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Regulatory Requirements for Registration of Pharmaceutical to Gain Market Access in 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.

INTRODUCTION

The value of the global pharmaceutical market is expected to grow at 5 percent CAGR, to be USD 1trillion 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. The structures of drug regulation that exist today i.e. drug laws, drug regulatory agencies, drug evaluation boards, quality control laboratories, drug information centers, etc., have evolved over time in response both to the increasingly sophisticated pharmaceutical sector, and to the apparent needs of society^[1].

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^[2].

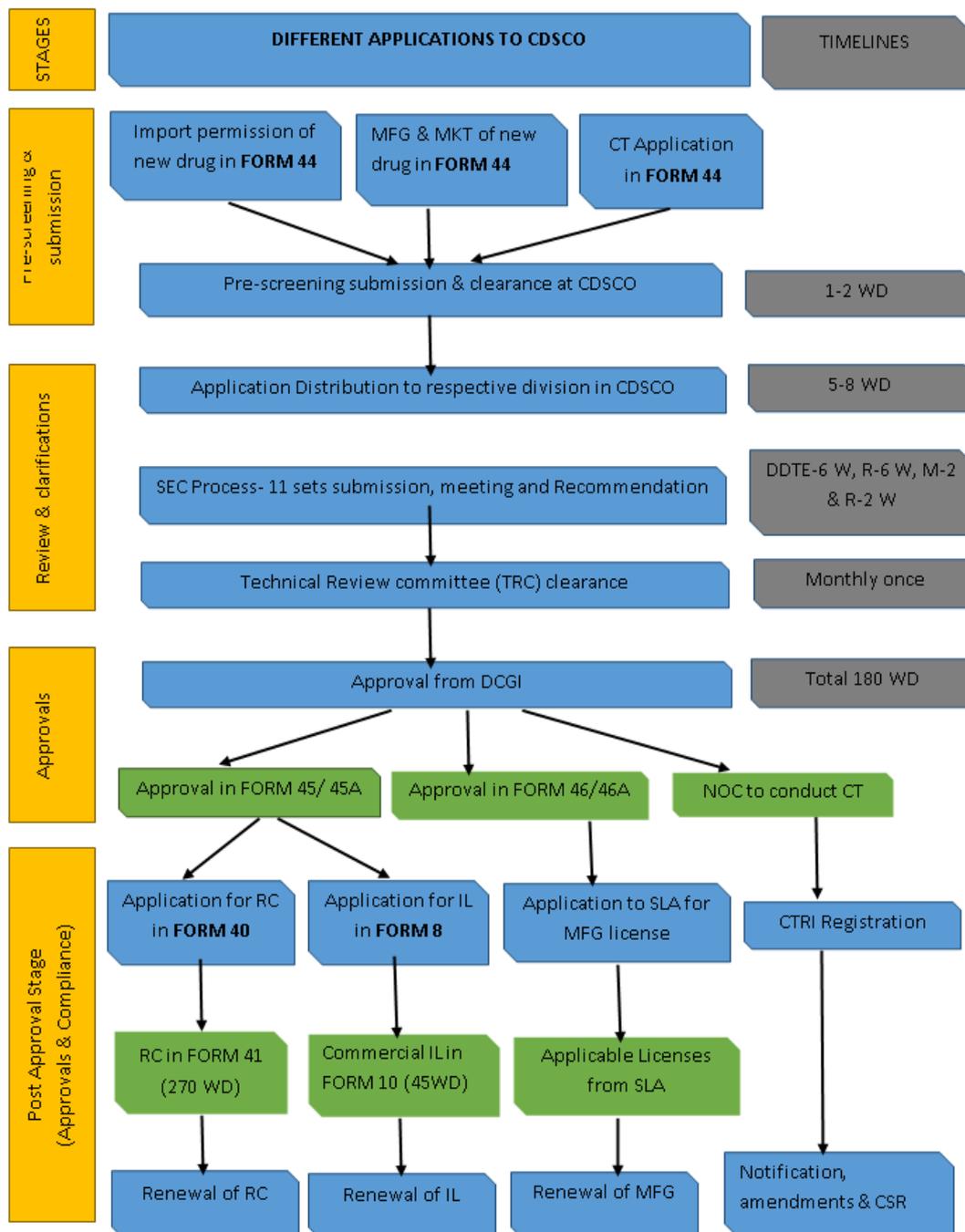
The new drug approval process have been made into three phases for simplification in understanding - the first phase is pre-marketing meant for discovery, development and clinical studies, second phase for marketing authorization of drug and third is for post marketing. Firstly, preclinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the CDSCO. 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 India 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 risk^[3].

Even after the approval of new drug, marketing authorization holder should monitor and report to CDSCO its safety, quality changes from time to time as part of quality and regulatory compliance^[4].

A pictorial representation of different applications process along with stages at regulatory body provided in Figure 1.

Figure 1: Regulatory Pathway For New Drugs Applications.



In India, an applicant is required to file application in Form 44 along with prescribed fees in the form of treasury challan and all relevant data as per Schedule Y of Drugs and Cosmetics Rules, for seeking permission to import or manufacture of new drug substances and its formulations for marketing in the country or conduct of clinical trials in India. The documents include chemical and pharmaceutical information, animal pharmacological and toxicological data, clinical data of safety and efficacy, regulatory status in other countries etc., and results of clinical trials on local population.

The regulatory process of different applications

The list of various application to CDSCO/ state licensing authorities (SLA) for drug import, site registration, manufacture and marketing authorization has been tabulated in below Table 1

Table 1: The list of various application to CDSCO/ state licensing authorities (SLA) for drug import, site registration, manufacture and marketing authorization

Application types	Application Form No.	License Form No.	Regulatory body	Validity	Timelines in Days
Import of drugs for the purpose of examination, test or analysis	Form 12	Form 11	CDSCO	1 Year	45
NOC for manufacture for the purpose of examination, test or analysis (Form 29)	-	NOC	CDSCO	-	60 [#]
Manufacture for the purpose of examination, test or analysis	Form 30	Form 29	SLA	1 Year	
Import of a new drug (DP)/ (DS)	Form 44	Form 45/ Form 45 A	CDSCO	-	180
Manufacture of New Drug (DP)/ (DS)	Form 44	Form 46/ Form 46 A	CDSCO	-	180
Permission to undertake clinical trial	Form 44	NOC	CDSCO		180
Registration certificate for import of Drugs into India	Form 40	Form 41	CDSCO	3 Years	270
Import license for drugs for commercial use	Form 8	Form 10	CDSCO	3 Years	45
Manufacture for sale or distribution (Mfr.)	Form 24	Form 25 (Fresh) Form 26 (Renewal)	SLA	5 Years	30
Mfr. of Drugs specified in schedule C & C(1) and not in schedule X	Form 27	Form 28 (Fresh) Form 26 (Renewal)		5 Years	30
Mfr. of LVP/Sera and Vaccines excluding those specified in Schedule X	Form 27 D	Form 28 D		5 Years	60
Mfr. of Loan licenses except schedule C & C(1) and X	Form 24 A	Form 25A (Fresh) Form 26A (Renewal)	Concerned SLA	5 Years	30*
Sale licence to sell, stock or exhibit or offer for sale or distribution of drugs (Drugs other than and X)	Form 19	Form 20 (Retail) Form 20 B (Wholesale)			30*
Sale license rugs specified in schedule X and not in schedule C & C(1)	Form 19 C	Form 20F (Retail) Form 20 G (Wholesale)			30*
[#] If inspection of premises involved, the time lines will be consider from the date of receipt of the inspection report [*] Timelines vary state to state licensing authority					

Import of drugs for examination, test or analysis in Form 11

Test licence or Form 11 licence is obtained for the import of small quantities of drugs, which is otherwise prohibited under section 10 of the Drugs and Cosmetics Act and Rules, 1945, for the purpose of examination, test or analysis

The application to be submitted in Form 12, requisite fee Rs. 100/- for single drug Rs. 50 for each additional drugs along with the supporting documents to CDSCO for approval in Form 11 having validity of 1 year.

The following conditions to be considered by the applicant as laid down in the D&C act and Rules:

- (a) No drug shall be imported for such purpose except under a licence in Form 11
- (b) The licensee shall use the substances imported under the licence exclusively for purposes of examination, test or analysis and shall carry on such examination, test or analysis in the place specified in the licence, or in such other places as the licensing authority may from time to time authorise;
- (c) The licensee shall allow Drug Inspector authorized by the licensing authority in this behalf to enter, with or without prior notice, the premises where the substances are kept, and to inspect the premises, and investigate the manner in which the substances are being used and to take samples thereof;
- (d) The licensee shall keep a record of, and shall report to the licensing authority, the substances imported under the licence, together with the quantities imported, the date of importation and the name of the manufacturer;
- (e) The licensee shall comply with such further requirements, if any, applicable to the holders of licences for examination, test or analysis as may be specified in any rules subsequently made under Chapter III of the Act and of which the licensing authority has given to him not less than one month's notice^[5].

Manufacture of drugs for examination, test or analysis in Form 29:

For development of any new drug the applicant is required to obtain license in Form-29 from State Licensing Authority based on NOC obtained from CDSCO. No objection certificate (NOC) to be sought from the CDSCO zonal office by submitting the application in prescribed format which comprise of product general information, manufacturing facility details, technical staff. Application in Form 30 along with prescribed fee Rs. 250/- for single product to be submitted to SLA for grant of form 29, upon receipt of NOC from zonal^[6,7].

Approval Mechanism and Recent Updates for Clinical Trials in India

For Clinical trials application, the data should be submitted in form 44 along with requisite fee and supportive details such as chemical and pharmaceutical data; generic & chemical name; dosage form; composition; animal pharmacology & toxicity data; animal toxicology and clinical data; as well as phase I, II, III & IV data to the DCGI. The protocol of the clinical trial with a consent form is also submitted. The authority also needs to know about the regulatory status of the drug in other countries, including names of countries where the drug is approved, and international package insert or the place where Investigational New Drug (IND) application is filed. Applicants have to report any Suspected or Unexpected Serious Adverse Reaction (SUSAR) from other participating countries, if any. Further, it is necessary to submit an affidavit from the sponsor stating that the study has not been discontinued in any country. In case of discontinuation, reasons for the same must be communicated to the DCGI. Furthermore, a letter of undertaking for compensation as per appendix XII of schedule Y and marketing authorization application submission to CDSCO once approved in country of origin ^[8].

For comprehensive details applicant can refer Schedule Y of the Drugs and Cosmetics Act 1940, and the rules therein, pre-screening checklist displayed on CDSCO website (www.cdsc.in).

Post submission the application shall be reviewed by CDSCO and experts, before issuance of approval, the detail steps have been mentioned in Figure 1.

Clinical trials can be initiated only upon receipt of approval from CDSCO and concerned ethics committee.

All the trials have to be registered prior to the initiation of clinical trials in Indian Council of Medical Research (ICMR) clinical trial registry which is mandatory since June 2009 onwards.

Recent amendments pertaining to clinical trials in India: The CDSCO has issued number of guidelines, circulars to strengthen clinical trial regulations in India from time to time.

Following are the compilation of these guideline to have overall understanding on the same. The recent amendments in schedule Y are

- ✚ Introduction of Rule 122DAB → Specifying the procedures for payment of compensation to the subjects of the trial in cases of injury or death
- ✚ Introduction of Rule 122DAC - Specifying various conditions for conduct and inspection of clinical trials
- ✚ Introduction of Rule 122DD - Specifying the detailed guidelines for registration of Ethics Committee. System for the pre-screening of the applications for registration of ethics committees. IEC in respect of periodic review of ongoing clinical trials
- ✚ Drugs and Cosmetics (Amendment) Bill 2013 - Yet to be introduced
- ✚ **Audio-Visual Recording of Consent:** Gazette Notification for Audio-Visual recording of informed consent. Audio-Video recording of informed consent has become mandatory
- ✚ **Prof. Ranjit Roy Chaudhary Report:** Recently Prof. Ranjit Roy Chaudhary committee has submitted reports which discuss about practices for conducive environment for growth of clinical trial industry also meeting the regulatory standards. Actions on the recommendations of Prof. Ranjit Roy Chaudhury expert committee to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs. On 03 Jul 2014, DCGI has issued circulars pertaining to the acceptance of Prof. Ranjit Roy Chaudhury Expert Committee's.
- ✚ **SAE Reporting and Compensation:** The process of SAEs reporting in case of injury/death has been revised in recent Schedule Y amendments and below is required information to be submitted along with the SAEs report. System of Pre-screening for submission of reports of SAEs to CDSCO. Panel of expert for reviewing of SAE of death. Formula to determine the quantum of compensation in the cases of clinical trial related serious adverse events (SAEs) of deaths occurring during clinical trials^[9].

New Drug Approval Process

Schedule Y deals with regulations pertaining to clinical trial requirements for import, manufacture and obtaining marketing approval for a new drug in India.

Rule 122 A -Application for permission to import new drug.

Rule 122 B -Application for permission to manufacture new drug.

Rule 122 D -Application for permission to import /manufacture FDC

Rule 122 DA –Application for permission to conduct clinical trials

Rule 122 E –Definition of New Drugs

- New Substance having therapeutic indication
- Modified or new claims, indications, dosage, dosage form and new route of administration for already approved drug.
- Fixed Dose Combination, individually approved earlier now for modified claim
- Vaccines are new drugs unless otherwise certified
- Considered new drug for 4 years from date of first approval^[10]

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing and marketing in the country. For new drug application, the dossier is to be applied in Form 44, treasury challan of Rs. 50,000/- and information should be submitted as per Schedule Y format, D & C act and subsequent amendment of D & C rules basic dosage and indication data, active and inactive data, patents information (if any exist), regulatory status in other countries, and marketing information. Post review by CDSCO officials and SEC, TRC opinion, DCGI will issue approval as follows, if the approval sought for import permission than in Form 45A for API, Form 45 for Drug product for import permission, after approval import and registration process to be initiated. If approval sought for permission to manufacture than DCGI will issue Form 46A for API, Form 46 for drug product for permission to manufacture of new drugs, accordingly applicant needs to seek manufacturing license from SLA^[11].

Registration of Site and Pharmaceutical Products and import licence

The drugs which are being imported must have to register with CDSCO before importation into India. Foreign manufacturers must apply for registration certification for their manufacturing premises and for the individual drugs to be imported.

Applications can be submitted by authorised agents of foreign firms in India. According to recent new legislation, import licences will be required for all types of drugs, rather than the existing import licence requirements for Schedule C and C (1) and Schedule X drugs only.

Import licence applications should be applied in Form 40, along with information and undertakings specified in Schedule D(I) and Schedule D(II) should duly signed by the manufacturer. Schedule D(I) and D(II) should comprise actual plant and drug data, such as the plant master file; the manufacturing licence in country of origin; a GMP certificate; a Certificate of Pharmaceutical Products (CPP) issued by the regulatory authority of the country of origin; drug substance information; finished formulation information; clinical documentation, and packaging and labelling information. Import registration is valid for three years for a drug. Based on this, applicant can apply commercial import licence in Form 8 or Form 8A, which is needed for import of intended products into Indian Territory^[12].

CONCLUSIONS

Based on the regulatory environment, it is difficult to adopt single marketing approval strategy for different categories of drugs. Hence, it is necessary to understand and define the clear regulatory strategy by looking at the complexity of target products, various application possibilities, data requirements, deadlines for launching products to be marketed in India. This facilitates the optimization of projects through minimization in timelines for drug approvals and subsequent launch, and reduces overall cost of research and development.

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.

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