

Navigating commercial approval of therapeutics: The evolution of the United States Food and Drug Administration

Dillon Jarrell¹, Megan Hamrick¹, Michaela Good¹, Anna Chopp² and Mark Brown^{3-5*}

¹Department of Chemical and Biological Engineering, Colorado State University, USA

²Department of Health and Exercise Sciences, Colorado State University, USA

³Department of Clinical Sciences, Colorado State University, USA

⁴Cell and Molecular Biology Program, Colorado State University, USA

⁵Colorado School of Public Health, Colorado State University, USA

Abstract

The Tufts Center for the Study of Drug Development determined that the average expenditures for developing prescription drugs, navigating regulatory hurdles, and commercializing a drug product in the United States was greater than \$2.6 billion in 2014. Critics of the U.S. Food and Drug Administration cite outdated, protracted, and overly complicated regulatory processes as a common pitfall contributing to unnecessary costs for drug developers. These issues are particularly acute among companies that are navigating such regulatory processes for the first time. In an effort to simplify and shorten drug approval processes, thereby increasing access to lifesaving therapeutics, U.S. Congress is considering new legislation called the 21st Century Cures Act. Herein, we provide an overview of the current organization of the U.S. Food and Drug Administration and highlight the projected benefits of Congress' long-awaited answer to the bottleneck of drug approvals.

Introduction

The Food and Drug Administration (FDA) is a division of the U.S. Department of Health and Human Services (HHS), which also includes the National Institutes of Health (NIH) as well as the Centers for Medicare and Medicaid [1]. The FDA was allocated a budget of \$2.6 billion for the 2015 fiscal year, making it the eighth-largest division of HHS. The purpose of the FDA is to protect and advance the public health of the population of the United States through the careful regulation and inspection of a wide scope of consumer goods. This oversight includes all products whose misuse, contamination, defectiveness, or mislabeling could result in harm to the consumer. As the name implies, the assurance of safe and effective pharmaceutical drugs and food products is central to the list of responsibilities of the FDA. However, the FDA also regulates tobacco, dietary supplements, medical devices, cosmetics, radiation-emitting products, manufacturing and production facilities, and countless other products and processes. Furthermore, the FDA seeks to promote the public health by ensuring that beneficial new technologies become available to the public in an expedient, safe, and affordable manner. Finally, the FDA plays a significant role in the United States' counterterrorism initiative. Public health threats mandate the existence of a government entity capable of screening the nation's food and drug supply as well as promoting the development of products capable of responding to these threats.

Though it is charged with promoting public health in the U.S., the FDA has been at the center of growing criticism related to what have been described as antiquated and overly complicated regulatory processes which drive increases in consumer drug costs while slowing access to life-saving therapeutics. These limitations are particularly problematic for seriously life-threatening conditions such as cancer.

On one hand, the financial burden of supporting the rising costs of cancer treatments threatens to topple both private and public insurance programs. On the other hand, cancer patients and their families are willing to go to extreme measures for even modest increases in life expectancy. Zaltrap, for example, which is marketed by Sanofi for the treatment of metastatic colorectal cancer, was approved in the U.S. with a price tag of \$11,000/month despite the fact that it prolongs median survival by less than two months [2]. In response to the public's sticker shock associated with seemingly unjustified drug prices, the pharmaceutical industry often cites the estimated costs of developing commercial drugs as determined by the Tufts Center for the Study of Drug Development [3]. As a result, the FDA has been vilified for its perceived contributions to these rising costs. In response to an increasing public outcry for regulatory and funding reforms, Congress has received strong support for its proposed 21st Century Cures Act [4], which is intended to aid the development and approval processes for prescription drugs in an effort to improve access while reducing costs. Herein, we provide a comprehensive overview of the FDA and comment on the projected benefits of Congress' latest attempt to respond to the protracted regulatory processes of drug approval.

Correspondence to: Mark A. Brown, Department of Clinical Sciences, Colorado State University, 1052 Campus Delivery, Fort Collins, CO 80523-1052, USA; E-mail: M.Brown@colostate.edu

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Discussion

The FDA was established in the wake of reckless mislabeling of food and drugs, a rapidly-progressing understanding of human anatomy, microbiology, and disease, and Upton Sinclair's infamous exposure of the early-twentieth-century meat-packing industry [2]. Due to constantly evolving economics, technology, and health studies, the organization of the FDA is fairly dynamic. New offices, departments, and centers are added and removed regularly. At its broadest, the 2015 FDA consists of five offices, including seven major centers [1].

While it is true that the FDA is largely composed of divisions that regulate various fields of public health, the Office of the Commissioner (OC) is not associated with the regulation of any specific products. Rather, the OC provides agency-wide direction and leadership. Headed by the President-appointed Commissioner of the FDA, the OC consists of nine offices. The responsibilities of these offices include: communication with Congress, media, and the general public; development of legislation and program administration; oversight of criminal and civil litigation hearings; women's health issues; and strategic planning for the entire administration. Ultimately, the OC provides the legal framework and authority within which the regulatory divisions of the FDA operate.

The National Center for Toxicological Research (NCTR) was established in 1971 and is the only major center of the OC. Fittingly, it is not associated with the regulation of a specific sector of public health products. The NCTR is also the only center not located in the Washington, D.C. area. Its state-of-the-art research facility, as the name implies, focuses on the field of toxicology, including the study of the nature, effects, and discovery of potential chemical poisons. The NCTR is divided into eight main divisions which specialize in organic and inorganic toxicological fields ranging from biometry and caloric intake studies to neurotoxicology, reproductive and developmental toxicology, and genetic toxicology. The NCTR assesses the toxicity of known compounds through a rigorous peer-review and experimental-replication process and also devotes a significant portion of its resources to original research and discovery in the field of toxicology. This research occurs across over 100 general-purpose labs, 82 primate labs, four "high-containment" labs for high-level biological agents, and an on-site, hazardous waste disposal facility. It ultimately establishes a basis against which the other divisions of the FDA can measure new products seeking approval for market. In addition to coordinating with other FDA divisions, the scientific findings of the NCTR are published and used by research universities and private research enterprises throughout the United States. The scientific basis for much of the legislation that arises from the OC can be traced to the research and publications of the NCTR.

The bulk of FDA regulatory activities is handled by only two of its offices, namely, the Office of Foods and Veterinary Medicine (OFVM), which regulates food and animal products, and the Office of Medical Products and Tobacco (OMDT), which oversees the regulation of all products in the field of human medicine. The OFVM consists of two of the FDA's six product-oriented centers including the Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM).

CFSAN is, by far, the largest of the seven centers of the FDA. This Center oversees nearly half of the firms under the FDA's jurisdiction, totaling approximately 49,000, that produce \$270 billion worth of domestic and imported foods and cosmetics. With the exception of food and color additives, the products that CFSAN regulates can legally

be sold without pre-market FDA approval. Thus, CFSAN depends largely on post-marketing surveillance and investigations. The focus of CFSAN can be reduced to three primary goals: 1) that foods are safe, nutritious, and wholesome; 2) that cosmetics are safe; and 3) that foods and cosmetics are honestly, accurately, and informatively labeled.

The ties between veterinary medicine and food safety and applied nutrition may seem too few to merit the grouping of these two centers into one office. However, these two fields are, in fact, co-dependent. CVM is responsible for the safety and efficacy of products intended for animals, including drugs, veterinary devices, and feeds. The connection to the food sector is manifest in the CVM's regulation of foods derived from food-producing animals. This responsibility has recently grown to include the regulation of genetic modification in animals to be used in the human food supply. Similarly to CFSAN's regulation of foodstuffs, the CVM does not regulate the entire industry of animal-derived foods. While it oversees the labeling, safety, and production of milk, dairy, fish, and shellfish, the oversight of meat and poultry (products resulting from the slaughter of food animals) has been tasked to the USDA. In addition, the EPA regulates all pesticides, used for both plant and animal food sources. Thus, the CVM ensures the safety and honesty of products made for animal consumption while also serving an essential role in the chain of human food production.

As previously mentioned, the OFVM contains two of the FDA's six product-oriented centers. The remaining four operate in the OMPT. A significant percentage of the OMDT's domain is the careful evaluation of new pharmaceutical drugs and tobacco, but it is also responsible for the regulation and approval of medical devices and radiation. It collaborates closely with the NCTR and oversees the FDA's medical programs and initiatives.

The Center for Drug Evaluation and Research (CDER) is to the pharmaceutical industry what CFSAN is to the food industry. CDER's regulation extends to all human drugs, defined as all of the products that cure, mitigate, treat, or diagnose disease via a chemical action in or on the body. CDER is the largest center with regard to employees, consisting of 12 main offices and 37 smaller divisions and offices. These offices span specific drug types (e.g. Office of Generic Drugs), anatomical regions (e.g. Division of Cardiovascular and Renal Products), and countless quality-control niches (e.g. Office of Manufacturing Quality, Office of Unapproved Drugs and Labeling Compliance, etc.). It should be noted that the 1938 Food, Drug and Cosmetic Act (FDCA) mandated that the safety of all new drugs be proven to the FDA prior to their distribution in the United States [1]. The revolutionary system of pre-market approval that the FDCA established is contrary to the post-market surveillance implemented by CFSAN regarding foodstuffs. Since 1938, the pre-market approval of drugs by the FDA has evolved into an extensive, meticulous process. The entire process averages 8-10 years and includes several checkpoints, namely preclinical trials, an Investigational New Drug (IND) application, four phases of clinical trials (only the first three must occur successfully prior to market approval), and a New Drug Application (NDA). Across decades of new-drug evaluation, CDER's applications and procedures have grown precipitously for two primary reasons: 1) progressing, collaborative research between CDER and the NCTR constantly adds to the list of harmful manufacturing processes, research and testing procedures, and specific compounds, and 2) lessons learned the hard way. Many issues with drugs have gone undetected until after they were approved for U.S. markets. CDER's regulatory process results in a significant delay between drug discovery and public availability and this delay is an issue of significant debate. While it is obviously essential that these products

are highly regulated, each new drug undergoes seemingly irrelevant screening as a result of past FDA failures. Despite the ongoing debates, significant common ground exists in that CDER certainly serves an essential, life-saving function in the global pharmaceutical industry.

The Center for Biologics Evaluation and Research (CBER) is similar to CDER both in name and operating procedure. CBER, rather than regulating traditional, inorganic, synthesized drugs, regulates biologics. Biologics serve the same purpose as inorganic drugs, but are derived from living sources. CBER also oversees donated organs and tissues, including blood, as well as biologically-derived treatments such as gene therapies and vaccines. CBER, like CDER, is divided into several offices which are further divided into nearly 50 laboratories dedicated to specific fields of biologics. These laboratories allow for careful testing and regulatory control of the products that firms seek to introduce to the market. The role of CBER in the OMPT continues to grow as the field of biologics accelerates in research institutions worldwide.

The Center for Devices and Radiological Health (CDRH) regulates a broad range of products. Medical devices, for example, do not chemically influence the body as drugs and biologics do. As a result, medical devices and radiation-emitting devices are not required to adhere to the same level of testing as most drugs and biologics. The CDRH also regulates devices that are not explicitly medical devices, but which could impact the health of an individual. For example, the domain of the CDRH extends to radar guns and microwave ovens through its Division of Electronics and Computer Science.

The Center for Tobacco Products (CTP) is the newest of the seven centers. Tobacco use is the leading cause of preventable disease in the U.S. despite widespread awareness campaigns. The CTP derives its authority from the 2009 Family Smoking Prevention and Tobacco Control Act, which authorizes the CTP to regulate the production, marketing, and distribution of tobacco products in the United States. It strives to inform the general public about the harm that tobacco can cause both in the body and to society.

The Office of Global Regulatory Operations and Policy (GO) is similar to the OC from a leadership and policy development standpoint, as both offices work directly with the other offices and centers of the FDA. However, the GO exhibits a greater focus on product quality at both a domestic and international scale. Its emphasis is the standardization of international regulatory standards through global data-sharing and collaboration.

As is necessary for any sizable enterprise, the FDA's Office of Operations (OO) handles the logistical front of the Administration. The OO contains ten offices spanning finances, budget formation, human resources, equal opportunity employment, crisis management, ethics, and facilities engineering and management. The OO maintains essential infrastructure for the entire administration and strives to improve and expedite the FDA's regulatory and review processes.

So how will the 21st Century Cures Act change the FDA? This legislation includes an increase in funding in the amount of \$10 billion over 5 years for the National Institutes of Health (NIH) which is sure to stimulate the early research and development of drugs and biologics which may ultimately reach the already bottlenecked FDA commercial regulatory processes¹. However, the bill also calls for an additional \$550 million over 5 years for the FDA which is intended to expand its review and approval capacities. Likewise, it calls for a wide range of regulatory reforms and support efforts to improve access to data, foster the employment of new generation biomarkers, and execute methods in precision medicine.

The financial support included in the bill is a much needed shot in the arm to the NIH, which is presently operating on a budget that is diminished by 12% relative to 2009, and the FDA, which is overextended and strapped for resources. There is, however, growing apprehension over the inclusion of language that requires the FDA to develop innovative trial study designs and more efficient standards for evaluating data. The prospect that these may result in the use of abbreviated clinical trials with reduced study sizes or limit the use of randomized, controlled studies is disconcerting. Other changes may include a fast track approval pathway for antibiotics under life threatening conditions and a simplification of the approval pathways for medical devices. Although there is widespread agreement for the need to allow special considerations under extraordinary conditions, there is growing apprehension that the language for these considerations in the 21st Century Cures Act may leave too much for interpretation.

Conclusions

Since its unofficial instatement in 1906, the FDA has evolved alongside the United States' technological, pharmaceutical, and industrial expansion. From everyday foodstuffs and over-the-counter drugs to revolutionary medical treatments, radioactive imaging, and animal welfare, the FDA plays an essential role in the United States' public health infrastructure. While it is true that improvements should and need to be implemented in order for the FDA to adapt to the changing and increasing needs of the pharmaceutical industry, it has demonstrated a brilliant ability to evolve when given the resources to do so. The 21st Century Cures Act may be just the resource-laden impetus necessary to drive the next evolution of the FDA.

While there is sound apprehension that the bill, in its current form, lacks critical measures to avert the application of discretionary practices which may jeopardize the safety and efficacy of prescription drugs and biologics, the 21st Century Cures Act will certainly be subjected to major re-drafts and revisions prior to an approval of the final version. Although this legislation was approved on May 21st in a unanimous decision by the U.S. House of Representatives' Committee on Energy and Commerce⁴, it is currently being dissected by FDA personnel, industry and legal experts, scientists, and others. The final bill has the capacity to drive significant improvements in the development of and access to life saving cancer therapeutics.

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