, oxytocin, Pitocin, Prepidil, pyridoxine, ritodrine, Syntocinon, Yutopar

Introduction

No other relationship is as fundamental to human development as that of the mother-fetus dyad. The 9 months a fetus spends in utero lays the foundation for the next 90 years of its life. A 2011 study using data from 2 large birth defect studies found that about 90% of women took at least 1 medication during pregnancy, with 70% taking at least 1 prescription medication. About 50% of postpartum women—whether breastfeeding or not—take at least 1 medication.[1] However, the development of drugs for use by pregnant women trails behind the development of drugs intended for other sectors of the population. As part of the compendium of articles presenting multiple perspectives about fostering collaboration during the development of medical therapies for use in pregnancy, our goal is to inform the obstetrics community about the US Food and Drug Administration (FDA)'s authority and role in approving drugs for marketing in the United States. The FDA's role in monitoring the safety of drugs after approval is beyond the scope of this article.

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Background of the Food and Drug Administration

Creation of the Food and Drug Administration

Several incidents in the late 19th century and early 20th century incited public concern about the unregulated nature of marketed food and drugs. Manufacturers were not required to list the ingredients in product labeling and made unsubstantiated claims about their drug products. For example, the manufacturer of "Mrs Winslow's Soothing Syrup" claimed that the syrup would greatly facilitate the process of teething, alleviate pain, and regulate the bowels. Because the syrup contained morphine and alcohol, many infants suffered addiction and withdrawal, became comatose, or died from a morphine overdose.[2] Upton Sinclair's description of food adulteration and unsanitary conditions in meat packing plants in "The Jungle" shocked the American public.[3] The outrage ensuing after exposing these conditions prompted the passage of the Pure Food and Drug Act of 1906, the first federal consumer protection law. The Pure Food and Drug Act aimed to foster consumer safety by requiring that products be accurately labeled with ingredients and dosage. This legislation laid the foundation for creation of the nation's first federal consumer protection agency, the FDA.

Over time it became clear that drugs should be demonstrated to be safe and effective before approval, leading to the

following 2 legislative enactments that together form the FDA's modern legal authority:

(1) The 1938 Federal Food, Drug, and Cosmetic (FD&C) Act required drug sponsors to establish safety before the marketing of new drugs and required submission of a new drug application to the FDA before marketing. The FD&C Act was spurred by the sulfanilamide tragedy, an antimicrobial agent that was dissolved in a sweet-tasting liquid targeted to pediatric patients. The drug sponsor did not conduct toxicity testing on the sweet solvent, which contained ethylene glycol (antifreeze), and it caused over 100 deaths, including that of many children.[4]

(2) The 1962-Kefauver-Harris Amendments required drug sponsors to establish the efficacy of new drugs, in addition to safety, and required that the FDA give positive approval before new drugs could be marketed. Thanks to Dr Frances O. Kelsey's careful review of the safety of thalidomide, a sedative for pregnant women that was highly teratogenic, this drug was never marketed in the United States, averting the clusters of rare, severe birth defects in thousands of babies seen in other countries.[5] The avoidance of a near disaster propelled passage of these amendments and fundamentally changed drug regulation.

Current Food and Drug Administration organization

Today, the FDA regulates and ensures the safety and effectiveness of products that account for 20% of all consumer expenditures in the United States, worth over a trillion dollars per year.[6] The FDA is part of the Department of Health and Human Services within the Executive branch of government. This branch implements the pertinent laws enacted by the legislative branch. Therefore, the FDA executes, but does not create laws related to drug regulation.

The FDA consists of individual centers, each dedicated to the evaluation of different products as indicated by their names.[7] For example, the Center for Drug Evaluation and Research (CDER) ensures that safe and effective drugs are available to improve the health of people in the United States, whereas the Center for Biologics Evaluation and Research ensures biological products (eg, vaccines and blood products) are safe and effective for those who need them. Similarly, the Center for Devices and Radiological Health ensures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products.

For this article, we focused on the work of the CDER, which ensures that safe and effective prescription, nonprescription, and generic drugs are available to the American people in a timely manner. The CDER fulfills this mission by regulating drug research and the development, manufacture, and marketing of drugs. The CDER personnel review the clinical and scientific evidence to determine if the evidence supports marketing approval of the proposed new drugs or new indications (new uses for already approved drugs for patients with specific diseases or conditions); monitor drug safety after approval; and ensure that drug labeling, drug information for patients, and drug promotional materials are truthful, helpful, and not misleading.

Drug development and the Food and Drug Administration drug review process

Drug development occurs in the following 2 ways: a new chemical entity or biological product is created, or a new indication is developed for an already approved drug to cure or palliate a certain disease or condition.

The CDER regulates but does not develop drugs or conduct clinical studies; drug sponsors are responsible for these activities, with important contributions from the academic and other research centers. Within the CDER's Office of New Drugs, 2 divisions—the Division of Urology, Obstetrics, and Gynecology and the Division of Pediatrics and Maternal Health—are dedicated to overseeing therapeutics in obstetrics and activities related to maternal health, respectively, in collaboration with other groups within the FDA.

Nonclinical studies

Nonclinical evaluation, which includes in vitro and animal studies, is the first step toward investigating the efficacy and safety during drug development. Drug sponsors do not need to notify the FDA or obtain the FDA's approval before conducting these nonclinical studies. The FDA requires nonclinical studies to be conducted to characterize the pharmacology and toxic effects of a drug product with respect to the target and nontarget organs, dose dependence, and relationship to exposure, which can guide and support the investigative use of drugs in human clinical trials.[8,9] The results of these studies aid in determining a safe starting dose for initial human clinical trials, dose titration, and the highest safe dose, while also characterizing potential adverse effects that might occur or that would need to be monitored during clinical trials (if applicable). As human clinical trials progress and become more complex in their type and duration, additional nonclinical studies provide supportive data to allow these clinical studies to proceed. There is a standard, nonclinical safety assessment that is necessary before a drug sponsor seeks FDA approval for their product, which includes evaluation of the general toxicity, pharmacology, absorption, distribution, metabolism and elimination, safety pharmacology, pharmacokinetics and toxicokinetics, reproductive toxicity, genotoxicity, and carcinogenicity. Additional studies may be warranted if the drug has certain biological properties, targets a unique study population based on age or gender, or has safety concerns.

With some exceptions, when adult men and women, especially those of childbearing potential, are to be enrolled in clinical trials, nonclinical reproductive and developmental toxicity studies are conducted to evaluate the effects of a drug product on fertility and early embryonic development, embryofetal development, and pre- and postnatal

development.[10,11] Often these reproductive and developmental toxicology data are the only evidence informing the safety of drug use during pregnancy, especially for newer drugs.

Nonclinical reproductive toxicity assessments include the following:

(1) Male and female fertility: damage to reproductive organs, alterations in endocrine regulation or function, effects on sperm count, motility, or morphology, mating behavior or the ability to mate, reduction in fertility, and effects on estrous cycling;
(2) Parturition: abnormal or difficult delivery (dystocia) or changes in the onset and duration of parturition;
(3) Lactation: concentration of the drug in breast milk through sampling; effects on the quantity and quality of milk would manifest as abnormal growth and development of the offspring.

Nonclinical developmental toxicity assessments include the following:

(1) Mortality: pre-or postimplantation loss, early or late resorption, abortion, stillbirth, neonatal death, or postweaning loss;
(2) Dysmorphogenesis (structural abnormalities): skeletal or soft tissue malformations or variations in the offspring;
(3) Alterations in growth: growth retardation, excessive growth, early maturation (via measurement of body weight, crown-rump length, and anogenital distance);
(4) Functional impairment: developmental neurobehavioral effects and reproductive function of offspring as measured through assessments on locomotor activity, learning and memory, reflex development, time to sexual maturation, mating behavior, and fertility.

Juvenile animal studies can also be conducted to identify postnatal developmental toxicities that may not be adequately assessed in reproductive and developmental toxicity assessments.[12,13] There are many organ systems that undergo considerable postnatal development in terms of both structure and function between birth and adolescence, including the brain, kidneys, lungs, and immune, skeletal, gastrointestinal, and hepatobiliary systems. If general toxicity studies in adult animals have identified target organ toxicities or pharmacology in organs that are known to markedly mature postnatally, juvenile animal studies can provide key safety information to determine the risk in those organ systems from prenatal or lactational exposure to a drug. These studies can also evaluate the risk across specific developmental stages, such as neonatal, infant, older children, and puberty or adolescence, that may not be captured in mature animal toxicity studies.

The FDA pharmacology and toxicology review team evaluates the totality of the general nonclinical and reproductive and developmental toxicology data to assess the relevance of risk for the proposed human use. This approach integrates a number of factors, such as the relevance of the data and test species to humans (pharmacology, dose, exposure), the observed signals in multiple animal species, multiple positive signals observed in a single species, class alerts for the drug product, signals for related toxicities, dose-response relationship, and evidence of maternal or paternal toxicity, among others. After integrating and collating all the data, the nonclinical team includes in the labeling the information supported by evidence, including positive findings, lack of findings, or no data available.

Clinical trials

Traditionally, there are usually 3 phases of clinical trials in the development of drugs. These phases are not necessarily sequential and can sometimes overlap or be combined and be re-iterative. The number of patients studied will depend on the disease and its prevalence. Completion of these clinical phases can take several years to well over a decade, with many programs failing along the way owing to safety concerns or a lack of efficacy.

Phase 1. These trials usually include 20 to 100 subjects, most likely healthy volunteers, and test mainly the drug's pharmacokinetics (the body's effect with regards to the absorption, distribution, metabolism, and elimination of the drug and include the peak drug concentration in the blood and the time it takes to reach the peak concentration after drug intake), pharmacodynamics (the drug's effect on the body with regards to, for example, changes in vital signs, laboratory values, or other clinical measures), and preliminary safety in humans.

Phase 2. These trials are usually for proof-of-concept and dose-finding purposes and conducted in the target patient population, which are further investigated in phase 3 trials. These trials include up to several hundred patients and provide more preliminary safety and efficacy information.

Phase 3. These trials are intended to establish the safety and effectiveness of a drug and usually include hundreds to thousands of patients. They are designed to provide the necessary clinical data to support a marketing application seeking approval for a drug product for a certain indication in the intended patient population.

Clinical trials evaluating a new drug, or an investigative use of an approved drug for a new indication, are conducted under Investigational New Drugs (INDs). The FDA has federal oversight of trials conducted under INDs, playing an important role along with others (eg, institutional review boards) in protecting the safety of study participants and ensuring that the trials are designed and conducted to meet their objectives. The FDA can place a hold on entire development programs, on specific trials, or on aspects of trials if the investigations raise considerable concerns, such as unreasonable risks to patients. All the points along the drug development process are interactive; the FDA and drug sponsors communicate regularly, usually with formal meetings or via written communications, to facilitate acquisition of the highest quality data and allow timely marketing of needed medications.

As a regulatory agency, the FDA sees the full spectrum of drug development processes, including successes, failures, delays, and barriers. We are uniquely positioned to work with drug sponsors to provide the appropriate guidance to obtain the necessary testing needed to establish the efficacy and safety of investigational products and help identify and address the challenges of drug development.

Marketing application

Here, we focus on marketing applications for drugs that are not generics (a generic is a duplicate of a previously approved drug and is approved by relying on the FDA's finding that the previously approved drug is safe and effective). A marketing application is a formal application that a drug sponsor submits to the FDA requesting approval to market a new product (drug or biologic) in the United States or for a new indication of an approved product. The marketing application must contain full reports of investigations about the safety and effectiveness of the drug for its intended use. This application may contain thousands of pages and includes information about the drug chemistry, quality, and manufacturing data; safety information from in vitro and animal data; clinical pharmacology data; and clinical trial data. The core review team consists of regulatory project managers, physicians, statisticians, chemists, nonclinical pharmacologists and toxicologists, clinical pharmacologists, experts in drug labeling and medication errors, epidemiologists, and inspection teams for manufacturing and clinical study sites.

Once the FDA receives the marketing application or after the application is considered fileable for review in the case of a new molecular entity, the review clock starts. For a standard review, the FDA completes a thorough review, may hold an advisory committee (AC) meeting (given below), and renders a decision regarding approval within 10 months of the start of the review clock (or within 6 months if it is a priority review). These timelines allow for the FDA's independent analyses of the data and requests for additional information from the drug sponsor, because more information or clarifications of the existing data may be needed. Concurrent with the review of the efficacy and safety of the marketing application, the FDA also conducts inspections of selected study sites to confirm the data integrity and of manufacturing sites to ensure acceptable product quality.

Benefit and risk assessment in the Food and Drug Administration's decision making

In deciding whether to approve a marketing application for its proposed use, the FDA determines (1) whether a drug is effective and (2) if its benefits outweigh the risks to patients. Both criteria must be met for approval. In recent years, the FDA has implemented a structured framework used to assess the benefits and risks and which serves as a standard approach for the drug review process and explains the FDA's decisions. As explained below, this structured approach considers the context of the target condition and the available treatments, the benefits of the drug, its important risks, and strategies to manage these risks.[14]

Analysis of the target condition and available treatment

This analysis provides the foundational context for weighing the drug's benefits against its risks. For example, certain risks may be acceptable for a life-threatening medical condition for which there is no available therapy, whereas the same risks may be unacceptable for a symptomatic condition or for 1 where there are available therapies without such toxicities.

Assessment of benefits and risks

This assessment is based primarily on the data submitted in the marketing application. The FDA determines whether the findings from the pivotal trials adequately inform the drug's efficacy. The FDA characterizes the safety profile by evaluating all the available data from nonclinical studies to phase 1 through phase 3 trials and the available postmarketing information (if the drug has been approved in the United States for another indication or elsewhere worldwide). Because clinical trials are conducted in a controlled setting and are limited by size, there are limitations to the available safety data, including the likelihood of not seeing more rare serious side effects or side effects that take a long time (years) to develop. Therefore, the drug's safety profile is unlikely to be completely characterized at the time of approval. Instead, as a drug is used by many more patients and in more diverse populations postapproval, the FDA's understanding of its safety profile will be further augmented in the postmarket setting.

Risk mitigation

All drugs have risks. The primary risk management tool is the FDA-approved drug label. The label contains all the information to ensure the safe and effective use of a drug and includes the known and potential risks and available strategies to prevent or reduce the occurrence or severity of those risks. If the drug labeling alone cannot adequately mitigate the risks, the FDA can require the development of a Risk Evaluation and Mitigation Strategy (REMS) to manage certain serious risks and would approve the drug if the REMS can ensure that the benefits of the drug outweigh its risks. In certain cases, however, drug approval is not possible because the serious risks are such that they cannot be sufficiently managed with the strongest warnings on the drug label, such as a "black" boxed warning and a REMS. A hypothetical example of such a risk requiring a boxed warning and a REMS is idiopathic, drug-induced liver failure by a drug that treats a nonserious condition and for which it is not possible to identify potential patients at risk or effective testing methods to prevent the occurrence of liver failure. A real-life example of a black boxed warning can be seen with the labeling for indomethacin, which highlights the risks for serious cardiovascular and gastrointestinal events.[15]

The Figure and a simplified example (Table) illustrate the concepts of a benefit-risk assessment for a theoretical

drug "Normotensive" for the prevention of recurrent preeclampsia.

This analysis helps to forge a clear and meaningful benefit-risk assessment that underlie the FDA's decision to approve or not to approve a new drug or a new indication.

Food and Drug Administration Advisory Committee meetings

The FDA convenes AC meetings to seek external and independent expert advice and recommendations about controversial scientific, clinical, or policy issues related to human and veterinary drugs, biological products, medical devices, and food. Open to the public, these meetings also provide an opportunity for members of the public, including patients, caregivers, academics, and patient advocacy groups, to present their perspective during the meeting's Open Public Hearing. When the FDA determines that AC input is warranted for a marketing application, this meeting is held before the FDA's deadline for a decision on the application.

In general, the AC include a chair, several members, plus a consumer, industry, and patient representative. To the extent feasible, committee members possess skills and experience in the development or use of the types of products to be referred to the committee and reflect a balanced composition of scientific expertise with diverse professional education, training, and experience.[20] Additional experts with specialized knowledge pertinent to a specific topic are added to individual meetings as appropriate. All AC members involved in the discussion and voting on the matters presented before the AC must undergo extensive screening to ensure that they are free of conflicts of interest. During the meeting, the drug sponsor and FDA teams present the relevant evidence, and the AC members then provide in-depth deliberation on specific discussion points and vote on specific questions, such as whether the benefits outweigh the risks to support approval of a drug.

The FDA is not obligated to follow the recommendations of the ACs; however, approximately 80% of the time, the FDA decisions regarding drugs and devices are in accordance with the recommendations by the ACs.[21]

ACs play an important role in transparency of the matter before the agency; unless a drug is approved, information about that drug usually only becomes public at an AC meeting. Through the AC system, the FDA can ensure independent, professional expertise in accomplishing its mission and maintaining the public trust. All the materials including the AC meeting calendars, meeting slides, written documents, and a transcript of the meetings are available at the FDA.gov website.[22]

Food and Drug Administration approval

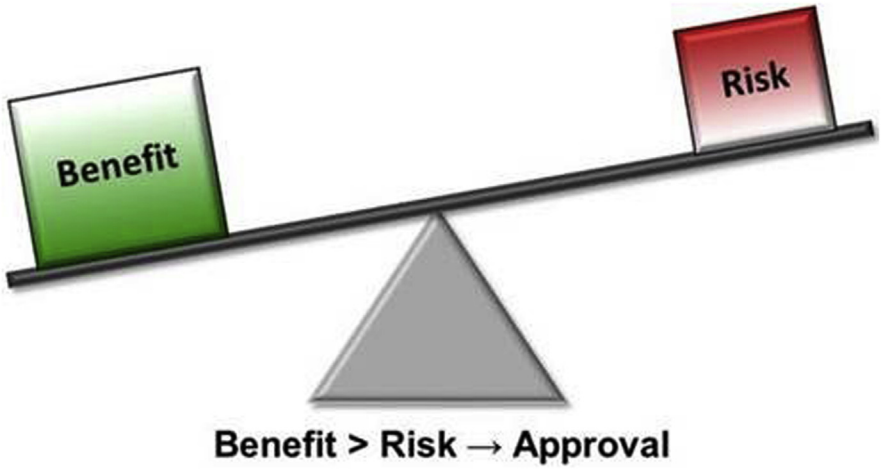
When deciding on the approvability of a marketing application, the FDA chooses between 1 of 2 possible decisions: "Complete Response" (CR) or "Approval." The FDA issues a CR decision if it determines that the application cannot be approved in its present form. The CR letter describes the specific deficiencies preventing approval and, when possible, recommends actions that the drug sponsor could take to resolve these deficiencies. An "Approval" permits marketing of the product in the United States for the agreed-upon indication from the date of the Approval Letter.

The FDA will approve a drug (1) if there is substantial evidence of the effectiveness for the proposed use and (2) if the benefits outweigh its known and potential risks for the intended population.

The FD&C Act provides the legal standard for establishing efficacy ("substantial evidence of effectiveness") for the FDA drug approval. In general, "substantial evidence" is based on positive findings from 2 or more adequate and well-controlled trials, each convincing on its own for independent substantiation of the drug's benefit. The independent substantiation principle with at least 2 well-controlled trials is important because a positive finding from a single trial is more likely to represent a chance finding and the single trial may have undetected biases.

In some circumstances, a single, large multicenter trial may be sufficient to provide substantial evidence of effectiveness. Reliance on a single, large multicenter trial to establish effectiveness should be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very persuasive effect on mortality, severe or irreversible morbidity, or prevention of a disease with potentially very serious outcomes, and confirmation of

FIGURE
Benefit vs risk assessment



Approval of a drug proceeds when the benefits outweigh the risks. When risks outweigh potential benefits, the marketing application receives a complete response.

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the result in a second trial would be impracticable or unethical.[23]

The FDA regulations[24] describe characteristics of an adequate and well-controlled clinical investigation, including the choice of control group, method of patient assignment to treatment (eg, randomization), adequate measures to minimize bias (eg, blinding), well-defined and reliable assessment of an individual's response to the drug (ie, efficacy endpoint), and adequate analysis of the clinical investigation's results to assess the effects of the drug (ie, statistical methods). Randomized, double-blinded, concurrently controlled, superiority designs are usually regarded as the most rigorous trial design.

The safety review integrates information from nonclinical studies (eg, animal toxicology studies), early clinical trials (eg, tolerability and drug-drug interactions), and phase 2 and phase 3 clinical trials in addition to postmarketing data, if the drug has been approved previously. The FDA broadly examines the safety data, because, unlike efficacy, the important safety outcomes are often not known in advance. The safety review is an integrated analysis, typically pooling data from phase 2 and phase 3 trials, when appropriate, to improve the precision of risk and enhance the power for detecting group differences. The safety review includes the extent of exposure to the study drug (number of research subjects exposed and duration of exposure) and critical analyses of the deaths, serious adverse events (eg, untoward effects that are life-threatening, lead to hospitalization, or cause congenital abnormalities), patient drop-out rates owing to adverse events, other adverse events, laboratory data, vital signs, electrocardiograms, unintended pregnancies, overdose experience, and any other investigations deemed necessary. In addition to an overall assessment, the FDA evaluates the impact of patient characteristics and risk factors (eg, dose dependency, time dependency, drug-demographic interactions, drug-disease interactions, and drug-drug interactions) on the incidence of adverse events. The goal is to accurately characterize the safety profile of the drug and determine strategies that could mitigate or prevent adverse reactions. In addition, information about adverse reactions detected during a clinical trial can guide the postmarketing risk management or the development of potential postmarketing evaluations (trials, observational studies, registries—for example, pregnancy registries) to gain additional safety information once the drug has been consumed by larger numbers of people.

Types of drug approval

The 2 most common drug approval pathways are the traditional and accelerated approval pathways, as described below:

(1) Traditional: this is the most common pathway for drug approval. A marketing application receives traditional (regular) approval when substantial evidence of the effectiveness of a drug on a clinical endpoint is demonstrated, such as 1 that directly measures how patients feel, function, or survive (ie, clinical benefit). An example of a clinical endpoint is the death rate linked to cardiovascular causes for a drug intended to treat congestive heart failure. Traditional approval can also be granted when a drug demonstrates effectiveness on a validated surrogate endpoint. Unlike clinical endpoints, surrogate endpoints do not directly measure how patients feel, function, or survive. A surrogate endpoint that is validated, however, is known to predict clinical benefit. For instance, a reduction in blood pressure, which does not directly measure patient survival, is known to reduce the risk for cardiovascular death.

(2) Accelerated: the accelerated approval pathway, instituted in 1992 in response to the HIV and AIDS epidemic, is intended to speed up the availability of promising therapies that treat serious or life-threatening conditions and that seem to provide an advantage over other available therapies. This approval pathway is especially useful when the drug treats a disease with a long disease course and an extended period is needed to measure its effect. This approval pathway must meet the same statutory evidentiary standards for safety and effectiveness—substantial evidence of the effectiveness of the drug and benefits of the drug that outweigh its risks—as those for traditional approval.

The key difference between accelerated and traditional approval pathways is the efficacy endpoint used as the basis for approval: an accelerated approval is based on the drug's effect on a surrogate endpoint that is "reasonably likely"—and not known—to predict the clinical benefit, or a clinical endpoint that occurs earlier but that may not be as certain as a standard clinical endpoint used for a traditional approval. The main risk of relying on this type of surrogate endpoint is the possibility that patients will be exposed to a drug that ultimately will not be shown to provide an actual clinical benefit. Because of this uncertainty, the drug sponsors must perform confirmatory clinical trials after accelerated approval to verify that the drug indeed provides the expected clinical benefit of interest. The FDA may withdraw the accelerated approval of a drug or indication if the confirmatory trial(s) failed to verify clinical benefit, if additional evidence demonstrates that the product is not shown to be safe or effective under the conditions of use, or if the drug sponsor fails to conduct the required confirmatory trials with due diligence.

A drug approved under accelerated approval and that is of interest to the obstetrical community is Makena (hydroxyprogesterone caproate injection). Makena is indicated for reducing the risk of recurrent preterm birth and is one of the few nononcologic drugs approved under accelerated approval. The FDA granted Makena accelerated approval after concluding that the drug reduced deliveries before 37 weeks of gestation, a surrogate endpoint that we determined was reasonably likely to

TABLE
Benefit-risk integrated assessment

Benefit-risk dimensions

Dimension	Evidence and uncertainties	Conclusions and reasons
Analysis of condition Questions to consider: Life-threatening? Serious?	Preeclampsia affects 2%—8% of pregnant women worldwide.[16] Potentially life-threatening: can cause vascular, hematologic, hepatic and renal injury; preeclampsia and eclampsia account for 10%—15% of direct maternal deaths.[17,18] A previous history of preeclampsia is a major risk factor for recurrent preeclampsia, although not all women will experience a recurrence. Fetal consequences can include growth restriction, oligohydramnios, placental abruption, nonreassuring fetal status, increased risk for spontaneous or indicated preterm delivery.[16]	Preeclampsia is a major public health concern and is a potentially life-threatening condition to both pregnant women and their fetuses.
Current treatment Questions to consider: Unmet medical need? Treatment options available?	No approved treatment. Professional guidelines recommend off-label use of low-dose aspirin initiated between 12 and 28 wk of gestation and continuing until delivery.[19]	This is an area of unmet medical need with no approved treatment.
Benefit Questions to consider: Benefit to woman, fetus or both?	Patients with a history of preeclampsia treated with Normotensive had a lower relative risk of developing recurrent preeclampsia than those treated with the placebo (RR, 0.7; 95% CI, 0.5—0.9). Patients with a history of preeclampsia treated with Normotensive had a lower relative risk of developing recurrent preeclampsia with severe features than those treated with placebo (RR, 0.8; 95% CI, 0.7—0.9). Neonates born to patients treated with Normotensive had a lower risk of fetal growth restriction than those treated with placebo (RR, 0.8; 95% CI, 0.7—0.9). No differences were seen between the treatment groups in the gestational age at delivery.	Benefits of Normotensive outweighs its risks. The drug label will recommend that neonates be observed in a monitored unit for at least 24 h after birth for respiratory complications. Required postmarketing study: evaluate safety outcomes of neonates to 2 y of age.
Risk and risk management Questions to consider: Risk to mother? Risk to fetus? Ways to mitigate risks?	Patients treated with Normotensive gave birth to neonates with a higher incidence of neonatal respiratory distress syndrome, requiring intubation (5%), than placebo (1%). Otherwise, there are no substantial differences in other serious risks in fetuses or neonates or pregnant women.	

CI, confidence interval; *RR*, relative risk.

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predict the clinical benefit to the newborn. Our decision to grant accelerated approval to Makena considered the substantial public health impact of newborns born prematurely, the lack of approved treatments for the prevention of preterm birth, and the delay in patient access to this promising treatment that would occur if the larger confirmatory trial measuring direct benefits to newborns was required for preapproval. As a condition of Makena's accelerated approval, we required the manufacturer to conduct a confirmatory clinical trial after approval to verify and describe the anticipated clinical benefit to newborns. This trial did not show an improvement in the outcomes of neonates born to mothers who were treated with Makena compared with the placebo. This trial also failed to show a reduced risk of preterm birth with Makena, contradicting the findings of the original trial conducted for approval. After extensive review of the findings, we could not identify a treatment benefit of Makena for any subgroup of patients in the new trial, including those at higher risk for preterm birth. Recently, the CDER proposed that Makena's approval be withdrawn for reasons of efficacy.[25]

Food and Drug Administration-approved drug label

A marketing application is approved with FDA-approved labeling, which includes the prescribing information (also known as the package insert or drug label) intended for the prescriber, that contains all the necessary information to ensure the safe and effective use of a drug. The main objective of the drug label is to provide the most important information for prescribers when making a prescribing decision for the individual patient in a shared decision-making process; it is not meant as practice guidelines. The drug label contains key information such as the approved indications, dosage and administration instructions, contraindications (those situations in which the benefits of the drug never outweigh the risks), warnings and precautions, adverse reactions, drug interactions, use in specific populations, including pregnant and lactating women, and efficacy findings in clinical trials. Although the drug sponsor technically owns the drug label, the FDA review teams thoroughly review and revise, as needed, the drug label to ensure that it contains informative and accurate information that is not promotional and that all claims are supported by evidence. The FDA must agree to the label's final content before approval. The drug label is a living document and is updated after approval as new information important for the safe and effective use of the drug becomes available or as regulations regarding its content change.

Pregnancy and lactation labeling rule. One section of the drug label of interest to obstetricians and gynecologists is the "use in specific populations" section, specifically Section 8. Implemented in 2014, the Pregnancy and Lactation Labeling Rule (PLLR) substantially modified this section of the drug label.[26] The PLLR eliminated the pregnancy ABCDX letter category for all drugs, including those approved in past years. Under the PLLR, all drug labels may contain up to 3 subsections, as appropriate, for safety information related to pregnancy (subsection 8.1), lactation (subsection 8.2), and females and males of reproductive potential (subsection 8.3).[27]

(1) Pregnancy subsection 8.1: in lieu of a pregnancy letter category, the pregnancy subsection 8.1 now contains summaries of the pertinent available evidence informing the safety of the drug in pregnancy. This subsection includes information on pregnancy exposure registries, if available, including how to enroll in the registry or obtain information about the registry. The risk summary informs decision making about drug use during pregnancy and sums up the risks for adverse developmental outcomes based on the available and relevant human data, animal data, and/or the drug's pharmacology. The risk summary also includes a statement referring to the background risk for major birth defects and miscarriages in the United States. This statement is to convey that there is a baseline risk for these adverse outcomes without drug exposure. The clinical considerations section discusses disease-associated maternal and embryofetal risks, dose adjustments during pregnancy and the postpartum period, maternal adverse reactions, fetal or neonatal adverse reactions, and effects on labor and delivery. Finally, human and animal data supporting the risk summary are presented. Harking back to similar outcomes evaluated in nonclinical studies, adverse developmental outcomes here include structural abnormalities, embryofetal or infant mortality, functional impairments, and alterations to growth.

(2) Lactation subsection 8.2: this subsection includes the risk summary of information about the presence of a drug and its active metabolite(s) in human breast milk, the effects of a drug and its active metabolite(s) on a breastfed child, and the effects of a drug and its active metabolite(s) on milk production. This includes a risk and benefit statement providing a framework for healthcare 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 vs potential risks to the infant. Clinical considerations include minimizing exposure of the breastfed infant to the drug and monitoring for adverse reactions. Again, human and/or animal data are presented.

(3) Females and males of reproductive potential subsection 8.3: this section discusses information about the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

The data informing these sections are usually submitted by the drug sponsors and reviewed by the FDA. The evidence informing these sections is often from nonclinical studies, available published literature, relevant cases reported to the

FDA's Adverse Event Reporting System, and ongoing pregnancy registries. The FDA review teams assess all the available data (including any published data that may not have been included in the submission) to ensure that the evidence presented is accurate and captures the key uncertainties, be they regarding the quality of the data or consistencies with the findings, and provide a balanced summary of the risks and advice, when appropriate, in the drug label.

The intent of the new PLLR regulation is to provide healthcare providers with the best available evidence to help prescribers and the individual patient make an informed decision when considering using or continuing to use medications during pregnancy and lactation. Clinical interpretation is still required on a case-by-case basis because the information does not usually provide a definitive "yes" or "no" answer. Importantly, although the PLLR provides a cohesive and standard structure according to which drug safety during pregnancy and lactation is labeled, it does not address or resolve the considerable dearth of data to inform drug safety in pregnant and lactating women.

Pregnancy registries. Pregnancy registries are important for systematically obtaining safety information using observational study methods for medications used during pregnancy and can be used to update the drug label. The FDA does not create pregnancy registries, but it can require drug sponsors to create pregnancy registries to learn more about a drug's effect on a woman and her fetus. The FDA's Office of Women's Health Website[28] posts pregnancy registries at the request of the sponsor or investigator, and the webpage is for informational purposes.

Prescription drugs in pregnancy

About 70% of pregnant women are prescribed 1 or more drugs during pregnancy (excluding over-the-counter vitamins and minerals)[1] for chronic health problems that require continued medication use, or for acute or new problems that arise during pregnancy. Prescription drug use in pregnancy include approved drugs (A) for an approved pregnancy-related condition, (B) for an approved medical indication ("on-label" use), or (C) for an unapproved use ("off-label" use).

Drugs approved for obstetrical indications

There are only 9 drugs that have ever been approved and marketed in the United States for obstetrical indications, which are described below:

(1) Methergine (methylergonovine maleate)—approved in 1946 based on the safety data 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 delivery of the anterior shoulder. The effectiveness of the drug was reviewed under the FDA's Drug Efficacy Study Implementation (DESI); Methergine was determined to be effective for its intended uses in 1968.[29]
(2) Syntocinon (oxytocin nasal spray)—approved based on safety data in 1960 and found to be effective for "initial milk letdown" in 1968, also through a DESI proceeding.[30] Syntocinon is no longer marketed.
(3) Pitocin (oxytocin for intramuscular or intravenous administration)—approved in 1980 for the "initiation or improvement of uterine contractions and to control postpartum bleeding."
(4) Yutopar (ritodrine)—approved in 1980 as a tocolytic, but it is no longer marketed.
(5) Prepidil (dinoprostone)—approved in 1992 "for ripening an unfavorable cervix in pregnant women at or near term with a medical or obstetrical need for labor induction."
(6) Cervidil (dinoprostone)—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."
(7) Magnesium sulfate—approved in 1995 for the "prevention and control of seizures in preeclampsia and eclampsia, respectively."
(8) Makena (hydroxyprogestserone caproate)—gained 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."
(9) Diclegis (doxylamine succinate and pyridoxine hydrochloride) — approved in 2014 (a product with the same combination of doxylamine and pyridoxine that had been marketed as Bendectin (1976) until 1983) "for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management."

No other specialty in medicine has such a short list of drug approvals with so few indications.

Drugs prescribed for approved indications during pregnancy

Many drugs are approved for medical conditions in adults, which include pregnant women, unless there is a clear contraindication against the drug use in pregnancy. Such use of medications for approved uses are "on-label" use, in which the general efficacy and safety for the pregnant woman is expected to be comparable to nonpregnant women when used according to the instructions in the drug label. In limited clinical settings, the appropriate doses during pregnancy are sometimes determined by obtaining blood levels of the drug (eg, antiseizure medications) or by pharmacodynamic observations (eg, antihypertensive drugs). The safety data for use during pregnancy are usually informed by reproductive toxicity studies in animals and varying amounts of data obtained following administration of the drug during human pregnancy. In most cases, however, there is often sparse safety information available about the drug use during pregnancy and some uncertainty about the appropriate dose or dosing regimen in pregnant women, because these drugs are usually not

formally evaluated during pregnancy. Examples of drugs used on-label during pregnancy include beta-adrenergic inhalers for relief of asthmatic bronchospasms, antiseizure medications for epilepsy, antibiotics for bacterial infections, and glucocorticoids for systemic lupus erythematosus and other autoimmune diseases.

Approved drugs prescribed for unapproved uses in pregnancy

Many drugs are used "off-label" during pregnancy, meaning the drug is used in a manner not specified in the FDA's approved drug label. Once the FDA approves a drug, healthcare providers may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient; this is known as "off-label" use. Important off-label uses in pregnancy include antenatal glucocorticoids (betamethasone and dexamethasone) to enhance fetal lung maturity and nonsteroidal anti-inflammatory drugs (indomethacin) to stop preterm labor.

Except for drugs approved for obstetrical indications, there is a dearth of evidence informing the efficacy, safety, and dose or dosing regimen of drugs prescribed in pregnancy for multiple reasons. There is no comprehensive data collection effort to enable researchers to determine all the conditions for which pregnant and lactating women take medications, and what outcomes can be attributed to drug exposure. Existing data resources, health record systems linking mother and infant records, and innovative analytics are suboptimal. Data on the pharmacokinetics and pharmacodynamics of drugs are lacking, as is training of obstetricians about pregnancy and lactation pharmacology. Pregnant and lactating women have traditionally been excluded from clinical trials owing to concerns about possible harms to the woman and/or the fetus or infant (with the potential for liability), a lack of a proactive approach to protocol development and study design, and burdensome regulatory barriers. There is a lack of funding to prioritize study in off-label use of drugs already being used by pregnant and lactating women and limited interest in conditions specific to pregnancy and lactation. There is a need for evidence-based communication with healthcare providers and pregnant and lactating women, highlighting the importance of research in this area.

To facilitate the acquisition of the appropriate data for use during pregnancy, the FDA has published the following guidance documents addressing drug development for use in pregnancy (the FDA guidance reflects the agency's current thinking about certain topics):

(1) Reviewer Guidance—Evaluating the Risks of Drug Exposure in Human Pregnancies.[31] This guidance is intended to help the FDA staff evaluate human fetal outcome data generated after medical product exposures during pregnancy. The goal of such evaluations is to assist in the development of product labeling that is useful to healthcare providers when they care for patients who are pregnant or planning to become pregnant. The review of human pregnancy drug exposure data and assessment of fetal risk (or lack of risk) requires consideration of human embryology and teratology, pharmacology, obstetrics, and epidemiology.

(2) Guidance for Industry—Pharmacokinetics in pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling.[32] This guidance describes a basic framework for designing and conducting pharmacokinetic and pharmacodynamic studies in pregnant women. It provides recommendations to drug companies about how to assess the influence of pregnancy on the pharmacokinetics, and, where appropriate, the pharmacodynamics of drugs or biological products and vaccines. In addition, this guidance provides recommendations to clinical researchers and clinical pharmacologists about the issues to consider when designing and conducting pharmacokinetic studies in pregnant women.

(3) The draft guidance "Pregnant Women: Scientific and Ethical considerations for Inclusion in Clinical Trials: guidance for Industry."[33] The FDA endorses an informed and balanced approach to gathering data informing the safe and effective use of drugs and biological products during pregnancy through judicious inclusion of pregnant women in clinical trials and careful attention to potential fetal risk. The guidance addresses scientific and ethical issues as they apply both to clinical trials that enroll pregnant subjects and to clinical trials that allow enrolled subjects who become pregnant to remain in the trial.

The future

Most women must use as least 1 medication during pregnancy. Much more data are needed to support informed benefit-risk decision making for drug use during pregnancy. Scientific knowledge about the "great obstetrical syndromes" (eg, preterm birth, preeclampsia, intrauterine growth restriction) is still evolving. There is a clear need to obtain more nonclinical (animal) and clinical data to better understand the pathophysiology of the obstetrical syndromes to identify women at increased risk for adverse pregnancy outcomes and apply targeted risk management and treatment. The FDA is committed to protecting and advancing the public health of pregnant women by guiding the development and ensuring the availability of effective and safe therapeutics. The FDA also strives to provide the public with timely, accurate, and science-based information necessary to use drugs to maintain and improve their health. ■

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GLOSSARY

Drug: Used interchangeably for drugs and biological products.
Marketing application :A new drug application for drugs or a Biologics License Application for a biological product.
Priority review: A drug may be granted a priority review if it treats a serious or life-threatening condition and it appears to offer an advantage over available therapies, such as evidence of increased effectiveness, documented improvement in patient compliance, or a substantial reduction or elimination of a treatment-limiting drug reaction.
REMS: Risk Evaluation and Mitigation Strategy. A REMS is a Food and Drug Administration (FDA)-required safety strategy, in addition to labeling, that helps to manage or mitigate a known or potential serious risk. A REMS may consist of a Medication Guide (an FDA-approved patient handout that pharmacists are required to distribute to the patient when a prescription is filled or refilled), a communication plan (eg, a Dear Healthcare Provider letter that alerts prescribers of an important safety concern), Elements to Assure Safe Use (eg, actions that healthcare providers must take before prescribing or dispensing the drug to the patient, such as confirming a negative pregnancy test), or some combination of these 3 tools.
Sponsor: The entity (company, organization, or individual) that is responsible for studies and applies for the marketing application of the therapeutic product.
Toxicokinetics: The use of bioanalytical sampling (eg, blood, plasma, excreta, exhaled air, tissues) to quantitatively study the disposition of a drug in the body over the course of time. The goal of toxicokinetics is to measure the systemic exposure of a drug in animals, correlate any findings of toxicity with a corresponding level of drug exposure, and then compare it to measured exposures in humans to predict toxicity.