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CURRENT APPROVAL PROCEDURE FOR NEW REGULATIONS, STANDARDS, POLICIES & GUIDANCE ISSUED BY REGULATORY AUTHORITIES

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Abstract:

A regulatory process by which a person/organization/sponsor/innovator gets authorization to launch a drug in themarket, 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 article will focus the similarities and differences in drug approval process of various regulatory bodies.

***Key Words**: Drug approval process, clinicaltrials, marketing.*

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INTRODUCTION:

National health authorities have the duty to ensure that available pharmaceutical products,whether imported or manufactured locally,are of good quality,safe and efficacious.This is particularly difficult for vaccines and biological products,the quality of which cannot be established entirely by tests on the material in the final container.A national control authority should therefore be established that is responsible for ensuring that the manufacturer is adhering to approved standards of good manufacturing practice and quality assurance specific to the product.The procedures through which the national control authority confirms the assurance of quality provided by the manufacturer will depend on the resources avalible and whether the product is manufactured locally or imported.

In general,biological products are distinguished from other drugs by being derived from living organisms(ranging from normal or genetically modified microorganisms to fluids and tissues derived from various animal and human sources) and frequently have a complex molecular structure.They require special quality considerations because of the biological nature of:(a) the starting materials; and /or (b) the manufacturing process;and/or (c)the test methods needed to characterize batches of the product.

Development in biological products have been extremely rapid in recent years,and the potential valve of such products in improving health care on a global scale is immense.There is an urgent need to match technological advances with appropriate mechanisms for assuring the safety,quality and efficacy of the products[1].

Laws & Regulations

The Basics of the Regulatory Process

Regulations are mandatory requirements that can apply to individuals, businesses, state or local governments, non-profit institutions, or others.

Congress passes the laws that govern the United States, but Congress has also authorized EPA and other federal agencies to help put those laws into effect by creating and enforcing regulations.

A basic description of how laws and regulations are developed, what they are, and where to find them, with an emphasis on environmental laws and regulations.

- Creating a law
- Putting the law to work
- Creating a regulation
- How you can get involved

Creating a law

Step 1: Congress Writes a Bill

A member of Congress proposes a bill. A bill is a document that, if approved, will become law. To see the text of bills Congress is considering or has considered, go to Congress.gov

Step 2: The President Approves or Vetoes the Bill

If both houses of Congress approve a bill, it goes to the President who has the option to either approve it or veto it. If approved, the new law is called an act or statute. Some of the better-known laws related to the environment are the Clean Air Act, the Clean Water Act, and the Safe Drinking Water Act.

- Summaries of the laws EPA administers
- Congress.gov: for more information about the legislative process

Step 3: The Act is Codified in the United States Code

Once an act is passed, the House of Representatives standardizes the text of the law and publishes it in the United States Code (U.S.C.). The U.S.C. is the codification by subject matter of the general and permanent laws of the United States. Since 1926, the U.S.C. has been published every six years. In between editions, annual cumulative supplements are published in order to present the most current information.

United States Code: This database is available from the Government Printing

Office (GPO). GPO is the sole agency authorized by the federal government to publish the U.S.C.

Putting the law to work

Once a law is official, here's how it is put into practice: Laws often do not include all the details needed to explain how an individual, business, state or local government, or others might follow the law. The United States Code would not tell you, for example, what the speed limit is in front of your house. In order to make the laws work on a dayto-day level, Congress authorizes certain government agencies - including EPA – to create regulations.

Regulations set specific requirements about what is legal and what isn't. For example, a regulation issued by EPA to implement the Clean Air Act might explain what levels of a pollutant - such as sulfur dioxide - adequately protect human health and the environment. It would tell industries how much sulfur dioxide they can legally emit into the air, and what the penalty will be if they emit too much. Once the regulation is in effect, EPA then works to help Americans comply with the law and to enforce it.

- Find out more about Compliance.
- Learn more about Enforcement.

Creating a regulation

When developing regulations, the first thing we do is ask if a regulation is needed at all. Every regulation is developed under slightly different circumstances, but this is the general process:

Step 1: EPA Proposes a Regulation

The Agency researches the issues and, if necessary, proposes a regulation, also known as a Notice of Proposed Rulemaking (NPRM). The proposal is listed in the Federal Register (FR) so that members of the public can consider it and send their comments to us. The proposed rule and supporting documents are also filed in EPA's official docket on Regulations.gov.

Step 2: EPA Considers Your Comments and Issues a Final Rule

Generally, once we consider the comments received when the proposed regulation was issued, we revise the regulation accordingly and issue a final rule. This final rule is also published in the FR and in EPA's official docket on Regulations.gov.

Step 3: The Regulation is Codified in the Code of Federal

Regulations

Once a regulation is completed and has been printed in the FR as a final rule, it is codified when it is added to the Code of Federal Regulations (CFR). The CFR is the official record of all regulations created by the federal government. It is divided into 50 volumes, called titles, each of which focuses on a particular area. Almost all environmental regulations appear in Title 40. The CFR is revised yearly, with one fourth of the volumes updated every three months. Title 40 is revised every July 1.

- Code of Federal Regulations database - a searchable database of the entire CFR from GPO.

How you can get involved

Go to the "Get Involved with EPA Regulations" page to learn how you can comment on our regulations and keep tabs on rulemakings.

Regulatory Issues in the Indian Pharmaceutical Industry

This section undertakes a review and assessment of regulatory issues in the Indian pharmaceutical industry. Understanding the regulatory scenario in this sector is extremely crucial not only due to the rapid and ongoing changes at the global level, largely with reference to good manufacturing practices (GMP), good clinical practices (GCP) and good laboratory practices (GLP) but also due to the onus on the regulatory bodies to ensure a healthy supply of quality drugs at affordable prices to the Indian masses.

The present section begins with a brief description of the major regulatory bodies monitoring the Indian pharmaceutical sector. It then undertakes a review of the prevailing mechanisms for drug regulation and temporal progression of some predominant policy measures and Acts. The section subsequently provides a comprehensive account of the status and key guidelines pertaining to the dimensions of drug pricing, patent related issues, GMP and clinical trials, in addition to a brief review of standards for medical devices and biotech products. It concludes with an assessment of the deficiencies of present regulatory regime and some new initiatives by the State to ensure the production and marketing of safe and efficacious drugs at affordable prices in the domestic sphere and to sustain current growth prospects in the global markets.

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;

The National Pharmaceutical Pricing Authority (NPPA), which was instituted in 1997 under the Department of Chemicals and Petrochemicals, which fixes or revises the prices of decontrolled bulk drugs and formulations at judicious intervals; periodically updates the list under price control through inclusion and exclusion of drugs in accordance with established guidelines; maintains data on production, exports and imports and market share of pharmaceutical firms; and enforces and monitors the availability of medicines in addition to imparting inputs to Parliament in issues pertaining to drug pricing.

The Department of Chemicals and Petrochemicals also oversees policy, planning, development and regulatory activities pertaining to the chemicals, petrochemicals and pharmaceutical sector. The responsibilities assumed by this body are relatively broader and varied in comparison to the other two bodies. The main aspects of pharmaceutical regulation are thus divided between the above two ministries. The Ministry of Health and Family Welfare examines pharmaceutical issues within the larger context of public health while the focus of the Ministry of Chemicals and Fertilizers is on industrial policy. However, other ministries also play a role in the regulation process. These include the Ministry of Environment and Forests, Ministry of Finance, Ministry of Commerce and Industry and the Ministry of Science and Technology. The process for drug approval entails the coordination of different

departments, in addition to the DCGI, depending on whether the application in question is for a biological drug or one based on recombinant DNA technology. Issues related to industrial policy such as the regulation of patents, drug exports and government support to the industry are governed by the Department of Industrial Policy and Promotion and Directorate General of Foreign Trade, both under the aegis of Ministry of Commerce and Industry and the Ministry of Chemicals and Fertilizers. With respect to licencing and quality control issues, market authorization is regulated by the Central Drug Controller, Ministry of Health and Family Welfare, Department of Biotechnology, Ministry of Science and Technology (DST) and Department of Environment, Ministry of Environment and Forests. State drug controllers have the authority to issue licences for the manufacture of approved drugs and monitor quality control, along with the Central Drug Standards Control Organization (CDSCO).

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 lastfew 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

In accordance with the Act of 1940, there exists a system of dual regulatory control or control at both Central and State government levels. The central regulatory authority undertakes approval of new drugs, clinical trials, standards setting, control over imported drugs and coordination of state bodies' activities. State authorities assume responsibility for issuing licenses and monitoring manufacture, distribution and sale of drugs and other related products.

The Patents Act of 1970, Drug Price Control Order 1970 and ForeignExchange 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.

The Pharmaceutical Policy 2002 carried forward earlier governmental initiatives in terms of ensuring quality drugs at reasonable prices, strengthening of indigenous capability for cost-effective production, reducing trade barriers and providing active encouragement to in-house R&D efforts of domestic firms.

In 2003, the Mashelkar Committee undertook a comprehensive examination of the problem of spurious and sub-standard drugs in the country and recommended a series of stringent measures at Central and state levels. The regulatory body came in for censure with the committee noting that there were only 17 quality-testing laboratories, of which only seven laboratories were fully functional.

The National Pharmaceuticals Policy 2006, among other initiatives, has proposed a slew of measures such as increasing the number of bulk drugs under regulation from 74 to 354, regulating trade margins and instituting a new framework for drug price negotiations in a move to make drugs more affordable for the Indian masses.

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. (Gehl Sampath 2008, Srivastava 2008).

As the report by NIPER, submitted to the Ministry of Chemicals and Fertilizers in 2007 points out, this may have led to tax disparities among firms located in tax exempt zones and tax non exempt areas. This has also led to small firms in non exempt areas requesting for tax subsidies from the government.

For drugs not under price control, firms can set the Minimum Retail Price (MRP). The NPPA only intervenes in cases where drugs have significant sales and where the annual price increases by 10%. This is a recent development, which came into effect in 2007, as in the past the NPPA would intervene only if the annual price increases were more than 20%. This development indicates the heightened sensitivity of the government towards consumer access to medicines at reasonable prices and keeping a check on profit mongering by the industry. (ibid)

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 Dr R.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.

As per the provisions of Article 39(3) of the TRIPS Agreement, member countries have to provide protection to regulatory data submitted for market approval of pharmaceutical products under specific circumstances. The government of India constituted an expert committee under the chairmanship of Mr Satwant Reddy to formulate adequate steps to deal with the issue of data protection. The Reddy Committee report, brought out in 2007, stated that in the context of pharmaceuticals, the present legal regime was inadequate to address the issues related to data protection with respect to Article 39(3) provisions. It also underscored the need for more clear and stringent mechanisms within the Drugs and Cosmetics Act to ensure that undisclosed test data was not put to unfair commercial use in India.

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 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. The Central Drugs Standards Control Organization has, however, yet to compile data on the extent of Schedule M compliance by the firms. The Najma Heptullah Committee on Subordinate Legislation, which tabled its report in Parliament recently, is scheduled to compile data on extent of Schedule M compliance shortly.

However, according to state regulatory sources, units in states like Gujarat, Karnataka, Maharashtra and Andhra Pradesh have achieved a high percentage of Schedule M compliance in comparison to units in other states.

International regulatory certification for Indian manufacturing units: A principal issue relating to good manufacturing practices is that WHO-GMP is no longer sufficient, particularly for exporting of drugs and related products to developed countries. Regulators from these countries visit Indian firms to carry out a thorough inspection of their manufacturing units before registering the concerned product. A large number of domestic players are seeking international regulatory approvals from agencies like US-FDA, MHRA UK, TGA Australia and MCC South Africa in order to export their products, mostly generics, in these markets. A large number of Indian firms are increasingly seeking at least WHO GMP approval in order to compete for exports to CIS countries and other Asian markets. India has the distinction of having the largest number of US-FDA approved manufacturing units, totaling 100, mainly for production of Active Pharmaceutical Ingredient (API), outside of the United States.

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.

Clinical trials to establish the safety and efficacy of drugs constitute nearly 70% of research and development costs and the total time taken for drug development constitutes nearly 7-10 years. Well-designed clinical trials provide the requisite data pertaining to safety and efficacy of drugs and impart meaningful results about a given therapeutic intervention in human beings. According to latest estimates made by the Tufts Centre for the Study of Drug Development, while total research costs have increased by 7.4% per year, the costs of clinical trials on human beings has risen by over 12 per cent. Considering the relatively low costs of R&D in India, several MNC pharmaceutical companies, as well as global clinical research organizations are increasingly making India a clinical research and development hub.

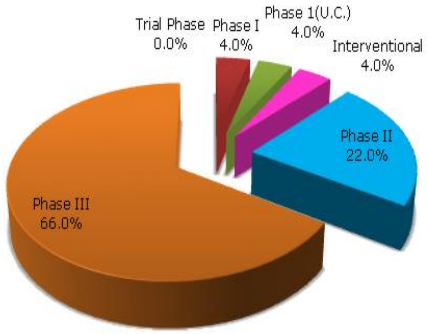

Fig 1: Phase-wise break-up of clinical trials carried out in India

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 1 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 postmarketing surveillance. The chart clearly indicates that the majority of trials carried out in India fall under the Phase III category.

India's clinical development sector has witnessed a tremendous growth in recent times. In 2005, the revenues from contract R&D for international sponsors totaled $100 million and the sector enjoys an annual growth rate of about 40 per cent. Several global CROs have entered the Indian market in the last few years. Some of these have also entered into alliances with local CROs.

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 Phase I 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).

Medical devices

In June 2007, the DCGI formulated a new set of guidelines for the import and manufacture of medical devices in the country. The guidelines were the aftermath of the JJ Hospital controversy, involving the use of unapproved and untested stents on 60 patients and the subsequent recommendations made by the Mashelkar Committee in 2004.

The immediate outcome of the JJ Hospital controversy was that the Department of Medical Education and Research (DMER) banned the use of unapproved stents and stressed on regulatory approvals from the country of manufacture or US-FDA approval for medical devices.

The Mashelkar Committee subsequently recommended the creation of a specific medical devices division within the CDSCO in order to address the management, approval, certification and quality assurance of all medical devices. This essentially consisted in alteration of the status of sterile medical devices, intended for internal or external use to medical drugs and creation of suitable provisions and amendments to the Drugs and Cosmetics Act of 1940.

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 largescale 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)

DISCUSSION:

The role of pharmaceuticals has become more prominent on international agendas as health indicators have been increasingly linked with a country's successful development. In addition, the legal and economic issues that surround pharmaceuticals have become more complex and politi- cized because of the increase in global trade.

pharmaceutical laws and regulations

The use of ineffective, poor-quality, or harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines, and sometimes death. It also under- mines confidence in health systems, health professionals, pharmaceutical manufacturers, and distributors. To protect public health, governments need to approve comprehensive laws and regulations and to establish effective national regu- latory authorities to ensure that the manufacture, trade, and use of medicines are regulated appropriately and that the public has access to accurate information on medicines

Differences between pharmaceutical laws, regulations, and guidelines

Laws today are usually written in fairly general terms to meet present and possibly future needs. Laws usually have language that enables the government to issueregulationsbased on the law. Passing new laws may require alengthyprocess, with the country's legislative branch givingfinalapproval.Regulationscanbepassedmorerapi

dlyandsim-ply than laws, sometimes requiring, for example, onlytheapproval of a single government minister on the adviceofexperts.Theycanalsobealteredmoreeasily.Afterapproval,aregulationhasthesamepowerasthelawitself.Guidelines,whichdonotcarrytheforceoflaw,canbemoreeasilymodi-fied and updated and offer informal information onwhatthe government's thinking is regarding the best waytoimplementregulations.Followingguidelineswill helpavoidmisinterpretationofandfacilitatecompliance withlawsandregulations.

Pharmaceuticals involve many parties, including patients, doctors, other health workers, salespeople, and manufactur-ers. The field also involves important risks: people can suf-fer or die not only from a lack of medicines, but also from drugs that are impure, wrongly prescribed, or used incor-rectly. Thus, it is easy to see why laws and regulationsareneeded. However, some argue that medicines—likemanyother commodities—should be subject only to thecontrolof the ultimate user.

Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations

Introduction

FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

The approval process for new drug and generic drug marketing applications includes a review of the manufacturer's compliance with the CGMP. FDA inspectors determine whether the firm has the necessary facilities, equipment, and skills to manufacture the new drug for which it has applied for approval. Decisions regarding compliance with CGMP regulations are based upon inspection of the facilities, sample analyses, and compliance history of the firm. This information is summarized in reports which represent several years of history of the firms.

FDA can issue a warning letter or initiate other regulatory actions against a company that fails to comply with Current Good Manufacturing Practice regulations. Failure to comply can also lead to a decision by FDA not to approve an application to market a drug.

This web page provides links to resources to help drug manufacturers comply with the Current Good Manufacturing Practice regulations.

Federal Regulations

Code of Federal Regulations (CFR). The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets theFederal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains most regulations pertaining to food and drugs. The regulations document the actions of drug sponsors that are required under Federal law.

- 21 Code of Federal Regulations Part 210. Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- 21 Code of Federal Regulations Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals.
- Federal Register Notices for Proposed Changes and Final Changes to CGMP. The Office of Compliance, Division of Manufacturing and Product Quality web page provides links to in-process changes in CGMP regulations announced in the Federal Register.

Guidance Documents

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and drug sponsors to provide guidelines for the processing, content, and evaluation of applications, and for the design, production, manufacturing, and testing of regulated products. They also provide consistency in the Agency's regulation, inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both.

- Guideline on the Preparation of Investigational New Drug Products (Human and Animal) (PDF - 795KB) (Issued 11/1992, Posted 3/2/1998). This guidance provides practices and procedures for preparing investigational new drug products that comply with certain section of the Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals (Title 21 of the *Code of Federal Regulations*, Parts 210 and211.)
- Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (PDF - 98KB). 10/2006 This guidance provides the

Agency's current thinking on how to evaluate suspect, or out of specification (OOS) test results. For purposes of this document, the term *OOS results* includes ***all***suspect results that fall outside the specifications or acceptance criteria established in new drug applications.

CDER Manual of Policies and Procedures (MaPPs)

MaPPs are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures.

- 4723.1 Standing Operating Procedures for NDA/ANDA Field Alert Reports (PDF - 15KB). (Issued 10/30/1998, posted 11/02/1998). This MaPP establishes a system for evaluating new drug application (NDA) and abbreviated new drug application (ANDA) Field Alert Reports and provides instructions to the responsible CDER units for handling those reports.

Compliance Policy Programs and Guidelines

- Compliance References. This web site from the Office of Regulatory Affairs provides links to compliance policy guides, regulatory procedures manuals, and other compliance related information. Chapter 4 of the Compliance Policy Guide covers human drugs.
- Compliance Program Guidance Manual. These programs and instructions are for FDA field inspectors.
- Consistent Application of Current Good Manufacturing Practice Determinations. FDA cannot approve applications to market new drugs from companies who have been cited for Current Good Manufacturing Practice violations. Similarly, disapproval of any drug marketing application based upon CGMP deficiencies must also lead to regulatory and/or administrative action against other products produced under the same conditions.

CONCLUSION:

Any medicinal agent to be marketed in the United Kingdom has to follow the guidelines and regulations framed by MHRA, a regulatory authority which approves the drug products. The objective of this review article is to highlight information regarding the requirements, the different types of submissions for the registration of a medicinal product in a market in the UK. It also includes all the details about the fee for the application and the time period for the approval of the application after the submission of the application. By knowing the requirements of the MHRA guidelines and regulations, it is easy for a product to get into the UK market.

Evaluating the effectiveness of pharmaceutical legislation and accompanying regulations is not always easy.The process of evaluation depends on the types of performance indicators and criteria used and on the availadility of adequate data.

The important factor in the effectiveness of pharmaceutical laws and regulations is the extent to which the legislative framework is in tune with national policy and the existing situation .Changes in policy needed to be reflected in the legislation and in its implementation.

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