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REVIEW ON DRUG REGULATORY AFFAIRS AND NEW DRUG APPROVAL PROCESS IN INDIA

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1. INTRODUCTION

Regulatory affairs (RA) is a career opportunity for regulating industries including such as pharmaceutical , medicinal device ,veterinary medicine , cosmetics and other so on .Regulatory affairs is a bridge between pharmaceutical companies and government authorities for controlling efficacy and safety of medicinal products and also include its registration process so also known as 'government affairs' . Regulatory affairs is a profession in the drug development world where one false move can bring years of research data to an unwelcome end. Therefore, an RA Professionals needs to understand all the information and to be hands on both the hardware and the software of the function. Most of companies ,they are major multinationals pharmaceutical corporations or small ,Biotechnology companies have specialist departments of regulatory affairs (RA) professionals **(1)**.

For any new pharmaceutical product coming into the market ,it will required about 10-15 years ,spending much time and many money ,but take an current example of COVID-19 Disease (Corona virus disease) is an infectious disease caused by a newly discovered corona virus (SARS-COV - 2),which has spread rapidly throughout the world. In march 2020,the World Health Organization (WHO) was declared the Covid -19 outbreak a pandemic. The Pandemic has destroyed health system, economic and social progress globally. For in that Emergency condition ,developing of a corona virus vaccine , WHO , ICH guidance , Regulatory authorities and the Government of respective countries have taken strong action under the regulation to make vaccine. developed corona virus vaccine and its authorization is country by country . e.g. covidshield , covaxin (CDSCO, India) , covid moderna-19 (USFDA) is an incredible and amazing surprise in the pharmaceutical business market with vaccine created in small time over a year . The Regulatory affairs system has a huge influence on the world. In Product management, clinical trials , and research and development , drug regulatory affairs is a research field. The global market is separated into two categories: Regulated and Semi-controlled markets **(2)**.

Drugs and medical devices are among the most stringently regulated products in the developed world. The fundamental purpose of regulation is the protection of public health. Regulatory authorities across the world have been working their way to develop regulations which can ensure that only safe and effective products, of high quality and purity, reach into the markets for commercial distribution. Most of the landmark advances in the regulatory development were triggered by adverse events. A keen look into the history of different regulatory authorities will clarify the fact that the current regulations are actually based on the distilled wisdom of bitter past experiences **(3)**.

2. HISTORICAL ASPECT

During 1950s, multiple tragedies i.e. sulfanilamide elixir , vaccine tragedy and thalidomide tragedy have resulted in substantial increase of legislations for drug products quality , safety and efficacy. This leads to tightening of norms for Marketing Authorization (MA) and Good Manufacturing Practice (GMPs).

The drug industry in India was at very primitive stage till 20th century. Most of the drugs were imported from foreign countries.

a) 1900-1960:

Government passed the Poisons Act , 1919 to check and hold the control on cheap drugs available in market. This Act helps in the administered possession of substance or sale of substances as specified as poison. It also stated the sale and protected custody of the poisons, packaging and labeling of poisons , maximum quantity to be sold and inspection as well as examination of the poison sold by vendor during the year.

The Poisons Act was followed by The Dangerous Drugs Act, 1930 which includes the regulation of cultivation, manufacturing possession and trade of opium. In 1985, Dangerous Drugs Act 1930 and Opium Act 1878 was revoked by passing of the Narcotics and Psychotropic Substances Act.

Following acts and rules were passed during this era :

- **Drugs and Cosmetics Act, 1940:** This act regulates the manufacturing distribution , import and sale of allopathic, homeopathic, unani and siddha drugs .

- **Drugs and Cosmetics Rules, 1945:** This act regulates manufacture of Ayurvedic drugs for sale only, and not for consumption and use or possession.

- **Pharmacy Act, 1948:** This law was amended in 1985 and it generally controls and regulates the profession of pharmacy in India.

- **Drugs and Magic Remedies** (**Objectionable Advertisements**) **Rule. 1955:** The regulates the advertisement of drugs in India.

- **Drugs Prices Control Order, 1955 (DPCO) (under the essential commodities Act) :** DPCO was further amended in 1995. As per this rule , government has a jurisdiction to review and fix maximum sale price for bulk drugs as well as formulation

b) 1960-1970:

The Indian Pharmaceutical industry was not mature enough and major market share was dominated by MNC and very few Indian manufacturers were in competition. Focus on pure research and development was very little because of deficiency of patent protection. The low availability and high drug price is because majority shares depend upon the high drug import

c) 1970-1980 : Government took control for the medicines regulation and issued few ach and rules

- **Indian Patent Act 1970** (which came in force on 20 Aprs 1972 and replaced Indian Patents and Designs Act of 1911) **:** It serves as the basis for patent protection in India . Under this Act product patent was not allowed but the process and method of manufacturing of Drug substance was allowed to get the parent

- **Drug price capped**: - Drug Prices Control Order (DPCC) was introduced to con the high price against consumers .

d) 1980-1990:

The Indian industry has started investing in process development of APL and created production infrastructure for the same .

e) 1990-2000 :

A rapid expansion in domestic market has observed in pharmaceutical industry. The companies have started entering into Research and Development

f) 2000-2010:- This period is considered to be the Innovation and Research era . During these years, innovative research activity , patenting of the drugs formula, process , indication as well as merger of companies was started .

Patent Amendment Act 2005:- Indian Government brought out the patents (Amendment) Ordinance, 2004 to address the issues relating to the patent in the country which was later replaced by the Indian Patent (Amendment) Act , 2005 . The new Act brought some crucial changes on the legal regime of patent protection so as to address patent issue in technology , chemical and pharmaceutical sector .

Compulsory Licenses: - Such licenses can be granted for manufacture and export of the drug products "to any country having insufficient or no manufacturing capacity, for the said product , to address public health problems ."

Few names are given below.

- **Drugs and Cosmetics (First Amendment) Rules, 2011 :-** It mandates registration of Clinical Research Organization (CRO) for conducting Clinical Trials (CT).
- **Clinical Trial Registry - India (CTRI) :-** It has been set up by the ICMR'S (Indian Council of Medical Research) National Institute of Medical Statistics (NIMS)
- **Pharmacovigilance Program of India (PvPI) :-** The Central Drug Standard Control Organization (CDSCO) has launched pharmacovigilance to assure drugs safety to Indian patients **(9)**.

3. NATIONAL REGULATORY AUTHORITY

India: Central Drug Standard Control Organization (CDSCO).

Drug Controller General Of India (DCGI)

US: - Food and Drug Administration (USFDA)

Europe: - European Directorate for Quality of Medicine (EDQM)

European medicine evolution agency (EMEA) **(2)**

The various committees formed to facilitate the regulatory process and decision making of DCGI, a statutory board and a committee have been framed called Drugs Technical Advisory Board (DTAB) and Drug Consultative Committee (DCC) separately for Modern Scientific System of Medicine and Indian traditional system of Medicine and a provision of Central Drug Laboratory at Central Research Institute, Kasauli (HP) for testing of drugs. DTAB comprises of technical experts who advises central and state governments on technical matters of Drug regulation. Amendment, if any, to Drug and Cosmetic are made after consulting this board. Drug Consultative Committee, which has central and state Drug Control officials as its members, ensures drug control measures in all over India. It is an advisory body for the Central Government, the State Government and DTAB **(11)**

Table 1: Different committees set up by ministry of health and family welfare

S. No	Committees	Roles and responsibilities
1	DCC	Drug Consultative Committee, which has central and state Drug Control officials as its members, ensures drug control measures in all over India. It is an advisory body for the Central Government, the State Government and DTAB
2	DTAB	DTAB comprises of technical experts who advises central and state governments on technical matters of Drug regulation. Amendment, if any, to Drug and Cosmetic are made after consulting this board
3	IND	The committee will advise DCGI in matters to undertake in-depth evaluation of non-clinical data including pharmacological toxicological data, clinical trial data (if any) furnished by the applicant for approval of IND substances of chemical and biological origin.
4	SEC and MDAC	Each of the panels set up to advise in matters related to review and regulatory approval of clinical trials and new drugs, except for Investigational New Drugs (INDs), relating to different (12) therapeutic areas for Subject Expert Committee (SEC) formerly called as NDAC and 07 MDAC. "The committee will advise DCGI in matters to undertake in-depth evaluation of non-clinical data including pharmacological toxicological data, clinical trial data (phase I, II, III, and IV) furnished by the applicant for approval of new drug substances of chemical and biological origin to be introduced first time in the country including vaccines and r-DNA derived products. MDAC for Medical Devices.
	TRC	Technical Review committee (TRC) shall review the recommendations provided by SEC on applications of clinical trials and new drugs after thorough evaluation. DCGI will grant approval of clinical trial and new drugs based on recommendations of TRC.
5	Technical committee	Clinical trial protocol will be referred for review by Technical after the same has been approved by NDAC. Technical Committee and Apex Committee meet once every month.
6	Apex committee	Apex committee will send their recommendations/ opinions after review of proposal sent by Technical committee for clinical trial application which have been approved by TRC.
7	Expert committee	The prof. Ranjit roy chaudhury expert committee to Formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs The Prof CK Kokate expert committee to Formulate policy and guidelines for approval of new drugs, clinical trials and banning of FDCs **(13)**

a) Health Authority (HA) :- The health authority to prepare drug regulatory guidelines and guidance documents which are conformity and complaint and conformity to existing laws and regulation and also coordinate with global and or regional

regulatory body and in consultation with pharmaceutical manufacturers association issue technical requirements and process for marketing Authorization Approval.

b) **Pharmaceutical Industry: -** According to regulatory necessity of quality, safety and efficacy of manufacturer develops drugs and applies for market Authorization **(9)**.

4. ROLE OF REGULATORY AFFAIRS (RA) DEPARTMENT

- The Regulatory Affairs (RA) department of the pharmaceutical industry is in responsibility or functioning of obtaining permission for new pharmaceutical medicine or drug that ensuring the approval maintenance process for as desiring firm or for as long **(4)**.
- Right from the start of a product development, regulatory affairs experts provide technology and strategic guidance to quality control, R &D, production department, among other contributing significantly both financially and scientifically to the advancement of a development initiative & the enterprise **(5)**.
- Keep in touch with customer practices, guidelines and international legislation.
- Ensure that a company's product comply with the current regulation.
- Keep up to the date with a company's product range.
- Manage review audit reports and compliance, regulatory and customer inspections.
- The Regulatory Affairs professional role is to keep track of the ever changing legislation in all the region in which company wishes to distribute to it's product with the advice on the legal and scientific restrains and requirements, and collect also evaluate the scientific data that their research and colleagues are generating **(6)**.
- Regulation is a binding instruction issued by an agency that tells how to clarify and comply with the law, failures to follow regulation many end up into the "issued warning letter "sections of the FDA website , which is a fair for pharma industry.
- Maintain approved application and the record of registration fees paid against submission of DMF's (Drug Master File) and other documents.
- Regulatory affairs professional help company that avoid problem caused by badly kept records and inappropriate scientific thinking or poor presentation of data.
- A good Regulatory Affairs professional will have 'right first time' approaches and will play a very major and important part in coordinating scientific end with regulatory demand throughout the life of the products, helping to maximize the cost - effective use of the company resources **(7).**
- Also in the role to provide physician and other healthcare professionals with accurate and complete information about the safety, quality and effectiveness of the products.
- The regulatory affairs Department also involved in the drug development marketing concepts.
- The regulatory affairs is a crucial requirements to approve the packaging and advertising of drug /product before it is used by commercially (**8)**.

Figure 1 :- Contribution of regulatory affairs in different departments

- **Preclinical Research: -** pharmacology and toxicology studies.
- **Clinical trails: -** paper writing, Evidence gathering and mathematical interpretation.
- **Manufacturing: -** includes extensive safeguards are in place to ensure that goods are efficient and clean.
- **Quality Control: -** Analyzing materials for purity, potency, safety and quality.
- **Quality Assurance: -** includes activities such as defeat audits, complains, auditing and record processing. **(1)**

India: Approval process of New Drug

The Drug and Cosmetic Act 1940 and rule 1945 was passed by Indian government at Parliament to export, import and production of medicinal products. National regulatory authority of India is Central Drug Standard Control Organization (CDSCO).

CDSCO is Indian government evaluatory agency that for applicant of new drug product for safety and product efficacy. CDSCO give review and analytical report to DCGI (Drug Controller General Of India) **(9)**.

DCGI is a provide license and authority of Licensing of India that approves and give permits a new drug product manufacturing and production and also marketing in India.

To start the marketing business in India with import or developing a new drug or new medicine in industry, it must require fill out FORM 44 and transfer the data that needed under Schedule Y of Drug and Cosmetics Act 1940 and rules 1945.(Rule 122A , 122B , and 122D with appendix I, IA, and VI) **(4,5)**.

Following are some provisions of the Drug and Cosmetics Rule 1945 –

- In Rule 122A involve a request for a new drug approval
- In Rule 122B involve application of import permission of new drug or new medication
- In Rule 122D Fixed Dosage Combination permission to import and export
- In Rule 122DA involve request to approval to perform clinical trials for IND (Investigational New Drug)
- In Rule 122 involving majorly DAB that include compensation of injuries /death during clinical trials **(1)**.

5. CDSCO: CENTRAL DRUG STANDARD CONTROL ORGANIZATION

It under Directorate General of Health Services , Ministry of Health and Family Welfare ,Government of India .

It is National Regulatory Authority (NRA) of India.

CDSCO Headquarter located at FDA Bhawan ,Kotla Road, New Delhi. It has 6 Zonal offices, 4 sub Zonal offices, 13 port office and 7 Laboratories allover in India.

Role of CDSCO:

1. For approval of new drug.
2. Processing and conducting the clinical trials.
3. Licensing and import registration.
4. Also approving license for blood banks, r-DNA Vaccine, LVPs vaccine, and some medicinal device and products.
5. New drug testing.
6. Drug and cosmetics banning.
7. Market surveillance through inspectorate center and state Authority **(1)**.

6. DRUG APPROVAL PROCESS IN INDIA

It is given in THREE phase

First phase:

1) Applicant is filling the application of IND (Investigational New Drug) with their informational studies to CDSCO headquarters.
2) All the information is examined by new drug division.
3) Then detailed review by IND committee.

4) With proper information of CDSCO – Recommendation to DCGI (Drug Controller General Of India).
5) Then IND application is approved .

Second phase:-

1) Application is given one copy of IND information to ethical committee with application.
2) Then ethical committee report the application of IND.
3) This process taken within 12 Weeks.

Third phase:-

1) In 1st phase, IND application is approved and in 2nd phase, ethical committee report is positive then 3rd phase is started.
2) In 3rd phase, clinical trials is started.
3) Then again give application for new drug registration to CDSCO.
4) Then finally review by DCGI .
5) If Review is positive or complete then **LICENSE IS GRANTED** .
6) If Review is not complete then refused to grant license **(4,5,6)**.

7. REQUIREMENT OF DRUG APPROVAL PROCESS IN INDIA

- Registration process of New drug approval is one time .
- Approval timeline is 2-18 months.
- Approval presentation format - paper .
- Process validation is required.
- Batch size is Pilot scale batch (5).

Table 2 :- Comparison of US , EUROPE , INDIA

Sr No.	REQUIREMENT	US	EU	INDIA
A) ADMINSTRATION				
1	Regulatory Authority	Food and drug Administration	European medicine agency	Central drug Standard and control organizations
2	Application	ANDA	MAA	MAA
3	Debarment certification	Required	NA	NA
4	No. of copies	3(archival, review, field)	1	1
5	Approval time line	18 month	12 month	12 Months
6	Clinical studies Fees		10-20 lakh	50000 Rs
7	Presentation	eCTD & paper	eCTD, paper alongwith	Paper

			NeeS	
8	Pharmacovigilance	Not required	Required	Required
9	Agent authorization	Required	Not required	Not required
B) FINISHED PRODUCT CONTROL				
1	Assay	90-100%	95-105%	90-110%
2	Disintegration	Not required	Required	Required
3	Colour identification	Not required	Required	Required
4	Water content	Required	Not required	Required
C) MANUFACTURING AND CONTROL				
1	No. of batches	1	3	1
2	Packaging	A minimum of 100000 unit	Not required	Not such required
3	Process validation	Not required atthe time of submission	Required	Required
D) LABELING REQUIREMENT				
1	Prescription status	Rx	POM	Rx
2	Labels	Vials/carton/PIL	Vials/carton/PIL	VIALS,AMPOULES,INJECT IONS
		REQUIRED		NOT SPECIFIED

3	Side by side comparison		Required	
E) STABILITY				
1	Date and time of submission	3 months accelerate and 3 months	6 months accelerate and 6 months long term	6 months accelerate and 6 months long term
2	Container orientation	Inverted upright	Do not address	Do not address
3	QP Certification	Not Required	Required	Required
4	Retention of sample	5 years from the date of filling the application	No such required but usually followed	3 years from the date of filling the application **(12)**

8. CONCLUSION

DRA is a rewarding and approachable field that include legal and scientific both dynamic aspects of new drug development. Regulatory Governing Bodies have been formed all around the world to ensure that medicines for human use satisfy global standards of quality, effectiveness, and safety. For example, FDA, TGA, CDSCO, EMEA, and others. It includes legislation that requires drugs to be trailed, manufactured, tested and developed in according to guidelines given by authority, so that they are safe and patients will be well healthy and protected.

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