JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 1, NO. 5, 2016
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2016.06.003

TRANSLATIONAL TOOLBOX

Drugs and Devices

Comparison of European and U.S. Approval Processes

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SUMMARY

The regulation of medical drugs and devices involves competing goals of assuring safety and efficacy while providing rapid movement of innovative therapies through the investigative and regulatory processes as quickly as possible. The United States and the European Union approach these challenges in different ways. Whereas the United States has always relied on a strictly centralized process through 1 agency, the Food and Drug Administration (FDA), the European Commission synchronized the regulations of 28 different countries as they combined to create the European Union. The FDA historically developed as a consumer protection agency, whereas the regulations from the European Commission arose out of a need to harmonize inter-state commercial interests while preserving national "autonomy." Thus, whereas the FDA has the advantages of centralization and common rules, the European Union regulates medical drug and device approvals through a network of centralized and decentralized agencies throughout its member states. This study explores some of the similarities and differences in European and U.S. regulation of drugs and devices, and discusses challenges facing each. (J Am Coll Cardiol Basic Trans Science 2016;1:399–412)

Regulation of the development and dissemination of medical drugs and/or devices (DADs) involves competing interests: ensuring that agents are both safe and effective, while facilitating the movement of innovative therapies as rapidly as possible through the investigative process to public use. Balancing these goals falls globally in large measure to the Federal Food and Drug Administration (FDA) in the United States, and to regional and centralized regulatory bodies in the European Union (EU) (1).

Controversy persists about the differences in U.S. and EU regulatory processes, costs, and the time it can take for a DAD to proceed from concept to approval under the regulations of each. A frequently held assertion is that slower FDA approval processes deprive American citizens of effective DADs that are available to Europeans (2), and critics have characterized FDA processes as "slow, risk averse, and expensive" (3). However, the Institute of Medicine determined that current FDA pre-marketing procedures for medical devices are insufficient to assure device safety, particularly those approved largely on their similarity to previously cleared "predicate" devices, rather than on prospective, randomized clinical trials (4). In the EU, concerns abound that DADs may be approved too quickly, to the detriment of patient safety. In recent years, there have been calls to tighten approval processes and to establish regulatory consistency between the FDA and the EU. Efforts include recent legislation in the U.S. Congress to facilitate release in the United States of drugs that have already achieved European approval (5). Proposed changes to regulations of the European Commission (EC) regarding device approval are under discussion (6), but are vigorously opposed by both industry and patient groups insisting that it will impede availability of innovative therapies to the public.

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Manuscript received June 21, 2016; accepted June 21, 2016.

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 1, NO. 5, 2016
AUGUST 2016:399–412

ABBREVIATIONS AND ACRONYMS

BMJ = *British Medical Journal*

CE = Conformité Européenne

DAD = drugs and devices

EC = European Commission

EMA = European Medicines Agency

EU = European Union

FDA = Food and Drug Administration

MHRA = Medicines and Healthcare Products Regulatory Agency

NB = Notified Bodies

PMA = pre-market approval

A 2-part series published earlier in *JACC: Basic to Translational Science* provided an overview of FDA approval processes for drugs and medical devices in the United States (7,8). This review compares European processes with those of the FDA, and discusses some of the challenges facing each.

BACKGROUND

The FDA was an outgrowth of a division of the U.S. Patent Office in the mid-19th century, initially charged with ensuring that medications on the public market were effective as advertised. The Federal Food, Drug and Cosmetics Act of 1938 subsequently invested the agency with more rigorous powers to ensure that drugs were not only effective, but "safe" (9), and the FDA was ultimately given authority to regulate medical devices in 1976 (10) through legislation that was later amended in the Medical Device User Fee and Modernization Act of 2002 (11). Although regulatory amendments have been implemented to facilitate DAD transit from concept to market, the powers and processes of the FDA have stayed largely consistent since the 1970s, and are authoritative for all 50 states.

The evolution of European regulation of DADs, by contrast, is much more recent, with significant changes after the formation of the EU in 1993. Before that, regulation and marketing approval for DADs fell to its (now) member states. Differences in regulations among the states often impeded marketing and disbursement of DADs across Europe, and in some cases fostered "protectionist" legislation within states to shield sovereign nations' companies from fierce market competition. Among the current 28 member states, many interstate agencies have been reorganized. Clinical trial applications are generally handled in the member state, whereas marketing applications are approved by both state and central agencies in accordance with regulations set forth by the EC.

EUROPEAN REGULATION OF DRUGS

Efforts to standardize European regulations regarding drug approval first came to fruition before the formation of the EU, with the passage of EC Directive 65/65/EEC in 1965 (12). The directive defined a medical product as "any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting, or modifying physiological functions in human beings or in animals." Under the directive, any medicinal product marketed in the member states would first pass approval in the originating state (1,12,13). The directive established consistent guidelines throughout the member states regarding the information that must be submitted for approval: these items parallel regulations of the FDA regarding investigational new drug applications and new drug approval applications.

DRUG APPROVAL PROCESSES. Many of the processes to approve drugs in the EU are similar to those of the FDA (**Figure 1**). An investigator of a proposed pharmaceutical first obtains pre-authorization for use of the drug in clinical trials. All European clinical trials were regulated under the Clinical Trials Directive of the European Commission (2001/20/EC) (14), later repealed and replaced in 2014 by Regulation No. 536/2014 of the European Parliament (15).

The drug then progresses through sequential studies analogous to those in the United States: Phase I trials conducted in a small number of healthy subjects to clarify pharmacology and dose range, Phase II trials conducted in several hundred patients with the target condition to investigate the dose-response relationship, and Phase III confirmatory trials in several hundred to several thousand patients to substantiate safety and efficacy. As in the United States, the EC provides means for approving "orphan drugs," or those that treat conditions that affect so few people that randomized controlled trials may be impossible to complete (16,17). There are also methods for obtaining conditional approval for drugs to be used in emergency conditions, or other conditional approvals (18).

The European Medicines Agency (EMA) was formed in 1995 with funding from the EU, pharmaceutical industry, and member states (19). The EMA was charged with harmonizing processes in the member state regulatory agencies to reduce annual costs to drug companies (that previously were required to obtain separate approvals in each member state) as well as to eliminate competition-restricting regulation in sovereign states. However, the EMA does not oversee all drug approvals the way the FDA does in the United States. In Europe, there are 4 routes by which a drug can be approved, depending on the drug class and manufacturer preference (6).

CENTRALIZED PROCESS. The centralized process is controlled through the EMA. Every member state of the EU is represented on the EMA Committee for Medicinal Products, which issues a single license valid in all EU member states. This route of approval is mandatory for some classes of drugs, such as treatments for HIV/AIDS, oncology, diabetes, neurodegenerative disorders, autoimmune disease, and viral diseases.