IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2023 Vol.:27, Issue:2

Regulatory Affairs – An Overview

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
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ISSN 2349-7203
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Submitted: 27 April 2023
Accepted: 02 May 2023
Published: 30 May 2023

www.ijppr.humanjournals.com

Keywords: Regulatory affairs, critical roles, pharmaceutical industry, healthcare products

ABSTRACT

Regulatory affairs (RA) professionals play critical roles in a pharmaceutical industry because it is concern about the healthcare product lifecycle, it provides strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world. Legislations are consistently upgrading; regulatory affairs professionals are involved in playing significant role in helping drug manufacturing follow the upcoming changes. Life enhancing drugs cannot be safely and effectively brought to market without them. Hence the prominence of regulations and regulatory affairs are the interest of this project. The strength of regulatory affairs is to reduce the time for essential products to reach the market. Countries with weak regulatory systems lack the capacity to control the import, export, manufacturing, marketing, use of pharmaceutical products, had the critical weakness, including lack of sustainable funding and human resources. The Drug approvals in the US, Europe, India are the most demanding in the world. The primary purpose of the rules governing medicinal products in the US, Europe and India is to safeguard public health. General, the drug regulation must state the roles, responsibilities and functions of all parties involved with drug regulation, including those of the regulators and regulates. Artificial Intelligence (AI) technologies can help to speed up the review process, enabling new medicines to reach the market more quickly. They help in companies use vast data sets to quickly identify patient response markers and develop viable drug targets more cheaply and efficiently.

INTRODUCTION [1-14]

Pharmaceutical Regulatory Affairs

Evolution of regulatory affairs

In 1950's generation, many tragedies came about due to the misinterpretation of the employees during manufacture & some purposive addition of contaminated substances into the pharmaceutical product which has move forward to the execution of the patients. After so many occurrences, the regulatory bodies launched the new laws and guidelines which are going to ameliorate the quality, safety and efficacy of the products. This is again developed into severe standards for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs). That is the tragedies of Sulphanilamide Elixir, Vaccine Tragedy & Thalidomide tragedy.

Figure: 01

FDA launched in 1906 as Bureau of chemistry, served simply to police claims made about food and drugs ingredients. At that time no formal government approval required to market new drugs. The disasters provoked a public outcry that led to the passage of the 1983 Food Drug & Cosmetics Act, which gave the FDA power to monitor the safety of new drug.

Regulatory Challenges in Indian Pharmaceutical Industries

Indian Pharmaceutical Industry needs couple with the stringent regulatory and compliance requirements (both of national and international), which will ensure a 'swift and smooth' sailing of the sector. A few such regulatory and compliance requirements are in the areas of clinical trials, inspections and the continuity of supply in medicinal products and medical devices, as well as the proposed postponement of implementation of the medical device

regulation (MDR) and in vitro diagnostics regulation (IVDR) Indeed, the contagious concerns in the Indian pharmaceutical industries such as USFDA, CGMP norms, drug pricing,

Rising number of US FDA inspections

The number of inspections is at an all-time high. This comes as no surprise considering India has the most USFDA approved sites. In recent time, the U.S. Food and Drug Administration (FDA) and the Indian government work together on pharma supply chain issues. From January 28–30, 2020, for example, a joint action called Operation Broadsword prevented approximately 500 shipments of illegal and unapproved prescription drugs and medical devices from reaching U.S. consumers. Now, two Indian pharma companies are voluntarily recalling lots of Metformin Hydrochloride Extended-Release Tablets because FDA analysis revealed they could contain nitrosodimethylamine (NDMA), a known carcinogen, above the acceptable limit.

Government Control on Drug pricing

This is directly impacting the confidence levels of companies to invest respectable amounts in R&D.

Fake Products

It does create a wrong perception globally especially when India is aspiring to be a superpower in this space.

India's significant dependence on Chinese Active Pharmaceutical Ingredients (API)

The impact of the SARS-CoV-2 corona virus outbreak, COVID-19, has exposed the dependency of the Indian pharma sector on China for its API procurement. Supply chain disruptions and product exportation restrictions from India resulted from manpower shortages in China's manufacturing plants. Supplies were further impacted by the disruption of logistics and transportation systems, restricting access and movement of products to and from ports.

Impact of the pandemic on clinical research

The COVID-19 pandemic has been a decisive point in clinical trials regulatory affairs. It has highlighted the complexity of managing multinational clinical trials that must meet changing national guidelines while maintaining patient safety and the scientific value of the research during a global crisis. The lesson learned is that a close collaboration between sponsors,

CROs, local affiliates, investigational sites, and health authorities is of utmost importance in choosing the correct strategy in difficult circumstances and when no precedent applies. It is too early to assess the pandemic's impact on clinical research fully. It is estimated that more than 2,850 clinical trials were being conducted during April 2020 in the world (including India) that became affected by COVID-19 restrictions, which included complete lockdown or more limited measures. About 900,000 patients were participating in clinical trials that faced an uncertain future as the crisis unfolded.

Patent and licensing issues

In January 2020, Chinese researchers at the Wuhan Institute of Virology filed for a patent covering the use of remdesivir, an experimental antiviral drug, to treat COVID-19. Indeed, this drug was also researched and produced by Gilead Sciences, a California-based pharmaceutical company, which had filed patent applications at several patent offices, including in China, covering a "method for treating Arenaviridae and coronaviridae virus infection". It is worth noting that the Wuhan Institute of Virology's patent application was filed before scientists started experiments investigating the effectiveness of remdesivir against COVID-19. In effect, the Wuhan Institute of Virology's first IN VITRO studies suggesting that both remdesivir and an antimalarial drug called chloroquine could effectively inhibit COVID-19 were published in early February 2020. In response to the public outcry, the Wuhan Institute of Virology defended its patent application by claiming it was made in the national interest. It added that it would be willing to forgo enforcing its patent rights if foreign pharmaceutical companies in this case, Gilead collaborate with Chinese authorities to stop the pandemic.

Product Life Cycle – Regulatory Affairs Perspective

The process of strategizing ways to continuously support and maintain a product is called product life cycle management. The term product life cycle refers to the length of time from when a product is introduced to consumers into the market until it's removed from the shelves. This concept is used by management and by marketing professionals as a factor in deciding when it is appropriate to increase advertising, reduce prices, expand to new markets, or redesign packaging.

OBJECTIVE [15-17]

1. To determine the strength and weakness of drug regulation.

2. To improve drug regulations by proposing new strategies.

3. To create an overview on the organizational structures of drug regulation in selected countries.

4. To find out how the functions are carried out.

5. Financial and human resources are available for its implementation.

MATERIALS AND METHODS [18-20]

The method used for the study of product life cycle management in regulatory markets is described by different phases. The phases of product life cycle are:

• International business development

• New product development

• Manufacturing / Production

• Common technical document compilation

• Submission in the regulatory affairs

• Approvals/ MA

• Post approval Compliance

• Variations (if any)

• Renewals (After expiry of license).

International business development (Phase-1) [21-23]

An international business development plan in exporting should define the company's commitment to international trade, export pricing strategy, reason for exporting, potential support markets and customers, export financing alternatives, legal requirements, methods of foreign trade, transportation method, overseas partnership and investment capabilities. The main purpose of the international business development plan is to read your business to enter the international market place. The general working principles guides to creating international business development plan-

- Product or services
- Planning
- Goal setting
- Industry analysis
- Market factor assessment
- Market and pricing strategy

New product development (Phase-2)

The main coordinating function works exclusively under new product development are following -

• Formulation and development-for formulation development feasibility;

• Analytical development laboratory-for manufacturing and product design feasibility;

• International regulatory affairs-for checking regulatory requirements of a product;

• International business development team.

Product development

Under this section formulation development and analytical development team will act coordinately with NPD team. The major coordinating activities done by NPD team with other departments are as follows:

• After finalization of the product, the NPD team will send the details of that particular product to the below mentioned departments and API-Sourcing for procuring samples for development;

• Formulation development and analytical development lab-for development plan;

• International regulatory affairs-For artworks, brand name and label designs.

The development procedure for the product development is mainly consists of following steps:

a) Preliminary formulation plan

b) Pre-formulation

c) Final formulation evaluation and testing

d) Records

Manufacturing/Production (Phase-3)

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved.

Quality assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

For the manufacture of sterile medicinal products 4 grades can be distinguished.

Grade A - The local zone for high risk operations, e.g.: filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station.

Grade B - For aseptic preparation and filling, this is the background environment for the grade a zone.

Grades C and D - Clean areas for carrying out less critical stages in the manufacture of sterile products.

Common technical document compilation (Phase-4)

CTD means common technical document, is an internationally agreed upon format for the preparation of well-structured applications to be submitted to regulatory authorities in the three ICH regions- Europe, US and Japan. The main objective is the preparation and verification of the full Module1-5 of dossier in CTD format for submission in Europe and ORM. This is valid for all types of applications-National, centralized, MRP (Mutual recognition procedure) and DCP (Decentralized procedure) CTD having 5 different sections or modules as follows:

- Regional administrative information (Module 1)
- Quality overall summary (Module 2)
- Quality (Module 3)
- Non clinical reports (Module 4)
- Clinical reports (Module 5)

Submission in the regulatory authority (Phase-5)

Before submission all 5 dossier modules shall be prepared to meet the submission plans. The main objective for submission in the regulatory authorities is to get the approval and grant of marketing authorization to market the approved product.

Types of Submission:

- Decentralized Procedure (DCP)
- Mutual Recognition Procedure (MRP)
- National registration process (country specific)

Marketing authorization

A medicinal product may only be placed on the market in the European Union when a marketing authorization has been issued by the competent authority of a Member State for its own territory (national authorization) or when an authorization has been granted in accordance with regulation (EEC) No.2309/93 for the entire community. The marketing authorization holder, which encompasses the terms 'holder of the marketing authorization' and 'person responsible for placing the medicinal product on the market', must be established.

The MA can be given to the applicant by the following procedures:

• Independent National procedures

• DCP-Decentralized procedures

• MRP-Mutual recognition procedure

• Centralized procedure.

MA grant/Approval (Phase-6)

The primary purpose of any rules governing medicinal products is to safeguard public health. However, this objective must be achieved by means, which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the community. Thus, the pharmaceutical legislation of the European community has consistently pursued the twin objective: the protection of public health and the free movement of medicinal products.

Post approval compliance (Phase-7)

This phase is come in to action after formal MA approval and/or during the commercial production and supply of goods to approved market. The main content that is wisely come under this phase of life cycle are: General Compliance Query from Customer, Technical or GMP Agreements, Batch release documents, Technical package for commercial productions.

Variations (Phase-8)

In accordance with the Directives 2001/83/EC for medicinal products for human use, and Council registration (EEC) 2309/93 a marketing authorization is granted for a period of 5 years, renewable upon application three months before expiry. Throughout the life of a medicinal product, the marketing authorization holder is responsible for the product which circulates in the market place and is also required to take into account technical and scientific progress, MA holders may, introduce an additional safeguard during the period of five years.

Renewals (after expiry of license) (Phase-9)

In accordance with directives 2001/83/EC for medicinal products for human use, and council regulation (EEC) 2309/93 a marketing authorization is granted for a period of 5 years, and if applicant wants the renewable of license, then it is mandatory to apply the application three months before expiry.

Comparative Study on Regulatory Bodies In Us, India And European Union

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore, it is necessary to have knowledge about regulatory requirement for MAA of each country.

Principle Differences in Us, Europe and India

Requirements	US	EU	INDIA
Agency	One Agency USFDA	Multiple Agencies : • EMEA • CHMP • National Health Agencies	One Agency DCGI
Registration process	One registration process	Multiple Registration Process : • Centralized (European Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member state)	One registration process
TSE/BSE Study data	TSE/BSE Study data not required	TSE/BSE Study data Required	TSE/BSE Study data required
Post-approval changes	Post-approval changes in the approved drug: • Minor changes • Moderate changes • Major changes	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation	Post approval changes: • Major quality changes • Moderate quality changes

Future Direction in Regulatory Affairs [24]

Rapid changes due to advances in science, digital disruption, a renewed focus on the centrality of the patient in all stages of therapeutic product development and greater collaboration between national regulatory authorities have been accelerated by the COVID-19 pandemic. This article will discuss the various trends that are impacting the development of new therapies for alleviating disease and how these trends therefore impact on the role of the regulatory affairs professional. We discuss some of the challenges and provide insights for the regulatory professional to remain at the forefront of these trends and prepare for their impacts on their work.

1. Megatrends

Understanding changes in global megatrends can help regulatory affairs professionals navigate the future impacts on their roles. Megatrends are global trends that may unfold over several years and have the potential to have substantial transformative impacts on society.

2. Skills for the future regulatory affairs workforce

These developments in healthcare, medicine and the pharmaceutical and medical device industry will impact the regulatory affairs team. The traditional heavy 'task' based workload will evolve with digital solutions and automation to require broader strategic leadership skills. It is therefore vital that regulatory professionals are equipped with the skills, knowledge, and mindset to develop them in order to advance their professional lives. The current world of work is said to be volatile, uncertain, complex, and ambiguous (VUCA) and the global pandemic has resulted in a "new normal" world of work where these factors are amplified. The World Economic Forum has identified a number of important skills for the future of work including analytical thinking and innovation, active learning, complex problem solving, critical thinking and analysis, creativity, originality and initiative. Additional skills identified for the future of work include leadership and social influence, the ability to utilize, design and monitor technology, resilience, an ability to tolerate stress, flexibility and reasoning, problem-solving and ideation.

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