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Medical Product Innovation and Regulation: Benefits and Risks

Prior to being marketed in the United States, medical products are reviewed for safety and effectiveness, among other things, by the Food and Drug Administration (FDA). Medical products regulated by FDA include prescription drugs, medical devices, and biologics. When evaluating a product, FDA weighs the potential benefits of a medical product against the potential for certain harms associated with the use of that same product. It is in this context that Congress and FDA have established both premarket and postmarket requirements for medical products, as well as expedited development and review pathways for certain medical products for serious diseases with few available treatment options. In establishing these expedited pathways, Congress and FDA have acknowledged an implicit trade-off between reducing time to marketing and a potentially less complete safety profile upon approval.

History of Medical Product Regulation

The Biologics Control Act of 1902 (P.L. 57-244) was the first attempt to regulate a pharmaceutical product at the national level. It was also the first premarket approval statute, in contrast to a retrospective postmarket product evaluation. The act focused on the manufacturing process and required that manufacturing facilities be inspected before a federal license was issued to market the biologic.

The regulation of drugs began with the Pure Food and Drugs Act of 1906 (P.L. 59-384). The 1906 law did not involve premarket control over new drugs to ensure safety and did not include inspections or any other regulation of manufacturing facilities. Rather, the law focused on the drug label, which could not be false or misleading, and required that the presence and amount of certain dangerous ingredients (e.g., alcohol, cocaine) be listed. In addition, it defined "adulterated" with reference to the *U.S. Pharmacopoeia and National Formulary* standards for purity, quality, and strength. It prohibited the introduction into interstate commerce of misbranded or adulterated drugs and food.

In 1938, Congress replaced the Pure Food and Drugs Act with the Federal Food, Drug, and Cosmetic Act (FFDCA). The FFDCA required that drug manufacturers submit, prior to marketing, a new drug application (NDA) demonstrating, among other things, that the product was safe. In addition, the FFDCA expanded the prohibition of the introduction into interstate commerce of misbranded or adulterated products to include therapeutic devices and cosmetics. The FFDCA also included some controls over manufacturing establishments, including an authority to inspect such facilities. In 1962, Congress passed the Kefauver-Harris Drug Amendments to the FFDCA (P.L. 87-781), which required that manufacturers provide "substantial evidence" of drug effectiveness, in addition to safety.

The Medical Device Amendments of 1976 (MDA, P.L. 94-295) was the first major legislation enacted to address the premarket review of medical devices, and it included a number of postmarket requirements as well (e.g., current good manufacturing practices, or CGMPs). The MDA established a risk-based method for classifying and regulating medical devices, and established two premarket regulatory pathways: premarket approval (PMA) and premarket notification (510(k)).

Speeding Access to Medical Products

Over the years, Congress and FDA have made modifications to the established standard premarket review pathways in an attempt to improve access to medical products that would meet a compelling unmet need. The aim of congressional reforms to FDA's review process has primarily been to speed medical product entry to market. These changes are often described as benefiting patients by allowing an innovative drug or device to be more rapidly available in a potentially dire situation for the patient. On the other hand, the less fully regulators explore the safety and effectiveness of medical products before marketing relative to standard review, the higher the odds of unidentified adverse events. The appropriate balance between this risk of unidentified adverse effects and having faster access to beneficial new drugs and devices—and therefore the ideal degree of scrutiny of their safety and effectiveness prior to their marketing—is and will continue to be a matter of debate.

Broadly, in an effort to improve access to medical products for serious or life-threatening diseases with limited treatment options, FDA and Congress have established mechanisms to (1) expand access to drugs and devices that are still under investigation, and (2) expedite the actual premarket development and review processes for new products coming onto the market. As used in the following sections, the term *drugs* generally includes biologics.

Investigational Medical Products

In general, a drug or device may be provided to patients only if FDA has cleared or approved its marketing application or authorized its use in a clinical trial under an investigational new drug (IND) or investigational device exemption (IDE) application. In certain circumstances, patients may be able to obtain access to investigational drugs and devices outside this framework through expanded access (compassionate use) programs. In 1987, FDA issued a rule creating procedures through which patients could request permission from FDA to obtain an investigational drug outside a clinical trial (treatment IND program; 52 *Federal Register* 19466). This pathway was codified in the FDA Modernization Act of 1997 (FDAMA, P.L. 105-115) and expanded to include investigational devices. In the

early 1990s, FDA issued additional policies to allow access to HIV/AIDS drugs for patients unable to enroll in a clinical trial (e.g., parallel track). In 2018, the Right to Try Act (P.L. 115-176) created a pathway for patients to obtain access to investigational drugs without FDA permission.

Expedited Development and Review Programs

In 1988, FDA issued an interim rule establishing what is now called *fast track* designation to "expedite the development, evaluation, and marketing of new therapies" by allowing, for certain serious and life-threatening conditions, FDA review to begin before clinical trials are completed (53 *Federal Register* 41516). In 1992, FDA issued a rule creating an *accelerated approval* pathway, allowing for the use of surrogate endpoints (e.g., biomarker test) to predict the likely success of a new treatment, rather than clinical endpoints (e.g., heart attack or death), with the requirement that postmarketing studies be completed to demonstrate actual benefit (57 *Federal Register* 53942).

Mechanisms to expedite drug development and review also have been established through legislation. For example, actual and perceived delays in the review of NDAs prior to marketing resulted in continued pressure from industry and patient groups on Congress and FDA for a faster drug review process. Toward this end, the Prescription Drug User Fee Act of 1992 (PDUFA, P.L. 102-571) gave FDA the authority to collect fees from the brand pharmaceutical industry and to use the revenue to support the drug review process by hiring additional personnel to evaluate NDAs. Medical device user fees were added 10 years later by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA, P.L. 107-250). In 2012, the FDA Safety and Innovation Act (FDASIA, P.L. 112-144) authorized FDA to collect fees to support the review process of generic drugs and biosimilar biological products. The five-year reauthorization cycle of FDA's user fees has served as a legislative vehicle for modifying FDA regulatory authorities. For example, Congress codified the fast track designation in FDAMA. FDASIA made changes to the fast track designation, codified accelerated approval, and created the *breakthrough therapy* designation, another expedited drug development and review pathway. FDA user fees are currently authorized through FY2022.

More recently, the 21st Century Cures Act (P.L. 114-255) established a new *breakthrough device* category allowing FDA to expedite development and prioritize review of devices that (1) provide more effective diagnosis or treatment of a life-threatening or irreversibly debilitating condition, and (2) represent breakthrough technologies for which no approved alternatives exist, offer significant advantages over existing alternatives, or are in the best interest of patients. The Cures Act included additional provisions intended to streamline medical product approval.

Some commentators have expressed concern with the increasing reliance on expedited programs. According to FDA, 73% of novel drug approvals—new molecular entities (NMEs) and new therapeutic biologics—in 2018 were designated in at least one expedited program. In 2017, 61% were (FDA's 2017 and 2018 New Drug Therapy Approvals reports). A December 2015 Government Accountability Office (GAO) report found that from October 2006 through December 2014, of the 216 NMEs approved (excluding new biologics), 51% used at least one expedited program. The most common product category for drugs that used at least one expedited program was oncology. Some also have expressed concern with the terminology used to describe these programs; for example, the term "breakthrough drug" may be misinterpreted by patients and physicians to mean that the "FDA designated breakthrough drug" is somehow more effective than other drugs when this has not been proven to be the case.

Other commentators, however, have characterized the current drug development and review processes as slow and requiring companies to invest in costly and time-intensive clinical testing. These commentators have generally supported further expediting drug development and review.

Postmarket Surveillance

FDA has several systems to monitor drug and device safety following approval or clearance. Drug manufacturers must report all serious and unexpected adverse events to FDA within 15 days of becoming aware of them, and all other adverse events in other mandated periodic reports to the agency. The reports are made publicly available through the FDA Adverse Event Reporting System (FAERS). Medical device manufacturers must report device-related deaths, serious injuries, and malfunctions to FDA within 30 days of becoming aware of them. These reports are made publicly available in the Manufacturer and User Facility Device Experience (MAUDE) database or Alternative Summary Reporting (ASR) data files that were made publicly available when the ASR program ended in June 2019. However, these passive surveillance systems have several limitations. As such, FDA also conducts active postmarket surveillance. For drugs, this occurs through FDA's Sentinel System, which uses electronic health records and other data sources to obtain information about a drug. For devices, FDA is in the process of developing the National Evaluation System for health Technology (NEST). The goal of NEST is to synthesize real-world evidence from multiple sources to inform medical device safety and effectiveness, and is intended to serve a similar purpose to the Sentinel System. However, NEST is not without its limitations (e.g., it does not link to electronic health records), and FDA's timeline for a full rollout of NEST is not clear.

In addition, while premarket studies are designed to identify safety issues, they may not identify all long-term or rare adverse events. As such, FDA may require a drug or device sponsor to conduct postmarket studies. These studies may be particularly useful when one of the expedited pathways is used because it allows for the marketing and benefits of the product to be realized sooner, while at the same time allowing for a fuller safety profile to be developed. Several GAO reports have identified some weaknesses in FDA's oversight of postmarketing safety studies and their timely completion.

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