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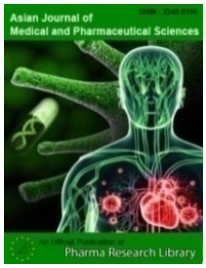

REVIEW ARTICLE

Regulations on Pharmaceutical Products and Medical Devices in USA

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ABSTRACT

The United States (U.S.) regulates medical devices using a classification system based on the risk to the patient from using the device. Medical devices are classified into Class I (least risk), II, and III (most risk). Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from any clearance or preapproval requirement before they can be sold in the U.S. In other words, Class I devices can generally be sold without preapproval. Most Class II devices must receive prior clearance from the FDA before they can be sold in the U.S. The clearance process is known as "premarket notification" (the manufacturer notifies the FDA of its intention to market the device) and the application is referred to as a "510(k) application" based on the section of the U.S. Food, Drug and Cosmetic Act (FDCA) which authorizes the process. Most Class III devices must undergo a more exacting and expensive process, typically requiring clinical trials, known as "premarket approval" (PMA) before they can be sold in the U.S.

Keywords: Medical devices, FDA, FDCA, PMA.

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CONTENTS

1. Introduction

In contrast with most other countries, the United States does not employ a form of drug price regulation to control spending on pharmaceuticals,1 mainly because of concern that regulatory controls drive down profits and discourage the flow of capital to support the development of new molecular entities (NMEs).2 Industry and government officials in the United States have targeted other countries for their implementation of national policies surrounding drug price regulation. For example, the Pharmaceutical Manufacturers Association of America has claimed that foreign governments are free riding on US innovation and are not paying for their fair share of drug development costs.3,4 In addition, US government officials have stated that the United States is now covering most of the costs of developing a new drug.3 The concern that regulatory controls in other countries may affect global pharmaceutical innovation has also affected US trade negotiations and domestic policy. The US government has placed pressure on other countries to modify their current price regulation of pharmaceuticals or formulary structure in 2003, the US Congress inserted a ban on government negotiation of drug prices in the Medicare Modernization Act of 2003, presumably because of concerns over the impact of drug price regulation on innovation.

2. Plan of work and methods employed

The information gathered from the official documents and websites of the concerned regulatory bodies like FDA and EMA and the data is extracted with the help of my institutional guide and suggestions and reviews are made.

PART-I

Overview of Health Care in the US:

The United States (US) has a population of over 315 million people, embodying one of the most complex health care systems in the world, with intertwining relationships between providers, payers, and patients receiving care. Historically and to this day, the US health care system is in a constant state of evolution. Trailing behind China and India, the US is the third most populous country in the world, spending $2.8 trillion on health care or 17.9% of the gross domestic product (GDP) in 2012 [1, 2] Switzerland and the United Kingdom spent 11.3% and 9.4% (GDP) respectively on health care in 2012. Growth in health care spending is mostly attributable to the growth in pharmaceutical drugs and devices since 2000 (84% attributable in 2010; 4% growth per year).

PART-II

United States Pharmacy Law and Drug Regulation Review:

In the United States, all food, drugs, cosmetics, and medical devices, for both humans and animals, are regulated under the authority of the Food and Drug Administration (FDA). The Food and Drug Administration and all of its regulations were created by the government in response to the pressing need to address the safety of the public with respect to its foods and medicinals. The purpose of this review is to describe and explain the nature and extent of these regulations as they apply to drugs in the United States. This review discusses the FDA's regulatory oversight and that of other agencies, the drug approval and development process, the mechanisms used to regulate manufacturing and marketing, as well as various violation and enforcement schema. The primary responsibility for the regulation and oversight of pharmaceuticals and the pharmaceutical industry lies with United States Food and Drug Administration (FDA). The FDA was created in 1931 and is one of several branches within the US Department of Health and Human Services (HHS). The FDA's counterparts within HHS include agencies such as the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and Healthcare Financing Administration (HCFA).

PART-III

Overview of Device Regulation:

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non- medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

Radiation-emitting Electronic Products:

Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type.

The basic regulatory requirements that manufacturers of medical devices distributed in the

U.S. must comply with are:

- Establishment registration,
- Medical Device Listing,
- Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA),
- Investigational Device Exemption (IDE) for clinical studies
- Quality System (QS) regulation,
- Labeling requirements, and
- Medical Device Reporting (MDR)

Establishment Registration - 21 CFR Part 807:

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA.

Quality System Regulation (QS) / Good Manufacturing Practices (GMP) - 21 CFR Part 820:

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.

Medical Device Reporting - 21 CFR Part 803:

Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving

medical devices. The goals of the regulation are to detect and correct problems in a timely manner.

Medical Device Regulation: comparison between The United States and Europe:

Medical devices are serving an increasingly central role in clinical practice, improving patients' health and quality of life. The medical device industry and the areas of patient care it touches have grown considerably in recent years. For example, the annual revenues of the US medical device industry rose from approximately $85 billion in 2001 to $146 billion in 2009. While part of this growth is due to the greater use of medical devices already on the market, a large portion was driven by new market entrants. During the 2000s, more than 30,000 medical devices were cleared by the US Food and Drug Administration (FDA)'s 510(k) premarket notification pathway, and more than 300 new devices received original premarket authorization. Along with the higher number of new devices, these technologies have become more complex.

United States

The 1976 Medical Device Amendments gave the FDA the primary authority to regulate medical devices and to substantiate "reasonable assurance of safety and effectiveness" before allowing manufacturers to market their products.14 This legislation has subsequently been updated with the Medical Device User Fee and Modernization Act (MDUFMA) of 2002, which established sponsor user fees for application reviews and set certain performance goals for the agency.

The FDA assigns devices to one of three regulatory classes based on their intended use, whether the device is invasive or implantable, and the risk posed by the device to the user. the device class determines the level of evidence and evaluation required to demonstrate safety and effectiveness. Low-risk Class I devices are generally exempt from premarket notification (510[k]) and FDA clearance before being marketed, although their manufacturers are subject to general controls, such as registering their name and products with the FDA. Medium-risk Class II devices usually are required to clear the 510(k) review process, which determines principally whether the new device is substantially equivalent to a legally marketed (predicate) device. Substantial equivalence means that the device performs in a manner similar to that of the predicate in its intended use, technological characteristics, and safety and effectiveness.15 If a device is determined to be substantially equivalent, a clinical trial is usually not required to prove its safety or effectiveness. Other requirements (special controls) may be imposed, however, such as those for labeling requirements and postmarket surveillance. If the FDA deems a device to not be substantially equivalent, the manufacturer can petition for reclassification or file a de novo application.

Europe

Until the 1990s, each member state had its own approach to regulating devices. To regulate a diverse and complex market and promote the "internal market" in Europe, new regulations, known as the New Approach Directives, were introduced by the European Council that defined the "Essential Requirements" to ensure devices' safety and performance. These requirements apply to all countries. Therefore, if a device meets the requirements and receives a CE mark in one country, it can be marketed in all member states. A CE mark certifies that a device is safe and functions according to the intended purpose described by the manufacturer. Under these directives, devices are categorized into four classes according to the degree of risk associated with their intended use.

Similar to those of the United States, Europe's evidence requirements for market authorization increase with the degree of risk associated with the device. Manufacturers of low-risk devices (Class I) are required only to self-declare conformity with the Essential Requirements to a national "Competent Authority," such as the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. More moderate-and high-risk devices (Classes IIa, IIb, and III) require a combination of clinical and nonclinical data on the device being evaluated. If available, data for an equivalent device already on the market may be submitted. Although clinical studies are generally requested for high-risk Class III devices, the evidence requirements are vague, not available to the public, and nonbinding for manufacturers and studies need not be randomized. For manufacturers claiming similarity to an existing product, a comparative literature review typically suffices.

Comparing the United States and Europe:

The US and European approaches to medical device regulation have fundamental differences. For example, the FDA was established to promote and protect public health through the regulation of medical products, whereas the European system of Notified Bodies developed as part of a broader initiative to strengthen innovation and industrial policy across Europe.

Notified Bodies therefore were not designed to function as public health agencies. Instead, the protection of public health lies largely with the Competent Authorities, with the extent of their role varying widely among member states. Kramer and colleagues believe that these differences help explain why the United States and Europe have adopted different regulatory processes and evidence requirements for devices. For instance, in Europe devices must prove only that they work as intended, whereas in the United States devices require evidence of effectiveness.

Outstanding Challenges in US and European Medical Device Regulation: Despite the differences between the US and European systems, both jurisdictions face similar outstanding challenges to effective medical device regulation. Next we discuss several issues needing improvement.

Strengthening Premarket Evidence Standards and Requirements:

The impact of the US reforms on device evidence standards and requirements is somewhat limited, with the most significant developments being changes to the *de novo* application process and the reclassification procedures.

In the past, the *de novo* process required manufacturers to submit a 510(k) application, which is exhaustively reviewed by the FDA before a device can receive a "not substantially

equivalent" determination. If deemed not equivalent, the device will automatically receive a Class III designation.

Improving Monitoring of Postmarket Patient Safety and Quality of Care:

In the United States and Europe, reforms have focused largely on improving post market regulation to better safeguard patients' safety and quality of care. Both jurisdictions introduced a unique device identifier (UDI) requirement to enhance the traceability of devices. In the United States, device manufacturers will be required to place a UDI on the device's label. Some devices will also need to be directly marked with the UDI itself. In addition, accompanying device information will be made available through the Global UDI Database (GUDID). As the FDA explained, the purpose of the UDI system is to provide speedy identification of devices associated with adverse events, assist with faster and more efficient resolution of device recalls, and deliver an easily accessible source of definitive device identification.

Post-market Surveillance:

Ensuring proactive, not passive, post-marketing systems is just as important as strengthening premarket authorization. While reforms on the use of UDIs are a good step toward enabling the tracking and identification of devices, the true benefit of the UDI system will require its broad adoption and use by manufacturers, payers, providers, patients, and other stakeholders involved throughout the life cycle of medical devices. Accordingly, we need strategies to facilitate the awareness, adoption, and implementation of the UDI system. Such efforts should focus on including UDIs in inventory logs, electronic health records, and claims data and linking different post-market databases, such as the GUDID and adverse event reporting repositories. Moreover, providers and patients should be engaged early to report, receive, and retain device information as well as to tailor strategies for communicating information (eg, smart phone applications that can link the identifier to the UDI database) to different end users.

PART-IV

How Drugs are Developed and Approved:

The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness.

CDER is the largest of FDA's six centers. It has responsibility for both prescription and nonprescription or over-the-counter (OTC) drugs. For more information on CDER activities, including performance of drug reviews, post-marketing risk assessment, and other highlights, please see About the Center for Drug Evaluation and Research. The other five FDA centers have responsibility for medical and radiological devices, food and cosmetics, biologics, veterinary drugs, and tobacco products.

FDA Approval

FDA approval of a drug means that data on the drug's effects have been reviewed by CDER, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population. The drug approval process takes place within a structured framework that includes:

- ✓ Analysis of the target condition and available treatments
- ✓ Assessment of benefits and risks from clinical data
- ✓ Strategies for managing risks

Patient-Reported Outcomes

Both the EMA and the FDA recognize the value of patient-reported outcomes (PROs) as important patient-centered endpoints when determining the efficacy of therapies and considering them for approval. The EMA began drafting recommendations regarding the use of PROs in 2004 for the Efficacy Working Party of the CHMP; these recommendations were adopted in June 2005. The FDA followed with draft guidance in 2006. Both these documents highlight the importance of PROs in considerations of therapeutic efficacy, but they are divergent in their approach.

3. Conclusion

Systems for approving new medical devices must provide pathways to market for important innovations while also ensuring that patients are adequately protected. To achieve these goals, the United States and European Union use a combination of premarket testing and post-market vigilance but with some marked contrasts in their approaches. Features of both environments require reform, as well as continuing research to assess policy changes.

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