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Research

Life Cycle of Drug Regulation

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Abstract

Pharmaceutical regulations across the world play an important role in ensuring the safety and efficacy of the approved drugs. They not only regulate the pricing of drugs but the quality as well. The regulations are required both for new innovations and already existing products, in order to improve health status. An important agenda of pharmaceutical companies is the establishment of therapeutic area strategies, drug modality, and geographic strategies for research and development. It is worthwhile to understand the changes in therapeutic area, modality and internationalization of the top-selling pharmaceutical drugs over the past. Hence, the purposes of this study are to investigate changes in therapeutic area, modality and internationalization of the top-selling drugs and to identify their life cycle patterns. We compared the top-selling drugs between 2011 and 2017, and found that the percentages of nichebuster cancer drugs and home region-oriented drugs have increased whereas the proportions of traditional blockbuster cardiovascular drugs and global drugs have decreased. We compared product life cycle patterns via a Kruskal–Wallis test, and identified the features of product life cycle patterns per therapeutic area and modality. We performed a case study on drugs in the same class with the same pharmacological mechanism but found no differences across cases. Our results provide insights into therapeutic area strategies that consider life cycle patterns and geographic strategies that consider the competitive advantages of home region-oriented drugs. Finally, we presented new and simple models of life cycle patterns. This approach may help such enterprises establish and maintain sustainable growth.

Keywords: (FDA), the European Medicines Agency (EMA) and the Japanese Pharmaceutical and Medical Devices Agency (PMDA).

INTRODUCTION

Drug regulation is the control of drug use by international agreement and/or by regulatory authorities such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Japanese Pharmaceutical and Medical Devices Agency (PMDA).

The harm has come from drug products containing toxic impurities, from drugs with unrecognized severe adverse reactions, from adulterated drug products, and from fake or counterfeit drugs. Because of these issues, effective drug regulation is required to ensure the safety and efficacy of drugs for the general public.

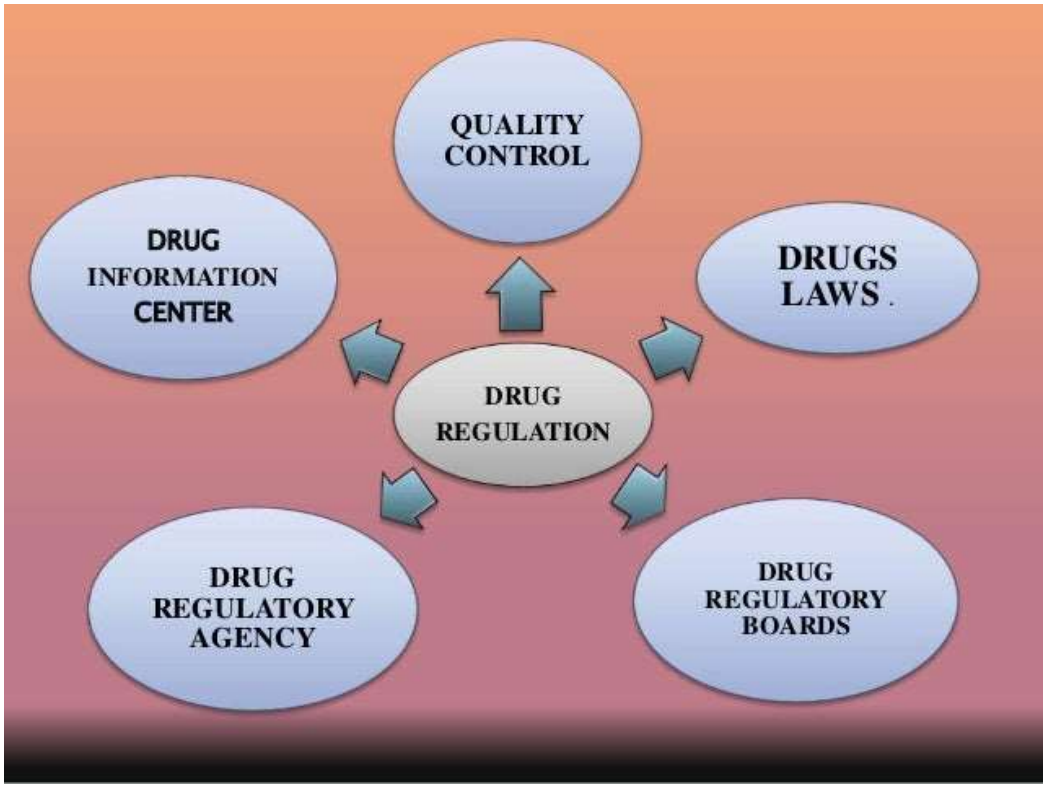

Fig 1: Drug Regulation Introduction

AIM AND OBJECTIVES

- The ultimate aim of drug development is to bring a new compound with proven therapeutic effect to the market. In this context, the transition from preclinical research to clinical stages marks a critical turning point, as it nears the new medicinal product to the market.
- Pharmaceutical regulations across the world play an important role in ensuring the safety and efficacy of the approved drugs. They not only regulate the pricing of drugs but the quality as well. The regulations are required both for new innovations and already existing products, in order to improve health status.
- The drug development life cycle is vital to delivering safe and effective drugs. But the pharmaceutical industry must work together to combat major challenges throughout the process.
- The drug development process is also uncertain and faces its own set of challenges, such as difficulty with target identification, drug approval market decrease, and increasing costs and pressure on pricing.
- The regulation of drugs and medicine is crucial to the health and safety of the public. Ensuring that a medicine is high quality is achieved by checking the efficacy, quality and safety of the drug. ... Regulation is important and followed continuously in every step and process that the drug material passes through. The product life-cycle is an important tool for marketers, management and designers alike. It specifies four individual stages of a product's life and offers guidance for developing strategies to make the best use of those stages and promote the overall success of the product in the marketplace

Regulation by government agencies[1]

Concerns related to the efficacy and safety of drugs have caused most governments to develop regulatory agencies to oversee development and marketing of drug products and medical devices. Use of any drug carries with it some degree of risk of an adverse event. For most drugs the risk-to-benefit ratio is favourable; that is, the benefit derived from using the drug far outweighs the risk incurred from its use. However, there have been unfortunate circumstances in which drugs have caused considerable harm. The harm has come from drug products containing toxic impurities, from drugs with unrecognized severe adverse reactions, from adulterated drug products, and from fake or counterfeit drugs. Because of these issues, effective drug regulation is required to ensure the safety and efficacy of drugs for the general public.

Public influence on drug regulation

The process of drug regulation has evolved over time. Laws regulating drug marketing and development, government regulatory agencies with oversight of drug development and use, drug evaluation boards, drug information centres, and quality control laboratories have become part of the cooperative venture that produces and develops drugs. In some countries drug laws omit or exempt certain areas of pharmaceutical activity from regulation. For example, some countries exempt herbal or homeopathic products from regulation. In other countries there is very little regulation imposed on drug importation. Over time, the scope of drug laws and the authority vested in regulatory agencies have gradually expanded. In some instances, strengthening of drug laws has been the result of a drug-related catastrophe that prompted public demand for more restrictive legislation to provide more protection for the public. One such example occurred in the 1960s with thalidomide that was prescribed to treat morning sickness in pregnant women. Thalidomide had been on the market for several years before it was realized to be the causative agent of a rare birth defect, known as phocomelia, that had begun appearing at epidemic proportions. There was a dramatic reaction to the devastation caused by thalidomide, especially because it was considered a needless drug.

At other times the public has perceived that drug regulation and regulatory authorities have been too restrictive or too cautious in approving drugs for the market. This concern typically has been related to individuals with serious or life-threatening illnesses who might benefit from drugs that have been denied market approval or whose approval has been inordinately delayed because regulations are too strict. At times, governments have responded to these concerns by streamlining drug laws and regulations. Examples of types of drugs given expedited approval are cancer drugs and AIDS drugs. Regulatory measures that make rapid approval of new drugs paramount sometimes have led to marketing of drugs with more toxicity than the public finds acceptable. Thus, drug regulations can and probably will remain in a state of flux, becoming more lax when the public perceives a need for new drugs and more strict following a drug catastrophe.

Objectives and organization of drug regulatory agencies

Effective regulation of drugs requires a variety of functions. Important functions include

- evaluation of safety and efficacy data from animal and clinical trials,
- licensing and inspection of manufacturing facilities and distribution channels to assure that drugs are not contaminated,
- monitoring of adverse drug reactions for investigational and marketed drugs, and
- quality control of drug promotion and advertising to assure that safety and efficacy claims are accurate. In some countries all functions surrounding drug regulation come under a single agency. In others, particularly those with a federal system of government, some drug regulatory authority is assumed by state or provincial governments.

Around the world, financing of drug regulatory agencies varies. Many governments provide support for such agencies with revenue from general tax funds. The theory behind this type of financing is that the common good is served by effective regulations that provide for safe and effective medicines. In other countries the agencies are supported entirely by fees paid by the pharmaceutical firms seeking regulatory approval. In still other countries the work of drug regulatory agencies is supported by a mixture of direct government support and user fees. The World Health Organization (WHO) has developed international panels of experts in medicine, law, and pharmaceutical development that are responsible for recommending standards for national drug laws and regulations.

Drug approval processes

Drug approval processes are designed to allow safe and effective drugs to be marketed. Drug regulatory agencies in various countries attempt to rely on premarketing scientific studies of the effects of drugs in animals and

humans in order to determine if new drugs have a favourable risk-to-benefit ratio. Although most countries require similar types of premarketing studies to be completed, differences in specific regulations and guidelines exist. Thus, if pharmaceutical firms wish to market their new drugs in many countries, they may face challenges created by the differing regulations and guidelines for premarketing studies. In order to simplify the approval process for multinational marketing of drugs, the WHO and many drug regulatory agencies have attempted to produce harmonization among regulations in various parts of the world. Harmonization, which aims to make regulations and guidelines more uniform, theoretically can decrease the cost of new drugs by decreasing the cost of development and regulatory approval. Because every new drug is somewhat different from preexisting ones, unforeseen safety or efficacy issues may arise during the regulatory review. Some of these issues may prompt an individual regulatory agency to require additional safety or efficacy studies. Thus, agreements on harmonization of regulations and guidelines can be more complicated and difficult to achieve than may seem to be the case.

The following sections describe in general terms the steps required for regulatory approval of drugs in one country—the United States. Although the descriptions are based on the Food and Drug Administration (FDA) regulations and guidelines, these requirements are similar to those in many other countries.

Drug applications

The Investigational New Drug application

Two important written documents are required from a pharmaceutical firm seeking regulatory approval from the U.S. FDA. The first is the Investigational New Drug (IND) application. The IND is required for approval to begin studies of a new drug in humans. Clinical trials for new drugs are conducted prior to marketing as part of the development process. The purpose of these trials is to determine if newly developed drugs are safe and effective in humans. Pharmaceutical companies provide selected physicians with developmental drugs to be studied in their patients. These physicians recruit patients, provide them with the study drug, evaluate the effect of the drug on their disease, and record observations and clinical data.

There are three phases—designated Phase 1, Phase 2, and Phase 3—of human clinical studies required for drug approval and marketing. Phase 1 studies describe the first use of a new drug in humans. These studies are designed to determine the pharmacological and pharmacokinetic profile of the drug and to assess the adverse effects associated with increasing drug doses. Phase 1 studies provide important data to allow for the design of scientifically sound Phase 2 and Phase 3 studies. Phase 1 studies generally enroll 20–200 subjects who either are healthy or are patients with the disease that the drug is intended to treat. Phase 2 studies are designed primarily to assess the efficacy of the drug in the disease to be treated, although some data on adverse events or toxicities may also be collected. Phase 2 studies usually enroll several hundred patients. Phase 3 studies enroll several hundred to several thousand patients and are designed to collect data concerning both adverse events and efficacy. When these data have been collected and analyzed, a judgment can be made about whether the drug should be marketed and if there should be specific restrictions on its use. An IND should contain information about the chemical makeup of the drug and the dosage form, summaries of animal pharmacology and toxicology studies, pharmacokinetic data, and information about any previous clinical investigations. Typically, Phase 1 protocols (descriptions of the trials to be conducted) are briefer and less detailed than Phase 2 and Phase 3 protocols.

Prior to its regulatory approval, a drug is generally restricted to use in patients who are formally enrolled in a clinical trial. In some cases a drug that has not yet been approved for marketing can be made available to patients with a life-threatening disease for whom no satisfactory alternative treatment is available. If the patient is not enrolled in one of the clinical trials, the drug can be made available under what is called a Treatment IND. A Treatment IND, which has sometimes been called a compassionate use protocol, is subject to regulatory requirements very similar to those of a regular IND.

The New Drug Application

The second important regulatory document required by the FDA is the New Drug Application (NDA). The NDA contains all of the information and data that the FDA requires for market approval of a drug. Depending on the intended use of the drug (one-time use or long-term use) and the risk associated with its intended use, INDs may be from tens to hundreds of pages long. In contrast, NDAs typically are much larger and much more detailed. In some instances they can represent stacks of documents up to several metres high. Basically, an NDA is a detailed and comprehensive report on what is known about the new drug under review. It contains technical sections on

- chemistry, manufacturing, and dosage forms,
- animal pharmacology and toxicology,
- human pharmacokinetics and bioavailability,
- comprehensive results of clinical trials,

- statistics, and
- microbiology (in the case of anti-infective or antiviral drugs).

Another important NDA component is the proposed labeling for the new drug. The label of a prescription drug is actually a comprehensive summary of information made available to health care providers. It contains the claims that the pharmaceutical company wants to make for the efficacy and safety of the drug. As part of the review process, the company and the FDA negotiate the exact wording of the label because it is the document that determines what claims the company legally can make for use of the drug once it is marketed.

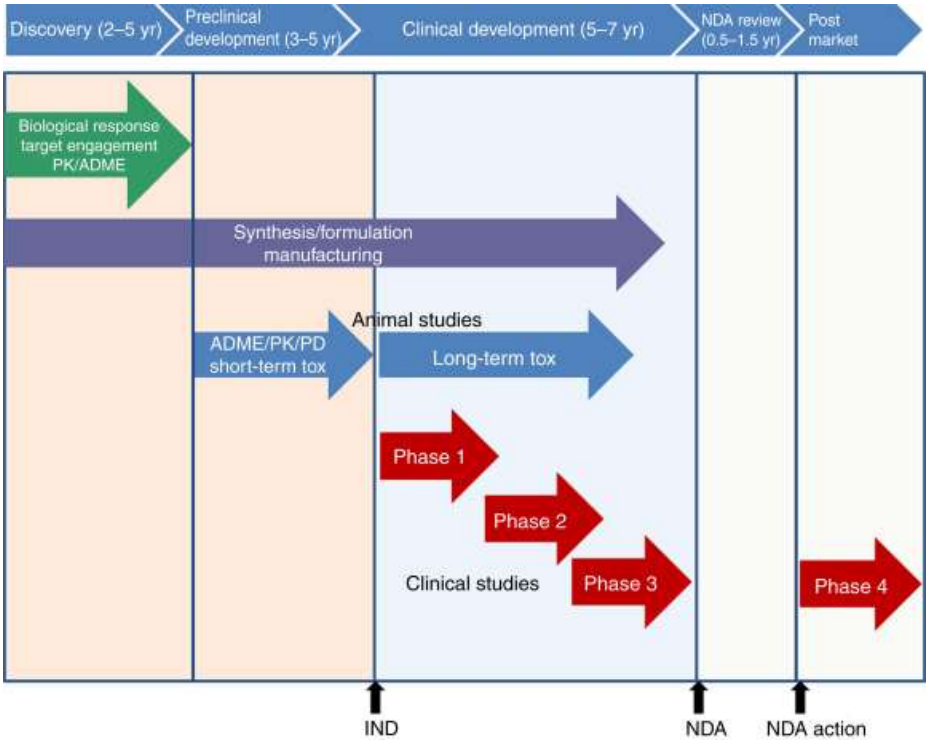

Fig 2: Regulatory Aspects for Drug development

Safety testing in animals

A number of safety tests are performed on animals, prior to clinical trials in humans, in order to select the most suitable lead chemical and dosage form for drug development. The safety tests can include studies of acute toxicity, subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity, and mutagenicity.

Toxicity tests

In acute toxicity studies, a single large or potentially toxic dose of the drug is administered to animals via the intended route of human administration, and the animals are observed for one to four weeks, depending on the drug. At the end of the observation period, organ and tissue toxicities are evaluated. Acute toxicity studies generally are required to be carried out in two mammalian species prior to beginning any Phase 1 (safety) study in humans. Subchronic toxicity studies (up to three months) and chronic toxicity studies (longer than three months) require daily drug administration and usually do not start until after Phase 1 studies are completed. This is because the drug may be withdrawn after Phase 1 testing and because data on the effect of the drug in humans may be important for the design of longer-duration animal studies. When these studies are required, they are conducted in two mammalian species and are designed to allow for detection of neurological, physiological, biochemical, and hematological abnormalities occurring during the course of the study. Organ and tissue toxicity and pathology are evaluated when the studies are terminated.

The number and type of animal safety tests required varies with the intended duration of human use of the drug. If the drug is to be used for only a few days in humans, acute and subacute animal toxicity studies may be all that is required. If the human drug use is for six months or longer, animal toxicity studies of six months or more may be required before the drug is marketed. Carcinogenicity (potential to cause cancer) studies are generally required if

humans will use the drug for longer than six months. They usually are conducted concurrently with Phase 3 (large-scale safety and efficacy) clinical trials but may begin earlier if there is reason to suspect that the drug is a carcinogen.

Teratogenicity and mutagenicity tests

If a drug is intended for use during pregnancy or in women of childbearing potential, animal reproductive and developmental toxicity studies are indicated. These studies include tests that evaluate male and female fertility, embryonic and fetal death, and teratogenicity (induction of severe birth defects). Also evaluated are the integrity of the lactation process and the quality of care for her young provided by the mother.

Genetic toxicity, or mutagenicity, studies have become an integral component of regulatory requirements. Since no one mutagenicity test can evaluate all types of genetic toxicity, two or three tests are usually performed. Typical mutagenicity tests include a bacterial point mutation test (the Ames test), a chromosomal aberrations test in mammalian cells in vitro, and an in vivo (intact animals) test.

Biopharmaceutical studies

Pharmacokinetic investigation

In addition to the animal toxicity studies outlined above, biopharmaceutical studies are required for all new drugs. The chemical makeup of the drug and the dosage form of the drug to be used in trials must be described. The stability of the drug in the dosage form and the ability of the dosage form to release the drug appropriately have to be evaluated. Bioavailability (how completely the drug is absorbed from its dosage form) and pharmacokinetic studies in animals and humans also have become important to include in a drug development plan. Pharmacokinetics is the study of the rates and extent of drug absorption, distribution within the body, metabolism, and excretion. Pharmacokinetic studies give investigators information about how often a drug should be taken to achieve adequate blood levels. The metabolism and excretion data can also provide clues about whether a new drug will interact with other drugs a patient may be taking. For example, if two drugs are inactivated (metabolized or excreted) via the same biological process, one or even both of the drugs might have its sojourn in the body prolonged, resulting in increased blood levels and increased toxicity. Conversely, some drugs induce the metabolism and shorten the body sojourn of other drugs, resulting in blood levels inadequate to produce the desired pharmacological effect.[1]

Regulation begins prior to marketing authorisation

As early as in the preclinical testing phase of a drug, regulatory control begins when safety studies on a novel drug candidate are initiated: preclinical safety studies must be performed in compliance with GLP (Good Laboratory Practice) in a GLP-certified laboratory.

Permission for clinical trials must be obtained from the Ethical Committee. Furthermore, advance notice of such trials must be given to Fimea, who can then request further clarification or decline the start of the trial. In Finland, 150–200 notices are submitted annually, all of them being processed nationally. Test results and adverse reactions found in the tests are also reported to Fimea.

Marketing authorisation can be obtained in several ways

A drug may only be sold if it has marketing authorisation or a special permission for compassionate use, or an exemption has been granted so as to release it for consumption. The majority of novel drug inventions obtain their marketing authorisation in the EU via what is known as the centralised marketing authorisation procedure, in which the EU Commission decides on a marketing authorisation for the territory of the entire Union on the basis of an opinion issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). CHMP comprises delegates from all Member States, and the actual evaluation of an application is carried out by expert teams formed by the CHMP delegates chosen as Rapporteur and Co-Rapporteur in each individual case from the agencies of their home countries.

Marketing authorisation in the EU can also be applied for directly from the medicines agency of a Member State. In Finland, such purely national marketing authorisation applications have become scarce: only a dozen are filed annually.

CONCLUSION

In pharmaceutical industry, it benefits through enhancing the lifespan of patent and pricing strategies. Improved patient compliance, revenue growth, expanded clinical benefits; cost advantages life extension exclusivity

and quicker market launch are amongst the main applications of product lifecycle management. New drug applications are reviewed primarily for safety and efficacy with regard to their claims for intended clinical use. The FDA's mission is to facilitate the development of the premarket review and evaluation of INDs and NDAs. A central theme over the past few years has been a standardized approach to evidence-based review and evaluation. The FDA emphasizes the Quality System approach to design of studies by providing oversight and objective review by setting thresholds for product safety and effectiveness by ensuring that organized data and appropriate labeling are present in support of the new drug's intended and clinical use.

Here, we reviewed changes in therapeutic area, modality, and internationalization of the top-selling drugs and found that they shifted from classic blockbusters to nichebusters and from global to home region orientation over the past decade. Furthermore, we identified the product lifecycle patterns per therapeutic area and discovered that drugs prescribed for cancers and endocrine and metabolic diseases contributed to the sustainable growth of pharmaceutical companies. We also performed a case study to investigate differences in the product life cycle patterns of drugs in the same class with the same mode of action. However, we detected no consistent results for the first-mover advantage. One limitation of this study is that a sample size was small and another one is that it did not consider competition within the therapeutic area or additional indications and dosage forms as elements of the drug life cycle strategy. Consequently, our understanding of individual drug life cycles is limited. Hence, we recommend conducting a micro-analysis of individual drugs such as examining the relationship between the timing of additional indications and sales growth as well as the relationship between the entry of competitors and sales decline due to overcoming the limitation. In addition, while this study was intended to contribute to decision-making at the product level, studies at the company level are needed to help pharmaceutical companies in optimal decision-making, such as identifying the best combination of products considering individual product life cycle patterns to maximize total sales as a company, which will require larger samples, more case studies and more comparative studies of sigmoid curve-shaped growth curves. Moreover, as our focus was on the top-selling drugs, our findings have to be complemented by the analysis results of the life cycle patterns of other types of drugs. We believe that this research area will continue to evolve as pharmaceutical companies still face challenges in comprehensive decision-making for sustainable growth.

Throughout the clinical lifecycle of a medicinal product, a myriad of documents are needed to effectively plan, run and then assess and communicate the outcome of the clinical studies performed. Many of these documents are complex compilations of data and thoughts, and also function in conjunction with other documents – meaning they all need to tell a consistent story.

It is important to have experienced stakeholders on the authoring teams, including a medical writer who has the experience with the document types to know how to advise teams on the needs of a particular document and to guide authors through the review and revision process. Planning well in advance and ensuring enough time is given to the authoring teams to allow them to think about, discuss and craft documents that accurately reflect what the data have to say, will ensure that these documents are fi t for purpose while making the writing activities less arduous for everyone involved.

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