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Review Article

GLOBALIZATION OF REGULATORY AFFAIRS IN HEALTHCARE INDUSTRY

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ABSTRACT

Globalization is a term that defines exchange of goods and services between the countries which has a positive impact on economic transactions across national borders. Healthcare services are also influenced by globalization. Every country has its own regulatory agency which is responsible for its public health, health care systems, and financial resources. As the demand for safe food and medical products is increasing, the responsibility of the regulatory agencies is also increasing. They ensure the purity and efficacy of the medical products to protect their citizens. The paper will discuss globalization from the point of view of Food and Drug Administration, European Medicines Agency, Pharmaceuticals and Medical Devices Agency, and Central Drugs Standard Control Organization and will also discuss the impact of globalization on developing countries such as India, China, Brazil, and South Africa. The paper will also deal with the importance of the International Conference on Harmonization which has played a key role in bringing different regulatory agencies of the world to achieve the common goal of promoting globalization in healthcare.

Keywords: Regulatory agency, Globalization, Biopharmaceuticals

INTRODUCTION

Among many consumer products that are regulated, pharmaceuticals, and biopharmaceuticals occupy the main stage. The regulation of these products has many verticals such as development, manufacturing, testing, pricing, and distribution [1] and the need for critically regulating these products stems from the fact that they have a direct effect on human health.

In the past, drug regulation has been one of the major concerns for the governments of many nations, particularly the developed nations and has been essentially been limited to national boundaries. However, over the past decade, in the face of emerging advances in the health, medicine, and biomedical industries, the concept of sovereignty in drug regulation stands void. The most stringent regulatory agencies: The Food and Drug Administration (FDA), The European Medicine Agency (EMA), and the Pharmaceutical and Medical Devices Agency (PMDA), Japan have been putting a lot of efforts and monetary inputs for international co-ordination and co-operation. Such a co-ordination among regulatory agencies is not an easy task and faces many obstacles such as multiple dimensions of regulation (testing protocols, information exchanges, etc.) [1].

International Conference on Harmonization (ICH) has issued a number of guidelines to harmonize the amount of data a company needs to submit for approval of Pharmaceuticals for Human Use in various markets (USA, Europe, and Japan). It is a joint effort by regulatory authorities and pharmaceutical industry to provide for uniform guidelines to be followed. With the advent of biosimilars and biopharmaceuticals, there is a need to harmonize the guidelines further.

THE FDA

FDA is a science-based regulatory agency and a critical component for America's successful public health, health care systems, and economy [2]. FDA has been continuously striving to keep itself abreast with all the advances in pharmaceutical and biopharmaceutical domain around the globe for the betterment of US citizens.

As stated by the FDA Commissioner, Margaret Hamburg, "Today we recognize that to successfully protect US Public Health, we must think, act and engage globally. Our interests must be broader than simply within our own borders [3]."

Most of the products relating to human health and safety such as food and medicinal products in the US are imported from around the world. As the demand for such products is increasing with time, FDA's responsibility to ensure purity and efficacy of such products to protect US citizens is also increasing and hence getting more challenging. According to the recent data by FDA, almost 40% of the finished drug products are imported into the US [3]. Owing to such globalization, Americans can greatly benefit by choosing from a wide variety of food products and health professionals can use medical devices and prescribe drugs that have been approved for use in the United States by the FDA [2].

FDA regulates a wide variety of medicinal products such as pharmaceuticals (brand name, generics, over the counter drugs), biologics (products derived from living organisms such as vaccines and gene therapy), and medical devices. Owing to the increased technological advances in the production of these products and devices, the imports of pharmaceutical and biologics have doubled and that of medical devices quadrupled. With such rapid globalization changes taking place, the FDA is faced with many regulatory challenges [2,3]. To start with, for a product to be approved by FDA, it has to be shown safe and effective for use on the targeted human population. For this purpose, clinical trials are conducted by the pharmaceutical companies in three phases (Phase I, II, and III). To ensure the safety of the subjects participating in clinical trials, FDA officials have the responsibility of inspecting the site and facility of clinical trials and to make sure that the trials are conducted in a fair and accurate way. If a clinical trial is conducted for a product which is manufactured outside the United States, the FDA officials have to visit that site.

Second, to earn higher profits, manufacturing companies of medicinal products might use the adulterated or sub-standard material to manufacture the products, or can do counterfeiting or falsification making the consumers extremely vulnerable to risks and threats posed by using such imported products. Furthermore, with e-commerce at its surge, consumers may directly purchase the products through the internet, thus jeopardizing their safety. Another challenge faced by FDA is the identification of defective medical devices in counterpart countries since one medical device can be sold with different names and forms in different countries. Such devices lack a unique identifier which could be used by the regulatory authorities to match the similar

product in their own country and see if there is a problem with the device used by them, thus limiting the ability of FDA officials to inform the medical and healthcare professionals. In the presence of such challenges, FDA has adopted several strategies to ease the process of globalization in terms of drug regulation and ensure that safe products are delivered to the citizens of United States. Such strategies include the establishment of international offices across the globe which serves as the point of contact for the countries to reach FDA to share knowledge and information and also help the FDA officials to inspect foreign sites. FDA, with support from the US Congress, established international offices and posted staff in strategic locations around the world. For instance, it has offices in China (Beijing, Shanghai, and Guangzhou), India (New Delhi and Mumbai), Europe (Brussels, Belgium, London, and the United Kingdom), and many other locations in the world. To strengthen its own regulatory efficiency and also help other countries to do the same, FDA focuses on providing training workshops, exchange programs, providing and sharing knowledge and expertise to the regulatory agencies of other countries on how to successfully assess and regulate the products. FDA is adopting new tools and technologies to evaluate the risk associated with the imported medicinal products by taking advantage of the advances in science and technology, for instance, the Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting system (PREDICT). It improves screening of imported products to prevent the entry of adulterated products and speed up the entry of genuine products. PREDICT scores each imported line on various risk factors; it increases the automated decisions for lower risk products thus giving more time to the reviewers to evaluate high risk products. The FDA is also planning to convert from a domestic agency to a global agency in the next 10 years by interacting with the regulatory agencies of other countries and working together with them to establish a safe and effective regulatory environment. FDA puts in a lot of effort in helping those countries from which it imports products to strengthen their regulatory framework, which would help in delivering safe and effective products and tries to minimize the risk associated with a product before it enters the United States. To meet these purposes, FDA hosts several forums to disseminate the knowledge and expertise required to regulate the products, such as, Centre for Drug Evaluation and Research Forum for International Drug Regulatory Authorities (2005) [3], forums for medical devices and biologics to help the foreign regulators know about the drug and devices regulation process of FDA.

These are few of the myriad steps taken by FDA to ensure effective utilization of globalization trends without compromising the safety of public health.

THE EMA

The European Union (EU) has 27 member states at present and earlier, the regulatory pathway for drugs and other medicinal products was not same for each member state, thus giving rise to a complex regulatory framework. The European pharmaceutical market was limited by lengthy registration procedures, variation in drug regulation policies across Europe, linguistic differences, and a different pace of drug approval among the member states.

The establishment of Committee for Proprietary Medicinal Products (CPMP) comprising of officials from the member states brought some transformation to the pharmaceutical market. The applications were reviewed to check the compliance with EU's policies on safety, efficacy, and quality standards and then an opinion was given regarding the marketing approval. However, the final decision rested with the member states regarding the approval, unlike FDA, which holds the ultimate authority.

The EU then adopted a centralized procedure in which the pharmaceutical companies could submit the applications directly to the EMA, which then sends the applications to CPMP for review. This procedure is particularly designed for biotechnology products and is now presently adopted by the biotech companies that wish to apply in the EU [17].

THE PMDA, JAPAN

With the aim of providing safe and effective pharmaceuticals and medical devices, the PMDA has been actively participating in the international community by trying to harmonize its services. To meet this objective, PMDA has constructed a strategic plan stating the policies for its international activities. The agency carries out confidential meetings and talks with the EMA and the FDA to share information, send its official to the EMA and the FDA and invites their personnel to its office with the view of exchanging ideas with the sole aim of improving the regulatory framework for the medicinal products. PMDA also ensures compliance with Good Manufacturing Practices (GMP), Good Laboratory Practices, and Good Clinical Practices [4]. It also actively engages itself in the various harmonization conferences such as ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As a major step toward improving globalization, the PMDA trains the concerned staff members to improve their foreign language speaking abilities such as English and sends them to attend several international conferences to foster their understanding of various regulatory markets [5].

CENTRAL DRUG STANDARD CONTROL ORGANIZATION (CDSCO), INDIA

CDSCO is the national drug regulatory authority of India whose responsibility is to ensure safety and efficacy of pharmaceuticals and medical devices. This is done according to the guidelines set by the Drug Controller General of India (DCGI). DCGI is guided by Drug Technical Advisory Board and the Drug Consultative Committee. CDSCO functions same as the EMA of EU, PMDA of Japan, and FDA of the United States [8].

Central Drug Controller is primarily responsible for the approval of new drugs, conducting clinical trials; standardize the new drug, regulation of imported drug, whereas State Drug Controller is mainly concerned with sales and distribution of the drug.

The new drug can be imported or manufactured only when the permission is granted by the Licensing Authority (Drug Controller General of India). Manufacturing, importing, or clinical trials are done on the basis of requirements and guidelines mentioned under Schedule Y of Drug and Cosmetics Act 1940 and Rules 1945. The Drug and Cosmetics Rules and Appendix have rules and requirements for the approval of clinical trials of such types of new drugs which are evaluated by a reviewer of CDSCO. The applicant who wants to develop a new drug should get a license. The State Authority issues a license in Form 29 which is based on NOC from CDSCO to the applicant who wishes to develop a new drug.

If a certain drug is approved in some other country, the result/data of clinical trials performed in that country can be submitted to the Licensing Authority to get the permission to import the drug considering that in the interest of public health. In such cases, the Licensing Authority allows the applicant to proceed for clinical trial from Phase III. Clinical data can be adjourned by the Licensing Authority depending on the Indian health scenario. Such a challenge is faced in case a person is diagnosed with a life-threatening condition for which no alternative therapeutic measure is available [6,8].

CDSCO was declared as the functional National Regulatory Authority by a 16 member team of World Health Organization (WHO) in 2012 and in such short period of time it has now has collaborations with US FDA, Health Canada, Brazil, and South Africa regulatory authorities to get maximum benefits to the health of the people of India. DCGI issues a Written Confirmatory Certificate for the export of Active Pharmaceutical Ingredient to EU. The Ministry of Health and Family Welfare has allowed the import of drugs from the port of Goa and Bengaluru in 2012. This

decision helped them to import and manufacture drug required during the recent outbreak of Swine Flu in the nation [6,8].

THE COMMON THREAD BETWEEN REGULATORS - THE ICH OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

The ICH has been a key player in bringing the FDA, EMA, and PMDA together for working toward the common goal of promoting globalization of medicinal products. It was started in the 1990 and has since then continuously strived to achieve harmonization in the drug development and registration procedures for the well-being of global health.

Among many benefits of regulatory harmonization, prevention of duplicity in clinical trial procedures and other testing protocols, minimization of animal testing, narrowing the regulatory assessment procedure for new drugs are of paramount importance for both the regulatory agencies and the pharmaceutical industries. Drug development is touching new heights of globalization, keeping this is mind, the ICH global co-operation group (GCG) was established for promoting drug development in the non-ICH regions [12]. The GCG was formed on March 11, 1999, with the purpose of making information available on ICH, ICH activities, and ICH guidelines to any country or company that requests for the information.

The common technical document (CTD), which was developed by the EMA, FDA, and PMDA and maintained by ICH, is a set of specifications for submitting drug applications in Europe, US, and Japan [18]. This document has proved to be an elixir for the manufacturers and the regulatory agencies in terms of saving time and resources because instead of submitting multiple documents related to the drug application, the pharmaceutical companies have to just submit this single dossier which speeds up the approval process. The formation of such a harmonized document makes more sense because prior to it, pharmaceutical companies had to adopt different application procedure for each regulatory agency they wished to apply. From the point of view of regulators, prior to CTD, it took almost a year or so to review every aspect of the application from a manufacturer and then after the review process of one application was over they had to review the other application in a completely new format, which again took time as they had to adapt themselves to the new format.

The proposal of CTD was not readily accepted by the regulators owing to the fear of disrupting the regulatory process. However, it was realized that the time taken to convert the drug application from FDA format to EMA format could have been utilized in an efficient way to review the application had the format been common to both the agencies and resources and money put in by the drug manufacturers to convert the format could have been used for doing better research and development for the new drug products [5]. To expedite the submission of CTD, the regulatory agencies now also accept it in the electronic format also known as the e-CTD. This electronic submission has not only helped the pharmaceutical companies save the burden of preparing it in the paper format but also saves a lot of paper wastage thus promoting sustainability of resources.

Another major step toward globalization of regulatory procedures is the regulators forums. The FDA hosted the first regulator's forum in Oregon in June 2008 [5] with a view to interact with regulators from those countries that have been implementing ICH guidelines, such as Australia, Singapore, and South Korea and also from those countries that are involved in significant drug development like India, China, Brazil, and Russia. Such forums have focused on improving interaction between the regulators around the world, getting updates from other regulators, understanding the variation in the implementation of the ICH guidelines, which are divided into guidelines for quality (for chemical and biotechnology-based drugs), analytical validation, impurities, specifications, GMP, pharmaceutical development, quality risk management, and several others.

THE EMERGING MARKETS

Although, the countries, such as the US, Europe, and Japan, have been the big players in terms of pharmaceuticals and biopharmaceutical innovations, the emerging markets such as the India, Brazil, South Africa, and China have proved themselves in scientific research and development. The increase in a number of publications, patents, and expenditures related to research speak for the efforts these countries have been putting in. These emerging markets are now competing globally leaving behind their image as suppliers and outsourcers to the developed countries [12].

India and China are focused on developing an innovative environment and enhancing their economy related to pharmaceuticals and biopharmaceuticals. Earlier the main objective of these emerging markets was to use the technology or products which were developed by the stronger markets such as the US, but now the focus has shifted to native innovation for promoting public health. Most of the medicinal products or drugs manufactured and marketed by the pharmaceutical companies located in developed countries are for the diseases common to these countries; less emphasis has been put on the development of drugs for diseases that are specific to developing countries [13]. This gap is now being filled by the companies located in the developing countries with the aim of developing drugs for neglected diseases and also providing them at reasonable costs. Many Asian companies are now establishing commercial level biopharmaceutical manufacturing facilities and increased technological sophistication and research and development activities are transforming the biotech sector of the developing countries. The strategy used by the manufacturers in emerging economies is to develop financially reasonable and simple technology-based products before they enter into the development of sophisticated products [14].

There are many factors that drove these companies toward developing products that can compete at a global level with the companies in the stronger markets, with most important being reverse engineering of the products that have been developed by big pharmaceutical and biotech companies. This enables the manufacturers to learn new technologies used in the development of drugs and helps them build strong expertise required for innovation. In this respect, South Africa has been the weakest as compared to other three countries because of the lack of a strong domestic market for pharmaceuticals.

Indian firms are particularly interested in the export of the pharmaceuticals and biotech products to the US. For this, Indian companies have upgraded the facilities and technologies used in the manufacturing according to the standards required by the FDA. Different countries have an interest in developing different products. For instance, India is mainly into the development of vaccines, Brazil, China, and South Africa manufacture mainly diagnostics; however, these countries have no longer limited themselves to manufacture only these products and are expanding their research and development activities in other areas also with a view of strengthening the economy further [15].

Indian companies have become the global manufacturers of vaccines and generate immense revenues of almost 50% for the biotech section; this surge in the manufacturing of vaccines by India and other developing countries is due to loss of interest of developed countries in vaccine development to pursue other money-spinning markets. The global alliance for vaccines and immunization (GAVI), set up in 2000, is a global health partnership and aims at improving the health of people, particularly children in developing countries by promoting immunization in these countries [9-11]. This partnership brings together the WHO, developed countries, UNICEF, vaccine industry in the developed and developing countries, and the research agencies. It has invigorated the international collaboration of organizations for providing vaccines to the children in the developing countries. It has been a pioneer in such international collaborations and served as a model

for other collaborations also such as a global fund for AIDS, malaria, and tuberculosis [7]. Although, GAVI has been able to accomplish its purpose to a large extent, there are flaws and complications attached to it which hinder the full accomplishment of its objectives, like there is a lack of accord within the international public health community on the extent to which immunization is critical for protecting children in developing countries. Furthermore, there has always been a difference of interest between the members of the GAVI and those of the countries in which GAVI is supposed to provide help [16]. Most developing countries are reluctant to prioritize vaccines for children unless there is a financial inducement; without the full support of in-country workers and the governments of developing countries, such a global initiative will fail to serve the purpose for which it was created.

CONCLUSION

To sum it up, the biotech and pharmaceutical sectors of the developing countries are touching new zeniths owing to the rapid technological and scientific advances and are no longer limited to domestic boundaries. Globalization has a major role to play in transforming the regulatory policies and principles around the world, providing with a common platform to the industries and the regulatory agencies to work together for providing high standard and safe medicinal products, thus improving the public health on one hand and strengthening the economic position on the other. The establishment of the ICH guidelines has further helped in the amalgamation of regulatory pathway and has fostered the interaction between the regulatory agencies around the world. Just like there are two faces of a coin, the same way with all the benefits of globalization come the limitations, because the emerging markets will grow rapidly over the next decade thus increasing the competition for natural resources and raw materials. Growing use of internet commerce has put human health to threats posed by the adulterated or sub-standard medicinal products and even promoting bioterrorism. Biopharmaceuticals also face the challenge of ethical issues particularly in developing countries, thus at present restricting their import and export and preventing research and development in this field. Having weighed all the pros and cons of the globalization of the health sector and discussed several issues associated with it, the bottom line remains that the benefits should outweigh the risks.

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