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TRANSLATIONAL TOOLBOX

Drugs, Devices, and the FDA: Part 1

An Overview of Approval Processes for Drugs

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SUMMARY

Over the last 150 years, the U.S. Food and Drug Administration (FDA) has evolved from a small division of the U.S. Patent Office to 1 of the largest consumer protection agencies in the world. Its mission includes ensuring that new medical treatments reach the public as quickly as possible while simultaneously ensuring that new treatments are both safe and effective. In the face of urgent consumer need, the FDA has faced criticism that its processes are too lengthy and costly and that the time to new drug release is significantly longer in the United States than in other Western countries. Calls from the public to loosen FDA regulations to facilitate more rapid approval of drugs and devices have been countered by the occurrence of patient harm and deaths after some approved drugs have reached the marketplace. New drug and device approval in the United States take an average of 12 and 7 years, respectively, from pre-clinical testing to approval. Costs for development of medical devices run into millions of dollars, and a recent study suggests that the entire cost for a new drug is in excess of $1 billion. For investigators seeking approval for new drugs and devices, FDA processes can be formidable. This 2-part series is intended to provide an overview of the steps involved in bringing new drugs and devices through the FDA process. Part 1 concerns the process of new drug approvals. Part 2 continues with approval of medical devices. (J Am Coll Cardiol Basic Trans Science 2016;1:170–9) © 2016 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Regulation of the development, production, marketing, and sales of medical pharmaceuticals and devices entails paradoxical goals. It must ensure that new and effective medical treatments reach the public rapidly while simultaneously providing protection from ineffective or even unsafe therapies and from predatory marketing practices that tout unproven remedies to vulnerable patients. In the United States, these regulatory functions fall to the U.S. Food and Drug Administration (FDA).

The FDA is the oldest consumer protection agency in the United States, originating in the U.S. Patent Office in 1848, and later inherited by the Department of Agriculture in 1862 (1). The modern function of the agency in oversight of drug and medical device marketing was ultimately codified in the Pure Food and Drug Act of 1906 (2,3), which was passed in response to a pressing need to curb interstate markets for adulterated and mishandled food and pharmaceuticals. The Federal Food, Drug, and Cosmetics Act of 1938 required all drugs to be approved for safety by the FDA (1). This mission was expanded in 1962 by the Kefauver-Harris amendments that added the requirement that drugs be proven "effective" as well as safe, and placed strict controls on the use of investigational drugs (2). Regulations regarding drug safety oversight were expanded in 1976 to include medical devices (1,2).

Over the course of the 20th century, the role of the FDA has undergone a significant metamorphosis due to expanding federal regulations, increasing complexity of drugs and devices, and the growth of the pharmaceutical industry into a major economic force in the United States. Today, the United States has among the most stringent regulations regarding medical drug and device development and marketing,

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and the FDA has grown from that small division in the patent office to 1 of the largest consumer safety agencies in the world. Its core mission remains the same: to provide consumers with assurance that medical drugs and devices that reach the marketplace have proven safety and efficacy in the roles for which they have been tested and approved. But, this mission has faced criticism and calls from an increasingly demanding consumer base to provide more rapid development, approval, and release of new products.

Strict regulation may have served the public with enhanced assurance of therapeutic safety, but progressive concerns of a so-called "drug lag" have resulted from an increasingly complex regulatory environment and the expense associated with drug development. Delay in the development and marketing of new pharmaceuticals was evidenced by a decline in the number of drugs approved by the FDA from an average of 50 drugs annually in the late 1950s to approximately 17 per year after 1965 (2,4). It is unclear whether FDA regulations were entirely responsible for the deceleration, because foreign countries also experienced a lag (2,5,6), but it was nevertheless obvious that new drugs and devices were often reaching the market in other countries months to years before achieving FDA approval in the United States (2). Modern regulations allowing for expanded access and accelerated approval for drugs to treat life-threatening conditions have their origins in the public outcry over delays in access to acquired immune deficiency syndrome treatments in the 1980s (7). But, movements to "deregulate" drug development by loosening FDA regulations have been weakened by the occurrence of major safety incidents, such as with benoxaprofen in 1982 (2). The nonsteroidal anti-inflammatory agent, marketed under the brand name Oraflex, was released to the public but then withdrawn when patient deaths were reported in the United Kingdom (8,9). Thus the drug/device development environment in the United States involves a constant balance between accelerating pressures to expedite effective therapies to the public, and the mission to minimize major adverse events (10).

Today, the path from initial demonstration that a molecule may have therapeutic potential to the production of an approved drug involves pre-clinical testing, complex clinical trials in humans, and post-trial regulatory approval by the FDA. For drugs, this process can take 10 to 15 years and cost millions of dollars (11). A recent analysis suggests that the actual cost of taking a new drug from concept to market as of 2014 is now above $1.3 billion (12). Approximately 1 in 1,000 potential drugs is graduated to human clinical trials after pre-clinical testing in the United States, and almost 9 of every 10 new drugs then fails in the human testing phase. In 1 study, 50% of all drugs reaching the final stage (Phase III) of clinical testing did not make it to market (13). The problem is not unique to the United States; a recent analysis concluded in 2011 by the Centre for Medicine Research in the United Kingdom found that in the prior 3 years Phase II and III clinical trials had experienced rising failure rates, with only 18% of drugs making it out of Phase II to Phase III testing (14,15).

ABBREVIATIONS AND ACRONYMS

CDER = Center for Drug Evaluation and Research

EIND = emergency investigational new drug

FDA = U.S. Food and Drug Administration

IND = investigational new drug

NDA = new drug application

The pathways for approval of medical devices are shorter and generally less costly when compared with the regulatory process for drugs. Although the drug development takes on average 12 years from concept to market, the same process for medical devices averages 3 to 7 years (16).

For researchers involved in the clinical development and testing of putative drugs and devices, the process of FDA approval can be daunting and difficult to navigate. This first part of a 2-part series is intended to provide an overview of the steps in bringing a drug through the process of clinical trials and FDA approval. The second part of this series will discuss the process of obtaining approval to study devices, which have their own unique pathway.

PART 1: FDA APPROVAL OF NEW DRUGS

WHAT IS A DRUG? Not every substance taken by patients "for their health" is considered a drug by the FDA (**Table 1**). The FDA defines herbal products, vitamins, and other complementary medical therapies as "dietary supplements" (17). As such, they are regulated by the Center for Drug Evaluation and Research (CDER) of the FDA and are subject to guidelines by the Dietary Supplement Health and Education Act of 1994 (18), but they are not subject to the rigorous tests required of substances that are defined as "drugs."

Prior to ever reaching a clinical researcher's hands, all new drug development follows a common pathway. Basic research leads to conceptualization of

TABLE 1 What Is a Drug: the FDA Definition

A substance recognized by an official pharmacopoeia or formulary
A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
A substance (other than food) intended to affect the structure or any function of the body
A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device

FDA = U.S. Food and Drug Administration.