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Medical Product Innovation and Regulation: Benefits vs. Risks

Prior to marketing in the United States, medical products are reviewed for safety and effectiveness by the Food and Drug Administration (FDA). Medical products regulated by FDA include prescription drugs, medical devices, and biologics. During the premarket review process, FDA balances the benefits that patients may receive from using the product against the harms or risks that some patients may experience.

Brief History of Medical Product Regulation

Congressional action to regulate medical products has often been in reaction to harm caused by an under regulated medical product. The Biologics Control Act of 1902 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 Biologics Control Act was passed in response to deaths, many in children, from tetanus contamination of smallpox vaccine and diphtheria antitoxin. The act focused on the manufacturing process and required that facilities be inspected before a federal license was issued to market a biological product.

The regulation of drugs began with the 1906 Food and Drugs Act. The 1906 law did not involve any type of premarket control over new drugs to ensure safety and did not include inspections or any other regulation of manufacturing facilities. 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 (such as alcohol, heroin, and cocaine) must be listed.

Responding to another safety incident, in 1938 Congress replaced the Food and Drugs Act with the Federal Food, Drug, and Cosmetic Act (FFDCA). To make the taste of a new sulfa drug more appealing to pediatric patients, a drug company added a solvent to its product, Elixir Sulfanilamide. The solvent in the untested product was highly toxic and caused the death of over 100 people, including many children. The FFDCA required that drug manufacturers submit, prior to marketing, a new drug application (NDA) demonstrating, among other things, that the product was safe. The FFDCA also included some controls over manufacturing establishments.

In 1962, Congress passed the Kefauver-Harris Drug Amendments to the FFDCA in reaction to the birth defects and deaths associated with the use of thalidomide by pregnant women in Europe. The 1962 law increased drug safety provisions and required that manufacturers provide evidence of drug effectiveness.

The Medical Device Amendments of 1976 was the first major legislation enacted to address the review of medical devices. The law was passed following the deaths of 17 women and the injury of thousands associated with the use of the Dalkon Shield, a contraceptive intrauterine device.

Efforts to Speed Product Access and FDA Review

Following the 1962 Kefauver-Harris Drug Amendments, early access (compassionate use) programs allowed some patients to use drugs that were still under investigation; FDA published a rule regarding such access to cancer drugs in 1979. In 1987, FDA formalized the steps to obtain an investigational drug outside a clinical trial (treatment IND, later codified by Congress). FDA established a policy in the early 1990s to allow access to HIV/AIDS drugs for patients unable to enroll in a clinical trial (parallel track).

FDA also created mechanisms to speed drug development and review. *Priority review* was begun by FDA in 1974 and modified by the agency in 1987 and 1992; it directs attention and resources to drugs that offer a treatment advance. FDA launched *fast track* in 1988 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. FDA created the *accelerated approval* pathway in 1992 for serious or life-threatening diseases that lack effective treatment. It allows use of a surrogate endpoint, via a biomarker test, to *predict likely* patient improvement from a new treatment, rather than a clinical endpoint (symptom or death) that *shows actual* improvement in how a patient feels or length of life. A January 2017 FDA report states, however, that most biomarkers have not been shown to reliably predict clinical outcomes due to the complexity of diseases and therapies.

Despite the use of these faster review mechanisms, industry and patient groups continued to press Congress for a more rapid drug review process. The Prescription Drug User Fee Act of 1992 (PDUFA, P.L. 102-571) gave FDA authority to collect fees from the 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 (P.L. 107-250).

Congress has addressed FDA user fee reauthorization in five-year increments and often amends FDA regulatory authorities at the same time. For example, Congress codified priority review in PDUFA, fast track in the Food and Drug Administration Modernization Act of 1997 (P.L. 105-115), and accelerated approval in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA, P.L. 112-144). Congress itself created the *breakthrough drug* category, another expedited review program added in FDASIA. However, studies have found that the term *breakthrough drug* is potentially misleading. The term is often misinterpreted by patients and physicians

to mean that the "FDA designated breakthrough drug" is more effective than other drugs when this has not been proven. Use of this term in promotional material and advertising is of concern to some in academic medicine.

In the 21st Century Cures Act (P.L. 114-255), Congress crafted a new *breakthrough device* category to provide priority review for 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. Proponents considered this necessary even though the time required for FDA premarket review of a device is less than drug review, and the standard of evidence for device review (reasonable assurance of safety and effectiveness) is lower than drug review (substantial evidence that the drug is safe and effective).

Congressional reforms to FDA's review process have primarily sought to speed market entry of medical products. These changes are often described as benefiting patients by making innovative drugs or devices more rapidly available, while also being advantageous to the manufacturer. However, others say that the less fully regulators explore the safety and effectiveness of medical products before marketing, the higher the odds of unidentified adverse effects for patients. For example, patient harm and deaths might have been minimized if human trials had been required prior to widespread use of implanted devices such as the DePuy metal-on-metal hip and the Medtronic Sprint Fidelis and St Jude Medical Riata cardiac leads (wires).

Examples of harm exist for drugs as well. A May 2017 *JAMA* study examined 222 novel therapeutics (183 drugs and 39 biologics) approved by FDA from 2001 through 2010 and found that 71, or 32%, were affected by postmarket safety events. As a result, three products were withdrawn from the market (new safety information profoundly changed the risk/benefit balance), there were 61 boxed warnings (for major, often life-threatening safety risks), and 59 safety communications (for non-life-threatening safety risks). Postmarket safety events were more frequent among biologics, therapeutics for the treatment of psychiatric disease, and therapeutics that received accelerated approval. The study did not assess fast track or breakthrough therapies.

A December 2017 *JAMA* report analyzed all 174 new drugs and biologics approved by FDA from 2012 through 2016 and found that 105, or 60%, used one or more expedited programs. It assessed the median development time which ranged from 8.0 years for products without an expedited program to 4.8 years for those with breakthrough status.

FDA has systems to monitor drug safety following approval. Drug manufacturers are required to report adverse events to FDA, and drugs with potential safety issues may be tracked via an internal database. FDA also may require a drug sponsor to conduct postmarket safety and effectiveness studies. Confirmatory trials are especially important when accelerated approval is used because the safety picture is less fully developed. However, numerous reports from Government Accountability Office (GAO), the Department of Health and Human Services (HHS) Inspector General (IG), the National Academies and others have criticized FDA monitoring systems and found weaknesses in its oversight of postmarket drug safety.

A December 2015 GAO report states that "FDA has supported efforts to shorten development and streamline the agency's review of drug applications through expedited pathways. However, we found problems with the agency's efforts to oversee and track potential safety issues and postmarket studies once those drugs are on the market." Moreover, it maintains that "FDA lacks comprehensive plans to address the problems with its tracked safety issue and postmarket study data." FDA oversight of medical products has been on the GAO High-Risk List since 2009. The GAO list identifies agencies and program areas that are high risk due to certain vulnerabilities or are most in need of transformation. FDA oversight of medical products also has been identified for over a decade by the HHS IG as one of the department's top 10 management challenges.

Regarding devices, FDA and others have identified a number of limitations associated with the current medical device postmarket surveillance system. A February 2017 GAO report on power morcellators illustrates the weakness of the current passive system: it relies on individuals recognizing the harm caused by a device and sending an adverse event report to FDA. Although the agency is expanding system capabilities, its new medical device postmarket monitoring system, the National Evaluation System for health Technology (NEST), is expected to be under development for the next several years.

Concluding Observations

Medical products are not completely safe, nor are they equally effective for all individuals. Larger and longer clinical trials would better detect rare or latent adverse events, but some believe the wait is unreasonably long and that any risks are offset by earlier access to the benefits of innovative new treatments. However, innovative products do not always result in therapeutic advances. In the rush to market, it is important not to conflate medical product "innovation" with an actual therapeutic advance for patients. An innovative mode of action in a drug or device may not necessarily improve the life of a patient. New is not always better. A January 2017 FDA report found that early studies can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. Shortening or otherwise diminishing the evidence-gathering phase on a new medical product may have harmful consequences for patients.

CRS Products

CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*

CRS Report R42130, *FDA Regulation of Medical Devices*

CRS Report R44620, *Biologics and Biosimilars: Background and Key Issues*

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