FDA Approval for Use of Medications in Pregnancy: An Uphill Battle

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The US Food and Drug Administration (FDA) has a difficult task. As an agency housed within the Department of Health and Human Services, it is responsible for protecting the public health by assuring the safety, efficacy, and security of drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. It is also responsible for (i) advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; (ii) regulating the manufacture, marketing, and distribution of tobacco products; and (iii) helping the public get the accurate, evidence-based information they need to use medicines and foods in a more responsible fashion.[1]

The process of drug approval in the United States is complex, expensive, and time consuming. Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs first have to be discovered, purified, characterized, and tested in the laboratory (in cell and animal studies) before ever undergoing clinical testing (Table 1). In all, about 1000 potential drugs are researched before just one reaches the point of being tested in a clinical trial. The estimated cost of bringing a new drug to market varies depending on the disease under study, the therapeutic benefit, the sponsor, and the time period required for evaluation, but estimated costs range from $500 million to $2 billion.[2-4] The time investment from the start of clinical testing to marketing approval averages between 75 and 90 months (6.3 and 7.5 years), although it can take decades.[3,4]

Nowhere is this challenge more vexing than in pregnancy.

The process of FDA approval for use of a drug in pregnancy faces a number of unique obstacles. These include the reluctance of pregnant women to enroll in clinical trials because of concern over the well-being of their fetus, the restricted market for pharmaceutical companies, and concerns from drug developers and manufacturers about medicolegal liability.[5] There is even less incentive for pharmaceutical companies to seek approval for use in pregnancy if the drug is already approved for use in nonpregnant patients because off-label use of drugs in pregnancy is widespread. Common examples include

Table 1
Clinical Trial Phases

Phase	Objective	Number of Human Subjects	Average Time
Preclinical	This phase involves in vitro and in vivo animal experiments using wide-ranging doses of the study drug to obtain preliminary information about likely efficacy, toxicity, and pharmacokinetics. Such tests assist pharmaceutical companies in deciding whether a candidate drug has scientific merit for further development.	None	Months to years
Phase 0 (optional)	Phase 0 trials (also known as human microdosing studies) were recently introduced for early human studies to help pharmaceutical companies decide whether to speed up development of promising drugs by establishing very early on in the process whether the drug behaves in human subjects as expected from preclinical studies. These studies typically involve the administration of a single subtherapeutic dose of the study drug to healthy volunteers to gather preliminary pharmacodynamic and pharmacokinetic data. A phase 0 study gives no data on safety or efficacy because, by definition, the dose being administered is too low to cause any therapeutic effect.	10-15 healthy volunteers	Months
Phase I	Phase I trials are designed to gain initial data on the safety, tolerability (side effects), pharmacokinetics, and pharmacodynamics of a drug. They are usually carried out in a group of healthy volunteers who are paid for their services. Such trials typically include dose escalation studies to identify the appropriate route of administration and dose for therapeutic use.	20-50 healthy volunteers	Months to years
Phase II	Once the initial safety of the study drug has been established, phase II trials are designed to determine how well the drug works (its efficacy) in a group of study subjects who actually have the disease. It also includes ongoing safety assessment (toxicity) in a larger group of healthy volunteers and diseased subjects using varying doses of the drug.	100-300 healthy volunteers and/or study subjects who have the disease	1-3 years
Phase III	Phase III studies are multicenter, randomized, controlled trials carried out on large patient groups aimed at providing a definitive assessment of how effective the drug is compared with the current gold-standard treatment. They also require continued assessment of the drug's safety profile. These are the most expensive, time-consuming, and difficult trials to design and execute.	300-3000 study subjects who have the disease	3-5 years
Phase IV (postmarketing)	Phase IV studies (also known as postmarketing surveillance or pharmacovigilance trials) were introduced by the FDA in 2007. They can be initiated by the regulatory agency or the sponsor to provide ongoing technical support of a drug after it has received permission to be sold, to collect additional data (eg, on drug-drug interactions or efficacy in certain subpopulations such as pregnant women or infants), and/or to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phase I-III clinical trials.	Large populations (several thousand patents who are actively using the drug)	5-10 years

the use of vaginal prostaglandin E1 (misoprostol) for cervical ripening, intravenous magnesium sulfate for seizure prophylaxis and neuroprotection, and low-molecular-weight heparins for both prophylaxis against and treatment of venous thromboembolic events.

On February 3, 2011, the FDA approved the use of progesterone supplementation—specifically, hydroxyprogesterone caproate injection (Makena™; Ther-Rx Corporation, St. Louis, MO)—to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a history of a prior spontaneous preterm delivery.[6] This is the first time that the FDA has approved a medication for the prevention of preterm birth, and *represents the first approval of a drug for use in pregnancy in almost 15 years*. The last drug to receive FDA approval for use in pregnancy was Cervidil® (Forest Laboratories, Inc., New York, NY), a vaginal prostaglandin E2 preparation that was approved for cervical ripening in 1995. Importantly, approval of Makena also represents proof of concept for a number of special programs recently introduced by the FDA to facilitate drug development and approval. For example, the company obtained approval under the FDA's accelerated approval program (which enabled it to rely on data from a single National Institutes of Health– sponsored clinical trial to demonstrate the drug's effectiveness[7]), it received expedited review, and it obtained 7 years of exclusivity under the Orphan Drug Act.[5,6] Without these special programs in place, it is almost certain that this approval would not have gone forward.

FDA approval of a drug should not be confused with FDA approval of a device. For a device to receive premarket approval, the most stringent type of device marketing application required by the FDA, the sponsor is asked to supply ". . . sufficient valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use or uses."[8] In practice, this means that the device fulfills two criteria: (i) it should not harm the subject, and (ii) it should reliably measure what it is designed to measure (eg, electrical activity or the level of a particular compound in a given biological sample). The sponsor does not need to test the device against the prevailing gold-standard intervention, and does not need to show that it improves clinical outcome.

The fact that so many drugs used in pregnancy are prescribed off label is far from ideal. Additional programs are needed to facilitate drug development for pregnancy-specific disorders, and to accelerate and modernize the approval process. Creative solutions will need to be found. But at no time should this be done at the expense of patient safety. ■

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