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Review

A New Current Regulations For Clinical Trials

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Abstract

Regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This work focuses on the drug approval process in India and USA.

Keywords: Drug approval process, Clinical trials, marketing.

INTRODUCTION

Regulatory affairs in pharmaceutical industry

Introduction to regulatory affairs

regulatory affairs(ra), also called government affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, biologics and functional foods). Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of regulatory affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents.

this department is responsible for knowing the regulatory requirements for getting new products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory affairs typically communicates with one of the centers (e.g., center for drug evaluation and research) at the fda headquarters, rather than the fda local district offices. Gimps do not directly apply to regulatory affairs; however, they must understand and evaluate changes to drug manufacturing and testing activities to determine if and when the fda must be notified.

importance of regulatory affairs

in today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its regulatory affairs activities is therefore of considerable economic importance for the company.

inadequate reporting of data may prevent a timely positive evaluation of marketing application. A new drug may have cost many millions of pounds, euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse1 failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients.

a good regulatory affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavor with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources.

the regulatory affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of the regulatory affairs professionals will condition the perceptions of the government officials to the company for better, or worse officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent.

the importance of the regulatory affairs function is such that senior regulatory affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies.

Responsibility of regulatory affairs professional's

The regulatory affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate, and evaluate the scientific data that their research and development colleagues are generating. They are responsible for the presentation of registration documents to regulatory agencies, and carry out all the subsequent negotiations necessary to obtain and maintain marketing authorization for the products concerned. They give strategic and technical advice at the highest level in their companies, right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development program and the company as a whole.

It may take anything up to 15 years to develop and launch a new pharmaceutical product and problems may arise in the process of scientific development and because of a changing regulatory environment. Regulatory affairs professionals help the company avoid problems caused by badly kept records, in appropriate scientific thinking or poor presentation of data. In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims which can be made for the product on labeling or in advertising.

Need of regulatory affairs in the pharmaceutical industry

regulatory affairs professionals are the link between pharmaceutical industries and worldwide regulatory agencies. They are required to be well versed in the laws, regulations, guidelines and guidance of the regulatory agencies. There is a growing need to incorporate the current requirements of pharmaceutical industries in the standard curriculum of pharmacy colleges to prepare the students with the latest developments to serve the industries.

as the pharmaceutical industries throughout the world are moving ahead towards becoming more and more competitive, these are realizing that the real battle of survival lies in executing the work by understanding the guidelines related to various activities carried out to give an assurance that the process is under regulation. Pharmaceutical industry, being one of the highly regulated industries in immense need of people than ever before who are capable of handling issues related to regulatory affairs in a comprehensive manner.

In india import, manufacturing, sale and distribution of drug is regulated under drugs and cosmetics act 1940 and drugs and cosmetic rules 1945 (hereinafter refer as act) made there under. At present, bulk drug (active pharmaceutical ingredients) and finished formulations are regulated under the said act. Any substance falling within the definition of drug (section 3b of the act) required to be registered before import into the country. Not only drug but the manufacturing site needs to be registered for import. If the drugs, fall within the definition of new drug (rule 122 e of the act), the new drug approval is the pre-requisite for submission of application for registration and or import of drug. The application for registration and import can be made to the licensing authority under the act i.e. To the drugs controller general (i) at cdsco, fdabhawan, kotla road, near balbhawan, new delhi by the local authorized agent of the foreign manufacturer having either manufacturing or sale license or by the foreign manufacturers' having a whole sale license in the country. A regulatory process by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs.

Major bodies regulating drugs and pharmaceuticals

The principal regulatory bodies entrusted with the responsibility of ensuring the approval, production and marketing of quality drugs in india at reasonable prices are:the central drug standards and control organization (cdsco), located under the aegis of the ministry of health and family welfare. The cdsco prescribes standards and measures for ensuring the safety, efficacy and quality of

drugs, cosmetics, diagnostics and devices in the country; regulates the market authorization of new drugs and clinical trials standards; supervises drug imports and approves licences to manufacture the above-mentioned products;

Prevailing mechanisms

This sub-section primarily focuses on major regulatory policies and mechanisms in relation to drug pricing and development of standards for ensuring safety and efficacy.

In india, drug manufacturing, quality and marketing is regulated in accordance with the drugs and cosmetics act of 1940 and rules 1945. This act has witnessed several amendments over the last few decades. The drugs controller general of india (dcgi), who heads the central drugs standards control organization (cdsco), assumes responsibility for the amendments to the acts and rules. Other major related acts and rules include the pharmacy act of 1948, the drugs and magic remedies act of 1954 and drug prices control order (dpco) 1995 and various other policies instituted by the department of chemicals and petrochemicals.

Some of the important schedules of the drugs and cosmetic actsi include: schedule d: dealing with exemption in drug imports, schedule m: which, deals with good manufacturing practices involving premises and plants and schedule y: which, specifies guidelines for clinical trials, import and manufacture of new drugs

Temporal progression of drug policies & acts

The patents act of 1970, drug price control order 1970 and foreign exchange regulation act 1973 played a significant role in terms of the building of indigenous capability with regard to manufacture of drugs. The new drug policy of 1978 provided an added thrust to indigenous self-reliance and availability of quality drugs at low prices.dpco 1987 heralded the increasing liberalization in the industry. One of the important features of this act was the reduction of the number of drugs under price control to 143.

The major objective of dpco 1995 was to decrease monopoly in any given market segment, further decrease the number of drugs under price control to 74 and the inclusion of products manufactured by small scale producers under price control list.

In 1997, the national pharmaceutical pricing authority was constituted in order to administer dpco and deal with issues related to price revision.

Drug pricing

As mentioned earlier, pricing policy and industry regulation constitutes one of the key responsibilities of the nppa. Price control on medicines was first introduced in india in 1962 and has subsequently persisted through the drug price control order (dpco). As per the directive of nppa, the criterion for price regulation is based on the nature of the drug in terms of whether it enjoys mass consumption and in terms of whether there is lack of adequate competition for the drug. The year 1978 witnessed selective price controls based on disease burden and prevalence. The list of prices under dpco subsequently witnessed a gradual decrease over a period of time. Around 80% of the market, with 342 drugs, was under price control in 1979. The number of drugs under dpco decreased from 142 drugs in 1987 to 74 in 1995.

Drugs with high sales and a market share of more than 50% are subjected to price regulation. These drugs are referred to as scheduled drugs. The nppa also regulates the prices of bulk drugs. The mrp excise on medicines was levied by the finance ministry in 2005. The objective was to increase revenue and lower prices of medicines by using fiscal deterrent on mrp. This change may have had some impact in terms of magnifying the advantage to industries located in the excise free zones. This also succeeded in attracting some small pharmaceutical firms to these zones. (gehlsampath 2008, srivastava 2008).

Fixed dose combinations and prevalence of counterfeit and spurious drugs

Recently, 294 fixed dose combinations were withdrawn by the central drug control authority on grounds that these drugs were therapeutically irrational. The order was subsequently stayed by the madras high court. The issue of the definition of counterfeit drugs is relevant in the context of different drug quality standards prevailing in the indian market. While exported drugs were of a higher quality (who/fda/emea/tga), to meet the required standards in the country of export, in the case of the domestic market, adherence to local quality standards, fixed by the regulatory body was sufficient. Also absence of transparency in licensing procedures has resulted in the market being flooded with counterfeit and substandard drugs. In this context, the mashelkar committee report has referred to a who study, which declared that nearly 30% of the indian market was flooded with spurious, substandard or counterfeit drugs. The government's own estimates have been in the range of 8-10% for substandard drugs and 0.2-0.5% for spurious drugs.

Patents and data protection related issues

The indian patent act, 1970 was amended through the patents amendment act (2005). A technical expert group was constituted under the chairmanship of drr.a. Mashelkar, then director general of the csir. The committee decision was that it would be trips incompatible to exclude microorganisms from patents and to limit the grant of the patent for pharmaceutical substance to a new chemical entity or a new medical entity involving one or more inventive steps. The committee also opposed the granting of frivolous patents and evergreening and recommended the formulation of detailed guidelines to ensure that only those patents proving 'substantial human intervention' and 'utility' were granted.

Good manufacturing practices

Good manufacturing practices (gmp) constitute an international set of guidelines for the manufacture of drugs and medical devices in order to ensure the production of quality products. In recent years, gmp protocols are being adopted and followed in over 100 countries, either in the form of regulations (japan, korea and united states), or directives (european union) or guides (united

kingdom) or codes (australia). The objective of gmps is to minimize risks with reference to the manufacturing, packaging, testing, labeling, distributing and importing of drugs, cosmetics, medical devices, blood and blood products, food items etc. These protocols are largely concerned with parameters such as drug quality, safety, efficacy and potency.

WHO gmp protocols

World health organization gmp guidelines were instituted in 1975 in order to assist regulatory authorities in different countries to ensure consistency in quality, safety and efficacy standards while importing and exporting drugs and related products. India is one of the signatories to the certification scheme. The who-gmp certification, which possesses two-year validity, may be granted both by cdsco and state regulatory authorities after a thorough inspection of the manufacturing premises.

Schedule m compliance

The requirements specified under the upgraded schedule 'm' for gmp have become mandatory for pharmaceutical units in india w.e.f. July 1, 2005. Schedule m classifies the various statutory requirements mandatory for drugs, medical devices and other categories of products as per the current good manufacturing practices (cgmp). Schedule m protocols have been revised to harmonize it along the lines of who and us-fda protocols. These revised protocols include detailed specifications on infrastructure and premises, environmental safety and health measures, production and operation controls, quality control and assurance and stability and validation studies.ii problems related to schedule m compliance are mostly confined to small-scale pharmaceutical units as large-scale firms have shown greater willingness to comply with the revised norms in order to increase their competitiveness in the global arena.

Clinical trials

In recent years, india has positioned itself as one of the major players in the clinical trials arena. The recognition for india as a centre for clinical trials has mainly arisen through the providing of contract services to the international pharmaceutical industry in the form of clinical development services. The clinical market in india is expected to grow at a consistent rate of 20-25 percent. The recent regulatory revisions in the pharmaceutical industry and stricter patent laws have made it easier to conduct trials, making it the fourth largest market in terms of volume.

Figure provides a phase-wise break up of clinical trials carried out in india. Phase i trials are essentially carried out to establish pharmacological indications and safety of the drug and are essentially exploratory in nature. Phase ii trials provide information related to the efficacy and safety of the new drug in patients. Phase iii trials are essentially multi-centric confirmatory trials carried out in larger groups of patients and healthy volunteers, while phase iv trials involve post-marketing surveillance. The chart clearly indicates that the majority of trials carried out in india fall under the phase iii category.

Policies relating to clinical trials

In this context, it would also be useful to review prominent changes in policies related to clinical trials in the last few decades. Till about a decade ago, regulatory and ethics based environment for the conduct of quality clinical trials in india were conspicuous by their absence. The central drugs standards control organization (cdsco) has played a critical role towards this end. The progression towards good clinical practice (gcp) has largely been a gradual and slow process.

It was in 1988 that local clinical trials for new drug introductions were first made mandatory in india. There was also a phase lag as permissions for trials were granted for one phase behind the rest of the world. Thus, phase ii and phase iii trials were permitted only after these had been carried out elsewhere in the world. The period before 2000 witnessed several incidents of ethical violations related to informed consent and conduct of trials by multinational firms and domestic players as well. In 2000, due to the proactive initiatives of regulators, the central ethics committee on human research (cechr) and indian council of medical research (icmr) conceptualized and issued ethical guidelines for biomedical research on human subjects. In 2001, a central expert committee was set up by central drugs standards control organization (cdsco) to develop good clinical practice (gcp) guidelines in line with the latest who and ich guidelines.

Subsequently, the requirements of data submission on animal testing for permission to undertake phase i, phase ii and phase iii clinical trials were laid down in the revised schedule y of the drugs and cosmetics rules.

As per these revisions, the relevant data submitted to the drugs control general of india (dcgi), is evaluated with the assistance of expert clinicians & scientists.

Similarly, for registration and approval of new drugs, which have already been registered and used in the country of origin, phase ii trials in about 100 patients is usually insisted upon by dcgi before allowing such products to be marketed in india. Normally, new drug approval is usually granted for a period of about two years. The trials are conducted only after clearances are obtained from the institutional ethics committees. Consent of patients for participation in such trials is an integral part of the regulatory framework.

In 2005, drugs technical advisory board (dtab) made glp practices mandatory for all laboratories and in-house units of pharmaceutical firms and contract research organizations (cros). In 2007, norms pertaining to the phase lag have also been revised and schedule y now permits phasei trials to be carried out concurrently in india along with the rest of the world. For an efficient and ethical growth of the clinical trials industry, the appropriate mechanisms to be adopted include the presence of a strong centralized regulatory regime to effectively monitor gcp guidelines and ensure transparency in the functioning of institutional ethics committees (iecs).

The drugs consultative committee approved these recommendations in 2005, ensuring that in future all devices would be licensed for manufacture, distributed and sold by the cdsco, with special evaluation committees in order to ensure that the concerned manufacturing units complied with the requisite gmp requirements.

The principal provisions of these guidelines are as follows

Ten categories of sterile devices: cardiac and drug eluting stents, catheters, bone cement, heart valves, scalp vein sets, orthopedic implants, internal prosthetic replacements, iv cannulae and intraocular lenses; would be considered as drugs and consequently regulated.

Importers would have to submit us-fda clearance, the eu medical device directive or similar approvals from other countries as proof of adherence to quality standards. Expert committees would be set up for evaluation and granting of licences to locally manufactured devices, in the absence of international quality certification.

The approval of the committees would be verified by both central and state licensing committees.

Some of the problems associated with compliance to these regulations include lack of awareness among smaller firms, high registration fees, delays in granting of licences, restrictions in the entry of new players in the sector and lack of preparation by the firms with respect to documentation requirements

Biotech products

The ministry of environment and forests under the environment (protection) act of 1986 have notified the rules for the manufacture, use, import, export and storage of hazardous microorganisms or genetically engineered organisms or cells. As per these rules, biological materials are regulated from the r&d stage to their release in the environment. The institutional biosafety committee (ibsc), review committee on genetic manipulation (rcgm) and the genetic engineering approval committee (geac) to monitor rdna research, product development and commercialization. The isbc functions as the nodal point for interaction within the institution for the implementation of the rdna biosafety guidelines. The rcgm essentially monitors the safety related aspects of activities involving genetically engineering organisms or hazardous microorganisms. The geac undertakes the responsibility of approval of activities involving large-scale use of genetically modified/ hazardous microorganisms and products thereof in research and industrial production and their safety in terms of environmental protection. In addition, the dcgi and state drug controllers as per the drugs and cosmetics act 1945 and its subsequent amendments regulate biologicals.

Deficiencies and limitations of the current regulatory regime

- Proliferation of spurious and substandard drugs in the indian market
- Dual licencing mechanism acts as a deterrent to uniform implementation of regulatory procedures
- Lack of transparency in licencing procedures
- Inadequate regulatory expertise and testing facilities to implement uniform standards
- Need for greater thrust on institutional support to small scale firms to enable speedy implementation of schedule m upgradation and standardization of drug quality
- Need for greater clarity on patentability of pharmaceutical substances and conditions under which firms can apply for compulsory licences to prevent legal battles between local firms, mncs and civil rights groups.
- Need for greater coordination, accountability and transparency in functioning among different ministries concerned with drug regulation.

Recent regulatory initiatives

- Move to establish an integrated regulatory system through the constitution of a national drug authority so that quality regulation and price control is performed by the same agency
- Establishment of pharmacovigilance centres at national, zonal and regional levels to monitor adverse drug reactions
- Move to bring nearly 374 bulk drugs under price control and regulate trade margins
- Capability strengthening to monitor clinical trials, including the setting up of the clinical trials registry of india (ctri)

Overview

Clinical trials often involve patients with specific health conditions who then benefit from receiving otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives for their inconvenience. During dosing periods, study subjects typically remain on site at the unit for durations of one to 40 nights, and occasionally longer, although this is not always the case.

Usually, one or more pilot experiments are conducted to gain insights for design of the clinical trial to follow. In medical jargon, effectiveness is how well a treatment works in practice and efficacy is how well it works in a clinical trial. In the us, the elderly comprise only 14% of the population, but they consume over one-third of drugs. Despite this, they are often excluded from trials because their more frequent health issues and drug use produce unreliable data. Women, children, and people with unrelated medical conditions are also frequently excluded.

In coordination with a panel of expert investigators (usually physicians well known for their publications and clinical experience), the sponsor decides what to compare the new agent with (one or more existing treatments or a placebo), and what kind of patients might benefit from the medication or device. If the sponsor cannot obtain enough patients with this specific disease or condition at one location, then investigators at other locations who can obtain the same kind of patients to receive the treatment would be recruited into the study.

During the clinical trial, the investigators: recruit patients with the predetermined characteristics, administer the treatment(s), and collect data on the patients' health for a defined time period. These patients are volunteers and they are not paid for participating in

clinical trials. These data include measurements like vital signs, concentration of the study drug in the blood, and whether the patient's health improves or not. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.
Clinical trial may be designed to do:

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient.
- Assess the safety and effectiveness of a different dose of a medication than is commonly used (e.g., 10-mg dose instead of 5-mg dose)
- Assess the safety and effectiveness of an already marketed medication or device for a new indication, i.e. A disease for which the drug is not specifically approved
- Assess whether the new medication or device is more effective for the patient's condition than the already used, standard medication or device ("the gold standard" or "standard therapy")
- Compare the effectiveness in patients with a specific disease of two or more already approved or common interventions for that disease (e.g., device a vs. Device b, therapy a vs. Therapy b)

While most clinical trials compare two medications or devices, some trials compare three or four medications, doses of medications, or devices against each other.

Except for very small trials limited to a single location, the clinical trial design and objectives are written into a document called a clinical trial protocol. The protocol is the 'operating manual' for the clinical trial and ensures the researchers in different locations all perform the trial in the same way on patients with the same characteristics. (this uniformity is designed to allow the data to be pooled.) A protocol is always used in multicenter trials.

Because the clinical trial is designed to test hypotheses and rigorously monitor and assess what happens, clinical trials can be seen as the application of the scientific method, and specifically the experimental step, to understanding human or animal biology.
The most commonly performed clinical trials evaluate new drugs, medical devices (like a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before the national regulatory authority approves marketing of the drug or device, or a new dose of the drug, for use on patients.

Phase's of clinical trials[8]

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase i to phase ii or from phase ii to phase iii. Therefore, it may be easier to think of early phase studies and late phase studies. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through phases i, ii, and iii, it will usually be approved by the national regulatory authority for use in the general population. Phase iv are 'post-approval' studies.

Phase i

Phase i trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers will be recruited. This phase is designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organizations (cro) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase i trials also normally include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer. The tested range of doses will usually be a fraction of the dose that caused harm in animal testing. Phase i trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have terminal cancer or hiv and the treatment is likely to make healthy individuals ill. These studies are usually conducted in tightly controlled clinics called cpus (central pharmacological units), where participants receive 24-hour medical attention and oversight. In addition to the previously mentioned unhealthy individuals, "patients who have typically already tried and failed to improve on the existing standard therapies "may also participate in phase i trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay depends on length of participation.

Phase ii

Phase ii studies are sometimes divided into phase iia and phase iib.
Phase iia is specifically designed to assess dosing requirements (how much drug should be given).
Phase iib is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).
Some trials combine phase i and phase ii, and test both efficacy and toxicity.

Phase iii

This phase is designed to assess the effectiveness of the new intervention and thereby, its value in clinical practice. It is designed to assess the effectiveness of the new intervention and thereby, its value in clinical practice. Phase iii studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, phase iii trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase iii trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This is sometimes called

the "pre-marketing phase" because it actually measures consumer response to the drug. Once a drug has proved satisfactory after phase iii trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing phase iii clinical trials can be marketed under fda norms with proper recommendations and guidelines through a new drug application (nda) containing all manufacturing, pre-clinical, and clinical data. In case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing phase iii clinical trials in the market.

Phase iv

Phase iv trial is also known as post marketing surveillance trial. Phase iv trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase iv studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the phase i-iii clinical trials.

DISCUSSIONS

NEW DRUG APPROVAL PROCEDURE IN INDIA

INTRODUCTION

The new drug approval is of two phase process the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect .

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular populations) should also be monitored.

DRUG APPROVAL PROCESS IN INDIA

1)investigation of new drug in india

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

The IND application must contain information in three broad areas

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

2) Procedure for new drug approval in India

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. The changes includes, establishing definitions for Phase I–IV trials and clear responsibilities for investigators and sponsors. The clinical trials were further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) Other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks. The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks.

An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. On healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, If the new drug substance is not marketed in any other country.

The new drug registration (using form # 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of about 12-18 months. Figure 10 represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored.

The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralised and State authorities. Other issues where the difference appears are, time taken for the approval of a CTA application, time taken in evaluation of marketing authorization application, registration fee, registration process and marketing exclusivity .

Some counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan , it is mandatory that the dossier prepared in CTD format, however, in some countries it is optional such as in India. IND-Investigational New Drug, DCGI-Drug Controller General of India, CDSCO-Centre for Drug Standards Control organization.

CTD GUIDELINE IN INDIA

Scope

This guideline applies to import / manufacture and marketing approval of new drugs including New chemical entity, new indication, new dosage forms, modified release form, new route of administration etc. under the definition of new drug under Rule 122E of Drugs & Cosmetics rules as a finished pharmaceutical product.

What is CTD? The CTD is only a format for submission of information to CDSCO. It does not define the content.

Difference in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analysis so unnecessary delay in approval. Thus common format of submission will help. Through the ICH process, CTD guidance developed for japan,EU& US. CDSCO also adopted the CTD.

CONCLUSION

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. In most of the counties, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs. Therefore, harmonization of drug approval processes either by ICH or WHO may be initiated at global level.

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