How Drugs are Developed and Approved by the FDA: Current Process and Future Directions

Arthur A. Ciociola, PhD, FACG[1], Lawrence B. Cohen, MD, FACG[2] and Prasad Kulkarni, MD, FACG[3] and the FDA-Related Matters Committee of the American College of Gastroenterology

OBJECTIVES: **This article provides an overview of FDA's regulatory processes for drug development and approval, and the estimated costs associated with the development of a drug, and also examines the issues and challenges facing the FDA in the near future.**

METHODS: **A literature search was performed using MEDLINE to summarize the current FDA drug approval processes and future directions. MEDLINE was further utilized to search for all cost analysis studies performed to evaluate the pharmaceutical industry R&D productivity and drug development cost estimates.**

RESULTS: **While the drug approval process remains at high risk and spans over multiple years, the FDA drug review and approval process has improved, with the median approval time for new molecular drugs been reduced from 19 months to 10 months. The overall cost to development of a drug remains quite high and has been estimated to range from $868M to $1,241M USD. Several new laws have been enacted, including the FDA Safety and Innovation Act (FDASIA) of 2013, which is designed to improve the drug approval process and enhance access to new medicines.**

CONCLUSIONS: **The FDA's improved processes for drug approval and post-market surveillance have achieved the goal of providing patients with timely access to effective drugs while minimizing the risk of drug-related harm. The FDA drug approval process is not without controversy, as a number of well-known gastroenterology drugs have been withdrawn from the US market over the past few years. With the approval of the new FDASIA law, the FDA will continue to improve their processes and, working together with the ACG through the FDA-Related Matters Committee, continue to develop safe and effective drugs for our patients.**

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The US Food and Drug Administration (FDA) is responsible, among its many other duties, for enforcing the nation's laws designed to protect the health and safety of American consumers. The Federal Food, Drug, and Cosmetic Act of 1938, the major US food and drug law, empowered the FDA with the authority to ensure that drugs and devices are safe and effective; that foods are safe and produced under sanitary conditions; that cosmetics are safe and made from appropriate ingredients; and that product labeling and packaging is truthful, informative, and not deceptive.

Beyond these far-reaching objectives, however, the FDA is charged with (a) helping to speed product innovations and (b) promoting proper use of medicines, devices, and foods by promulgating scientifically sound information to the public. Although it is widely known that FDA regulates all food and drugs sold in the United States, the FDA is also responsible for the oversight of many consumer products such as cosmetics, bottled water, infant formulas, dietary supplements, vaccines, blood products, biologics, electronic products that give off radiation, ultrasonic equipment, veterinary, and tobacco products. Because each of these product categories has widely divergent rules and regulations for approval and/or sale, the FDA has created criteria to help define which category regulations should apply. For example, if a product is intended to cure, treat, mitigate, diagnose, or prevent disease in humans, or is intended to affect the structure or function of the human body, it is likely to be considered a drug and is subject to FDA's drug regulations.

This article provides an overview of FDA's regulatory processes for drug development and approval, and examines issues and challenges facing the FDA in the near future.

[1]Global Regulatory Affairs, Alcon Laboratories, Fort Worth, Texas, USA; [2]Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [3]Gastroenterology, University of South Florida, Tampa, Florida, USA. **Correspondence:** Arthur A. Ciociola, PhD, FACG, Global Regulatory Affairs, Alcon Laboratories, 6201 South Freeway TC45, Fort Worth, Texas 76134, USA. E-mail: arthur.ciociola@alcon.com

The drug development and approval process

The main FDA division responsible for approving drugs is the Center for Drug Evaluation and Research (CDER). CDER evaluates all new drugs before they can be marketed in the United States and ensures that drugs, both brand name and generic, are safe and efficacious and that the health benefits outweigh the known risks. Drug companies seeking to sell a drug in the United States must first perform a series of scientific investigations to determine whether the drug is safe and effective. The process of drug development, from initial discovery through final market approval, requires 10 years on average.

The starting point of the regulatory process generally begins with submission of an investigational new drug application (IND) to the FDA. The IND provides detailed information on the chemistry, manufacturing, pharmacology, and toxicology of the drug and outlines the human tests the company "sponsor" proposes to conduct in order to demonstrate safety and efficacy. The FDA's review of an IND is intended to assess the scientific validity of the proposed research, ensure that patients are not exposed to undue risk, and to decide if it is reasonable for the sponsor to move forward with drug testing in human subjects. A clinical trial may begin only if the FDA has raised no objections and the study design is approved by an overseeing ethics review board.

Clinical investigations of a study drug are designated as phase 1, phase 2, and phase 3 studies and are conducted sequentially. Phase 4 studies are conducted after the drug is approved for marketing in the United States. Phase 1 studies, often representing the first in-human exposure to the drug, are designed to determine the metabolic and pharmacologic profiles of the agent in humans, identify possible side effects, and, if possible, gain evidence of drug effectiveness. Phase 1 studies are typically single-blind studies that involve a small number of subjects (20–80). They are intended to minimize potential risk to future study subjects while providing sufficient information to enable the design of scientifically valid phase 2 studies. Phase 2 trials are controlled clinical studies to evaluate the effectiveness of the drug in a specific disease, and to define an effective dose that provides the optimal benefit–risk profile for the use of the drug. Phase 2 studies typically involve several hundred patients. Phase 3 studies are large-scale clinical studies, often performed in tandem using identical study design, involving several thousand patients. Phase 3 trials are intended to confirm the effectiveness and safety findings from previous studies. Phase 4 studies, undertaken following drug approval, are usually required by the FDA to provide additional information regarding the product's safety, efficacy, or manufacturing processes (**Table 1**). Throughout the development process, FDA provides sponsors with strategic guidance either in writing or during meetings to facilitate drug development. For example, a "pre-IND" meeting may be requested to discuss the drug's preclinical data and to design the initial phase 1 clinical studies.

Upon completion of drug investigations, the sponsor summarizes all of the data obtained from manufacturing, preclinical, and clinical studies into a new drug marketing application (NDA) that is submitted to the FDA. Provided the application is adjudged by the agency to be substantially complete, the NDA proceeds through five review areas: medical, pharmacology, chemistry, biopharmaceutical, and statistical. Communication between FDA and sponsors, in the form of telephone conversations, letters, or meetings, is common during the NDA review process. The agency's reviewers attempt to confirm and validate the sponsor's findings and conclusions that the drug is safe and effective for its proposed use and meets manufacturing and quality standards. The FDA may call upon an advisory committee, comprised of external experts whose membership includes scientific members who are technically qualified experts in their field (e.g., clinical medicine, biostatistics), consumer, and patient group representatives as well as industry representatives who act on behalf of the regulated industry to provide independent opinions and recommendations

Table 1. The drug development and approval process

Stage	Average no. of years	Population tested	Purpose	Estimated success rate	Capitalized cost (millions USD)
Preclinical (CMC) testing and animal studies	5.5	Laboratory and animal studies	To assess biological activity and safety	5 to 20 out of 5,000 to 10,000 compounds	185.6 (7)
Phase 1	2	20 to 80 Healthy volunteers	Determine drug kinetics, its dosage, and safety in humans	2 to 5 of above	30.5 (8)
Phase 2	2	100 to 300 Patient volunteers	Evaluate the drug for efficacy and safety (adverse events)	2 to 5 of above	41.6 (8)
Phase 3	2 to 4	1,000 to 3,000 Patient volunteers	Larger scale usage to confirm efficacy and to monitor for adverse events from long-term use	2 to 5 of above	119.2 (8)
FDA review	1 to 2		Unbiased independent review process for approval or denial	1 compound selected	1.96 (direct cost) (3)
Phase 4	15	Entire user population	Additional post-marketing surveillance required by FDA or sponsor-initiated	NA	Variable

CMC, Chemistry, Manufacturing, and Controls; FDA, Food and Drug Administration; NA, not available; USD, United States dollar.

on the approvability of the NDA, particularly for drugs with new pharmacologic actions or significant safety risks (http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/MembershipTypes/default.htm). Although the FDA takes the recommendations of the advisory committee into consideration, they are not required to accept its conclusions. Upon completion of the NDA review, an FDA Therapeutic Division Director and management evaluates the technical reviews and decides the action the division will take regarding approval of the application. The agency's action letters, which are provided to sponsors at the completion of an NDA review, have recently been redesigned. An "approval" letter indicates that the study drug is approved for marketing in the United States. The "approvable" and "not approvable" letters that were previously issued have now been replaced by a "complete response letter," which indicates that the NDA is not approved in its present form. The action letter describes the specific deficiencies identified with the application. A sponsor's options include (a) resubmission of additional data addressing the deficiencies, (b) withdrawal of the NDA, or (c) request a hearing with the agency for further clarification of the deficiencies. An NDA approval will often include various postmarket commitments, covering a broad range of clinical as well as non-clinical activities, to more fully characterize the risk–benefit profile of the drug within special patient populations and develop strategies to minimize its inappropriate use.

The Prescription Drug User Fee Act (PDUFA) of 1992 established performance standards for completion of an NDA review. This law was prompted by public criticism over the frequently extended periods of review for NDAs that sometimes lasted 24 to 36 months. Today, CDER is expected to review and act on at least 90% of NDAs for standard drugs no later than 10 months after filing of the application, and no later than 6 months for priority drugs. In exchange, the law permits the FDA to collect fees from sponsors of NDAs to pay for the resources needed to review these applications. In 2011 (last data available), FDA collected over US$593 million in PDUFA fees that supported the costs of 3,877 full-time FDA staff responsible for reviewing the drug applications (1). The PDUFA user fees represented 18% of the FDA's 2011 total annual budget of US$3.3 billion (2). In 2013, FDA estimates it will collect over US$700 million in drug user fees and the cost of an NDA filing will be US$1.96 million (3). In general, the PDUFA program has been considered successful, as the median approval time for new molecular drugs has been reduced from 19 months to 10 months.

The overall cost of drug development is controversial and has been cited in part as justification for the cost of drugs to consumers (4). A number of financial model studies have estimated the total capitalized cost of an approved drug to range from US$868 to US$1,241 million (**Table 2**). A review by Morgan *et al.* (10) also reported a wide range of costs, suggesting that differences were likely due to lack of transparency of the data sources and analytical methods. Pronker *et al.* (11) conducted a similar review of the cost of drug development and suggested there is no standard methodology to assess attrition rates and investment costs critical to determine the overall costs.

Future directions for FDA's drug regulations

The US Congress and President Obama recently approved the FDA Safety and Innovation Act of 2013 that is designed to improve the drug approval process and enhance access to new medicines. The FDA Safety and Innovation Act law authorizes the FDA to continue to collect user fees from companies including application fees for generic drug approval. The new law also provides FDA with funding to review "biosimilar" drugs, products that are similar to an approved biological product. The law is intended to provide additional therapeutic options and stimulate price competition within the biologic drug marketplace. FDA Safety and Innovation Act also renewed and made permanent three laws to improve the safety and effectiveness of pediatric drugs, biological products, and medical devices, i.e., Pediatric Research Equity Act, Best Pharmaceuticals for Children Act, and the Pediatric Medical Device Safety and Improvement Act. Pediatric Research Equity Act requires that NDA have a mandatory assessment of the safety and effectiveness of the drug or biologic for the new indications in all pediatric populations. The pediatric assessment will typically require pharmacokinetic, pharmacodynamic data, and/or safety studies across the various pediatric subpopulations. In an effort to stimulate drug research in children, Best Pharmaceuticals for Children Act authorizes FDA to request that companies may voluntarily conduct studies in pediatric populations in exchange for a 6-month extension of the drug's marketing exclusivity. Such a

Table 2. Capitalized cost per approved drug

Study	Drugs evaluated (*N*)	Non-clinical costs (USD)	Clinical costs (USD)	Total capitalized costs (year USD)
Adams and Brantner (5)	3,181	381M	487M	868M (2000 USD)
Adams and Brantner (6)	2,245	NA	NA	1,214M (1999 USD)
DiMasi and Grabowski (7)	522 17 (total costs)	615M	626M	1,241M (2005 USD)
DiMasi *et al.* (8)	538 68 (total costs)	355M	467M	802M (2000 USD)
Vernon *et al.* (9)	538 68 (total costs)	NA	NA	992 (2000 USD)

M, millions; NA, not available or reported; year USD, United States dollar value for the noted year corrected for inflation.

"written request" may only be issued by the FDA pediatric committee and specifies the required studies needed to allow FDA to grant an extension to the drug's US market exclusivity.

In the future, FDA is likely to enhance their pharmacovigilance processes as the Institute of Medicine recently issued a report recommending that the FDA restructure its post-market surveillance processes to improve drug safety monitoring by requiring post-market observational studies that provide real-time data alerting FDA to early signals of drug toxicity.

The FDA is likely to continue to support the development of personalized medicines, which utilizes genetics or biomarkers to identify a small subset of patients who would most likely benefit from a drug. For example, FDA recently approved cetuximab for use only in patients with *K-ras* mutation-negative metastatic colorectal cancer.

Conclusion

The processes for drug approval and post-market surveillance have arguably achieved the goal of providing patients with timely access to effective drugs while minimizing the risk of drug-related harm. However, the FDA drug approval process is not without controversy as a number of well-known gastroenterology drugs have been withdrawn from the US market including Zelnorm (tegaserod) in 2007, Bextra (valdecoxib) in 2005, Vioxx (rofecoxib) in 2004, Lotronex (alosetron), Rezulin (troglitazone), and Propulsid (cisapride) in 2000 owing to lack of safety or effectiveness. Even more recently in 2011, the FDA determined that Halflytely and Bisacodyl Tablets Bowel Prep Kit oral solution and two bisacodyl delayed release tablets (5 and 10 mg) should be withdrawn from the US market for reasons of safety or lack of effectiveness. Such controversies are even more evident in the medical device area as reported by Zuckerman *et al.* (12), who identified 113 high-risk medical device recalls in the United States from January 2005 through December 2009. Of these high-risk recalls, the authors report that the more rigorous premarket approval process was used to approve only 21 of the 113 (19%) devices, while most of the remaining recalled medical devices were cleared through a less rigorous alternative pathway to the premarket approval known as the 510(k) provision, which requires the sponsor to only demonstrate that the device is "substantially equivalent" to another "predicate" device that is currently on the US market. The authors conclude that their findings reveal critical flaws in the current FDA medical device approval system and corrections will require either congressional action or major changes in FDA regulatory policy (12). Nonetheless, the FDA remains the subject of criticism from both government and non-government groups with claims of excessive regulation, overly lax regulation, and biases in the drug approval process. Some believe the drug industry user fees, which support the drug approval process, inherently biases drug approvals in favor of drug manufacturers. Patient and physician advocacy groups continue to call for greater transparency in the drug review and safety surveillance processes. It is clear that drug development would be enhanced by expanding the role of patients and clinicians in all stages of drug development. With approval of the new FDA Safety and Innovation Act law, the FDA has clearly made moves in that direction. Similarly, the ACG through a number of activities including the FDA-Related Matters Committee is making significant efforts to expand its relationships with FDA to mutually support the development of safe and effective drugs for our patients.

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CONFLICT OF INTEREST

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