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REGULATORY ISSUES FOR IMPORT OF PHARMACEUTICAL PRODUCTS INTO INDIA

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Abstract:

The value of the global pharmaceutical market is expected to grow at 5 percent CAGR, to be USD 1 trillion in 2014 according to Urch publishing. The pharmaceutical industry is one of the highly regulated industries, to protect the health and well-being of the public. In the present scenario, India have stringent regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application (MAA) of a new drug product belonging to various categories of drugs (NCE, Biologicals, Controlled Drugs etc.) is utmost difficult. Therefore, the knowledge of precise and detailed regulatory requirements for MAA of different categories of drugs should be known to establish a suitable regulatory strategy. This article focuses on the drug approval process from regulatory authorities for different categories of pharma products. Finally, there needs to be a reaffirmation and fine balance between the tenacities of gaining market access of pharmaceuticals is to protect the public health and facilitate healthy growth of pharmaceutical manufacturers. Pharmaceutical product approval process should be seen as a critical step in ensuring access to safe and effective drugs.

Keywords: *CDSCO, Clinical trials, DCGI, Marketing Authorization Application, Regulatory process.*

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INTRODUCTION:

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, FDA Bhawan, Kotla Road, Near Bal Bhawan, 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.

The proposed Guidance for applicants for submission of documents for Import of bulk drug(s) and finished formulation(s) are being uploaded for information of all the stakeholders likely to be affected thereby for comments, if any.

All stakeholders are requested to send their comments and or suggestions on this document in writing for consideration of the CDSCO within a period of 20 days from the date of its uploading through post to the Drugs Control General (India), CDSCO, FDA Bhavan, Kotla Road, New Delhi – 110002 and through email at dci@nb.nic.in

The document is intended to provide non-binding guidance for use in the Import & Registration of bulk drug(s) and finished formulation(s) in India.

I.PURPOSE:

To provide guidance for submission of application in Form 40 to CDSCO for Registration Certificate and issuing License for import of drugs into Indiawith CDCSO authority India, for issuance of import registration certificate for import of drugs into India.

II.SCOPE:

This guidance is applicable to those drugs manufactured outside India, and the import registration to be issued(under Form 41) by the Central Drugs Standard Control Organization,(CDSCO) Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

III. REFERENCE:

1. Drugs & Cosmetics Act, 1940 and Rules there under.
2. Schedule D(I) (for registration of the manufacturing Premises)
3. Schedule D(II) (for registration of the drugs).

IV.RESPONSIBILITY:

CDSCO: For implementing and to revise the same as notified, from time to time by the authority.

V. Guidance:

1. An application shall be made to the Licencing Authority in Form 40, either bythemanufacturer himself, having a valid wholesale License, for sale or distribution of drugs or by his authorized agent in India either having a valid License to manufacture for sale of a drug or having a valid wholesale License for sale or distribution of drugs.

2. DETAILS TO BE CAPTURED IN FORM 40:

The authorized signatory name, designation, department, along with the complete address of the Company.

AIM AND OBJECTIVES:

The aim is to directed to all parties involved in the importation of pharmaceutical products , including national drug regulatory authorities , comprtent trade ministries , customs authorities , port authorities and importing agent and are intended to promote efficiency in applying relevant regulations , to simplify the checking and handling of consignments of pharmaceutical products in international transit and , inter alia , to provide a basis for collaboration between the various interested parties .

DISCUSSION

i) Authorized Signatory:

The person authorized preferably Director approved by the Board of Directors in case of company or by the proprietor in case of proprietorship firm. The application to accompany affidavit in respect of authorized person or the Power of Attorney in the name of the authorized person.

The Form shall detail the Foreign Manufacturer's contact person in the manufacturing site complete address, (i.e. address of the manufacturing premises), with corporate office address, along with the Telephone number, Fax number and E-mail address.

The Form shall detail the Foreign Manufacturer's contact person in the manufacturing site complete address, (i.e. address of the manufacturing premises), with corporate office address, along with the Telephone number, Fax number and E-mail address.

ii) The address of manufacturing premises shall be captured as below:
Undertaking on the document contents by the responsible person at the manufacturing site (contact person in the manufacturing site)
- In respect of import of more than one drug or class of drugs manufactured by the same manufacturer, provided that drug or the classes of drugs, are manufactured at one factory or more than one factory functioning conjointly as a single manufacturing unit.
- In respect of the drugs manufactured in two or more factories situated in different places, for the manufacturing of the same or different drugs the name and address of both the manufacturing
site should be included e.g. if the tablets are manufactured at one location and packed at another location, Name and Address of both the locations indicating the activity of each location

- The Form shall contain the complete and correct Name of the Drugs to be imported in India.

iii) The drug(s) name shall be captured as below:
- The brand name shall be captured.
- Different pack, pack size and/or different strengths of the same brand shall be captured.
Importer‘s undertaking letter declaring for the information specified in Schedule D (I) and Schedule D (II), provided by the original manufacturer.

The registration Fees amount (Challan number and date) shall be mentioned on Original TR 6 challan having complete name and address of the applicant and details of application to be enclosed.

iv) Fee structure for Import Registration under Form 40
- Fees and Form(s) and the undertakings as per Schedule D(I) (for registration of the manufacturing premises) and Schedule D(II) (for registration of the drugs):
- Applicant shall make a payment of 1500 USD (or its equivalent to Indian Currency), as registration fee for the Manufacturing premises.

- Applicant shall make an payment of 1000 USD (or its equivalent to Indian Currency), as registration fee for a single drug and additional fee of 1000 USD for each additional drug in case the manufacturing site remains the same. Fees shall be paid through a Challan in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110 001 or any other Bank, as notified, from time to time by the authority.

III.Guidelines on import procedures for pharmaceutical products
Public health considerations demand that pharmaceutical products should not be treated in the same way as ordinary commodities. Their manufacture and subsequent handling within the distribution chain, both nationally and internationally, must conform to prescribed standards and be rigorously controlled. These precautions serve to assure the quality of authentic products, and to prevent the infiltration of illicit products into the supply system.

Within the context of its revised drug strategy. adopted in 1986 by the Thirty-ninth World Health Assembly in resolution WHA39.27, WHO developed “Guiding principles for small national drug regulatory authorities” (1, 2) which established a regulatory approach in line with the resources available within a small national regulatory authority, and were intended to assure not only the quality. but also the safety and efficacy, of pharmaceutical products distributed under its aegis.

The principles emphasize the need for the effective use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. This constitutes a formal agreement between participating Member States to provide information on any product under consideration for export, notably on its registration status in the country of origin and whether or not the manufacturer complies with WHO’s guidelines on good manufacturing practices (GMP) for pharmaceutical products (3).

To be fully effective, the Scheme needs to be complemented by administrative and other safeguards aimed at ensuring that consignments of imported products are in conformity in all particulars with the relevant import licence and that they remain secure within the distribution chain. Storage and transit tacilities must be proof against tampering and adverse climatic conditions, and relevant controls must be applied at every stage of transportation.

Pharmaceutical products containing substances controlled under the international conventions ha e long been subjected to rigorous border controls. Some of these controls, and particularly those designed to prevent the diversion and illicit interchange of products during transit, are relevant to all pharmaceutical products. and are therefore included in these guidelines. Full details of the special import controls required for narcotic drup•s and psychotropic substances are p•iven in the Appendix.

Objectives and scope
The following guidelines, which stem from the above considerations, have been developed in consultation with national drug regulatory authorities, the pharmaceutical industry, the World Customs Organi- zation, and the United Nations International Drug Control Programme.

The guidelines are directed to all parties involved in the importation of pharmaceutical products, including national drug regulatory authorities, competent trade ministries, customs authorities, port authorities, and importing agents.

They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of consignments of pharmaceutical products in international transit and, inter alia, to provide a basis for collaboration between the various interested parties.

They are applicable to any pharmaceutical product destined for use within the country of import, and are intended to be adapted to prevailing national conditions and legal requirements.

Legal responsibilities

The importation of pharmaceutical products should be effected in conformity with regulations promulgated under the national drugs act or other relevant legislation and enforced by the national drug regulatory authority. National guidelines providing recommendations on the implementation of these regulations should be drawn up by the national drug regulatory authority in collaboration with the customs authority and other interested agencies and organizations.

All transactions relating to the importation of consignments of pharmaceutical products should be conducted either through the governmental drug procurement agency or through independent wholesale dealers specifically designated and licensed by the national drug regulatory authority for this purpose

The importation of all consignments of pharmaceutical products should be channelled exclusively through customs posts specifically designated for this purpose.

All formalities undertalcen on importation should be coordinated by the customs service, which should have the authority to request the services of an official pharmaceutical inspector as occasion demands. When justified by the workload, a pharmaceutical inspector may be stationed full time at one or more of the designated ports of entry.

The customs authority should have the discretionary powers to request technical advice and opinions from other appropriately qualified persons, should this be warranted by particular circumstances.

IV.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).

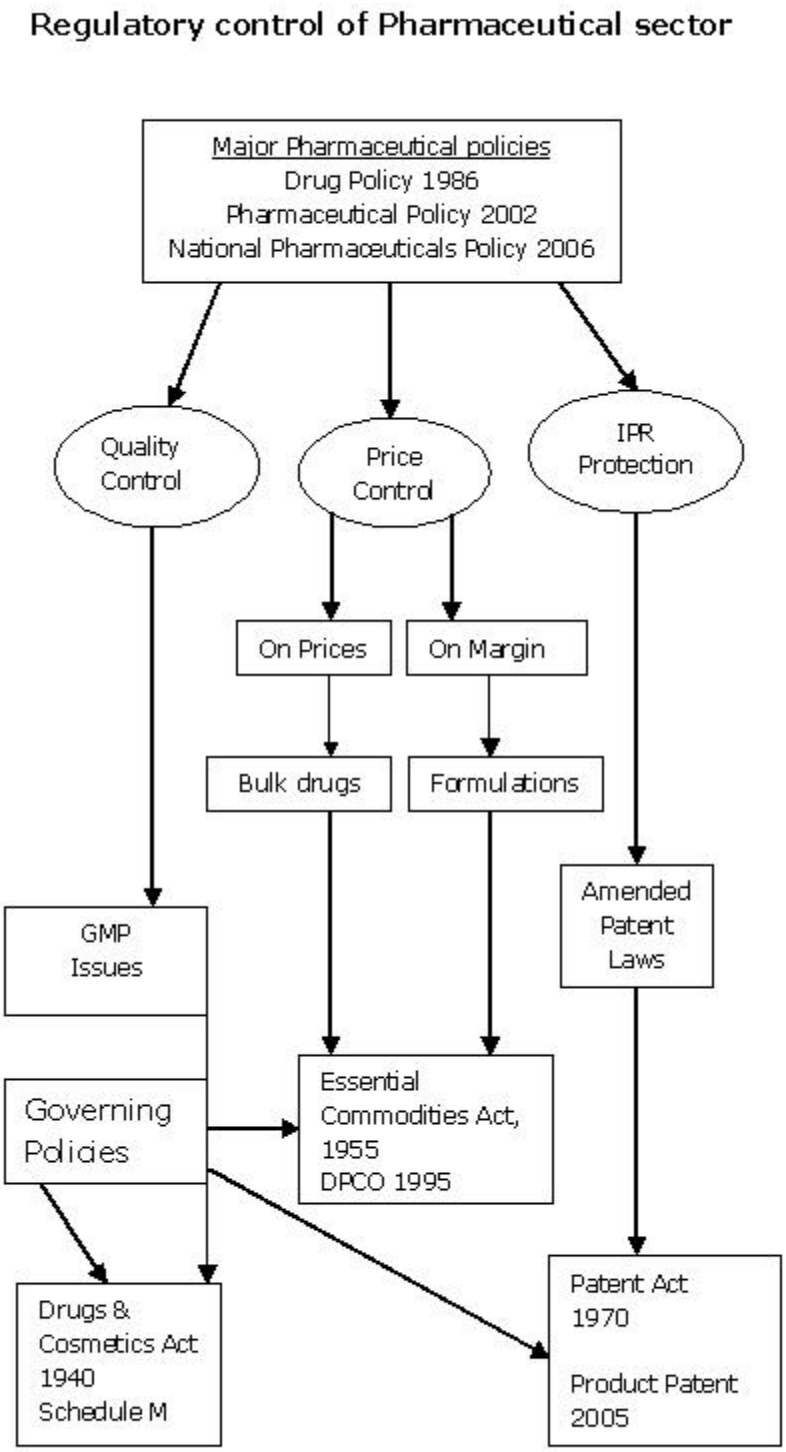
Prevailing Mechanisms

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 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

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.



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. 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 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. 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.

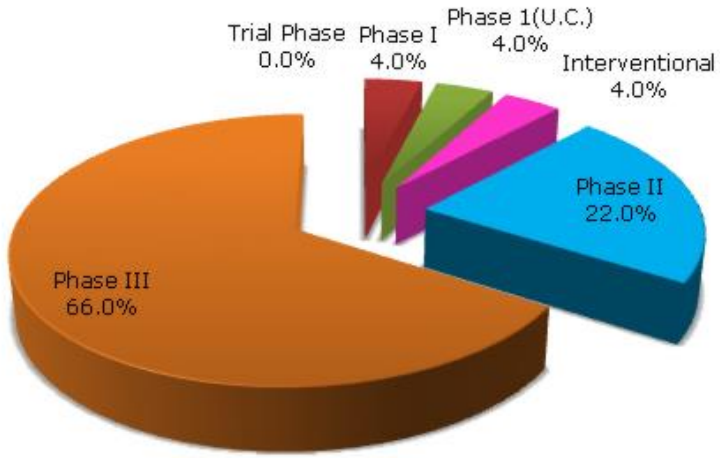


Fig 1: Phase-wise break-up of clinical trials carried out in India

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 post-marketing 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.

CLINICAL TRIAL COST DIFFERENCES IN INDIA & U.S.

	United States	*India*
Phase 1	$ 20 mn.	< $10mn.
Phase 2	$ 50 mn.	< $30mn.
Phase 3	$ 100mn.	< $60mn.

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 Product
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)

CONCLUSION:
The Indian Pharmaceutical Industry has shown great potential and continues to grow consistently. The Indian generic drug sector is robust and is establishing its presence in foreign markets too. The new- drug sector is also expected to record a healthy growth owing to significant industrywise increase in R&D expenditure and proposed new drug launches. However, since health is an important subject, the industry continues to be heavily regulated. Multiple Ministries continue to regulate the pharmaceutical industry such as the Health Ministry, Chemicals and Fertilizers Ministry, Science and Technology Ministry, Food Ministry etc. Numerous legislations, regulations and judgments affecting the industry have come into existence recently and numerous others have been proposed. The Industry will have to realign itself with these legal changes in order to ensure continuance of its success story.

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