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Drug Regulatory Affairs

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I. INTRODUCTION

The Central Drugs Standard Control Organisation(CDSCO) under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India is the National Regulatory Authority (NRA) of India. Its headquarter is located at FDA Bhawan, Kotla Road, New Delhi 110002 and also has six zonal offices, four sub zonal offices, thirteen Port offices and seven laboratories spread across the country.

The Drugs & Cosmetics Act,1940 and rules 1945 have entrusted various responsibilities to central & state regulators for regulation of drugs & cosmetics. It envisages uniform implementation of the provisions of the Act & Rules made there under for ensuring the safety, rights and well being of the patients by regulating the drugs and cosmetics. CDSCO is constantly thriving upon to bring out transparency, accountability and uniformity in its services in order to ensure safety, efficacy and quality of the medical product manufactured, imported and distributed in the country.

Under the Drugs and Cosmetics Act, CDSCO is responsible for approval of New Drugs, Conduct of Clinical Trials, laying down the standards for Drugs, control over the quality of imported Drugs in the country and coordination of the activities of State Drug Control Organizations by providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Further CDSCO along with state regulators, is jointly responsible for grant of licenses of certain specialized categories of critical Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera.

1.1 New Drug Application (NDA)

New Drug Application (NDA) is an application submitted preclinical and clinical test data for analysing the drug information and description of manufacturing procedures.

After agency received the NDA possibilities:

- Approval
- Approvable
- Not Approvable

Drug Development Teams

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. The process of drug discovery and development is very long and needs around 10-12 years which includes the close interaction of large number of scientific disciplines.

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Drug Development Team Responsibilities

1. Planning research studies to further characterization of drug candidate.
2. Integration of new research results with previously generated data.
3. Preparation of detailed drug development plan (designing the Development milestones, generating timelines for completion and defining critical path)
4. Viewing research results from experiments conducted by various scientific disciplines.
5. Monitoring the status of ongoing research studies and modifying the plan as per new data.
6. Comparing research results and development status of drug molecules of competitors

- The new drug approval is of two phase process: First phase for clinical trials and second phase for marketing authorization of drug.
- Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV).
- These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings.
- After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted.
- The competent authority reviews the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect.
- Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects.

II. NON-CLINICAL DRUG DEVELOPMENT

2.1 Pre-clinical Trial:

A laboratory test for a novel drug or a new medical device is usually done on animal subjects, to see if the hoped for treatment really works and if it is safe to test on humans. It include various studies,

- in silico: via computer simulation in vivo: within the living
- in vitro: within the glass (outside the living organism)

This process of non-clinical development of medicine is very complex, time consuming and regulatory driven.

The primary aims of the non-clinical development phase is to analyse and determine which candidate has the greatest probability of success, assess its safety, and raise firm scientific foundations before transition to the clinical development phase.

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Pharmacology: Study of effects of chemical substances on living systems It holds all the aspects of drug discovery, ranging from details of interaction between drug molecule and its target to consequences of placing the drug in the market.

Selectivity Testing:

It consists of two main stages i.e. screening for selectivity and Binding assay.

To determine the potency of drug, the selectivity of a compound for a chosen molecular target needs to be assessed.

Pharmacological Profiling:

This includes the determination of pharmacodynamics effect of new compound, either on in-vitro models or in-vivo models.

2.2 Safety Pharmacology

This includes the scientific evaluation and study of potentially life threatening pharmacological effects of a potential drug which is unrelated to the desired therapeutic effect and therefore may present a hazard. These tests are conducted at doses not too much in excess of the intended clinical dose.

Safety pharmacology seeks to identify unanticipated effects of new drugs on major organ function It is aimed at detecting possible undesirable or dangerous effects of exposure of the drug in therapeutic doses

Toxicological Approaches to Drug Discovery

Acute Toxicity:

Acute toxicity studies: at least two species, usually mice and ratsusing the same route as intended for humans. In addition, at least two more routes should be used to ensure systemic absorption of the drug; this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. The symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. Long-Term Toxicity: These studies should be carried out in at least two mammalian species and out of these two mammalian species one should be a non-rodent. The duration of study will depend on the factor that whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials.

If a species is known to metabolize the drug in the same way as humans, it should be preferred in long-term toxicity studies. The drug should be administered 7 days a week by the route intended for clinical use in humans.

Regulatory Organizations in Different Countries USFDA (Unites States)

CDSCO-Central drugs standard control organization

(India) EMEA- European Agency for the evaluation of medicinal products (European Union) MoH (Sri Lanka)

DDA- Department of drug Administration (Nepal)

Different Types of Drug Applications that can be Submitted to FDA

- IND (Investigational New Drug Application
- NDA (New Drug Application)
- ANDA (Abbreviated New Drug Application)
- BLA (Biologic License Application)
- FDA is responsible for protecting and promoting public health.

The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed.

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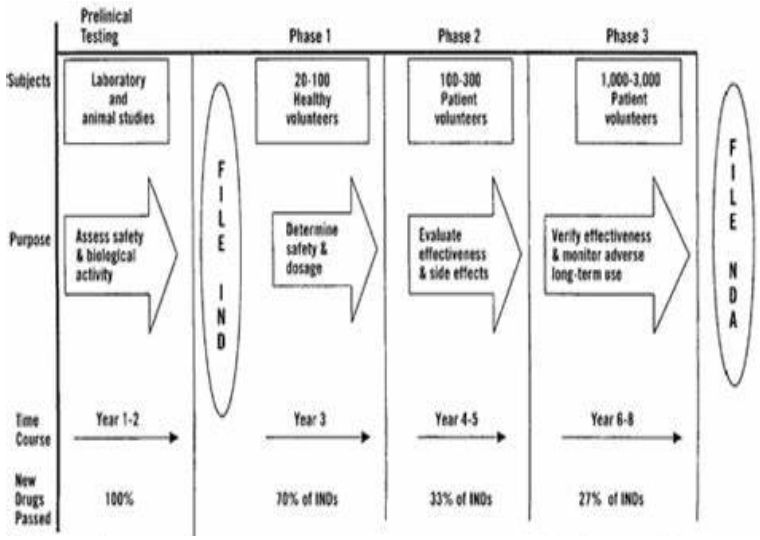

Investigational New Drug Application (INDIA)

Its application filed to FDA in order to start clinical trials in humans if the drug was found to be safe form the report of Preclinical trials.

A pre-IND meeting can be arranged with the FDA to discuss a number of issues:

The design of Animal research. Protocol for conducting the Clinical trials. >Review the chemistry, manufacturing, and control of the investigational drug

new drug on humans.

IND application is filled to provide the data showing that it is reasonable to begin tests of a new drug on humans.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development.

When a product is identified viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

2.3 Types of IND Applications

- Investigator IND application
- Emergency Use IND application
- Treatment IND application
- Screening IND application
- Investigator IND application:

Submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. Physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Emergency Use IND

Allows FDA to authorize use of an experimental drug in an emergency situation. Does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.34.

Treatment IND

Submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

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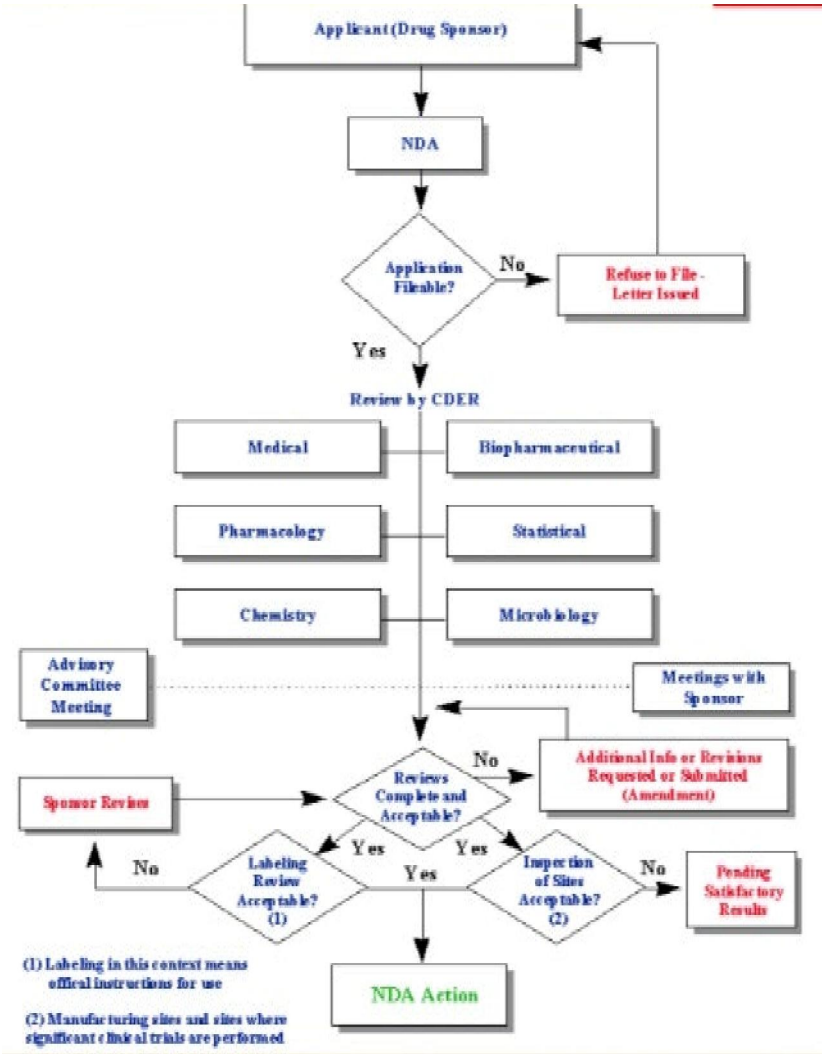

Introduction To Medical Device

Medical device means any instrument, apparatus, implement machine, appliance, implant, reagent for in vitro use, software material intended by the manufacture to be used, alone or in combination, for human beings or animals for one or more of the specific medical purposes of Diagnosis, monitoring, treatment, mitigation or prevention of diseases or disorders. Medical device can be used both extremally and internally.

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Significance of Medical Devices

The medical development in terms of drugs or devices has brought about the robust change in the life of the people. Medical devices have extended the ability of physicians to diagnose and treat diseases, making great contributions to health and quality of life.

The capability of devices to enable patients to survive or just improve their quality of life.

Introduction of Regulation of Medical Devices

Medical devices in India are regulated under the Medical Device Rules.

Published on 31st January 2017

Effective from 1st January 2018

The Indian medical regulatory system has become more complicated in recent years. In the past, medical devices did not need to be approved at all, but that is not the case today. In India, there are about 30 device families that outline which specific medical devices need to be registered.

Regulation on India

In India medical devices are governed by CDSCO(Central Drugs Standard Control Organization) which is regulated by Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

CDSCO is the only government body which regulate the medical devices.

India's medical device regulatory structure

Ministry of Health and welfare

Drug controller general of India

Central drugs standard control organization (CDSCO) medical devices division

TheCentral Drug Standards Control Organization (CDSCO)is India's main regulatory body for pharmaceuticals and medical devices.

The Drug Controller General of India (DCGI) is the key official within the CDSCO. **3)The DCGI** is responsible for the approval of the manufacturing of certain drugs (vaccines, large volume parenteral, blood products, r-DNA derived), specific medical devices, and new drugs.No medical device regulations exited in India prior to 2005.However, today there are registration procedures for certain types of medical devices regulated under the Medical Device Rules.

The new rules are based on Global harmonization task force.

In India, the manufacturing, import, sale, and distribution of medical devices are regulated under **India's Drugs &Cosmetic act and Rule (1945).**

22 medical devices are currently notified under the drugs and cosmetics Act.

Controls and inspections are carried out by the CDSCO, state drug controllers and central/state laboratories

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Device Classification in India

No specific medical device classification currently exists in India.

Devices notified (regulated) by the Indian government must register with the **CDSCO.**

Non-notified devices do not require CDSCO registered, and may be imparted into India according to formal customs rules.

Regulatory Body for Medical Devices

1. Drug Controller Genaral of India (DCG)
2. Deputy Drug Controller
3. Assistant Drug Controller

Function of Medical Device Division

1. Import Registration and licensing of Medical Devices
2. Approval of New Medical Devices
3. Manufacturing license to Indigenous Manufacturer under CLAA Scheme
4. Grant of Test License
5. NOC's for Import/Clarifications
6. Neutral Code for Export
7. Clinical trails

Classification of Medical Devices

Classification of medical devices is based on risk factor.

Class A (Low Risk)	**Class B (Low Moderate Risk)**	**Class C (Moderate High Risk)**	**Class D (High Risk)**
1.Bandages 2.Tongue depressors 3.Surgical dressing	1.Hypodermic Needles 2.Suction Equipment	1.Lung Ventilator 2.Bone fixation plate	1.Heart valves 2.Implantable defibrillator 3.Copper T

Registration Medical Devices

ASEAN:-Association of southeast Asian Nations

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United Nations:

1. Formed in 1945.
2. Headquartered in New York City, US
3. No. of Founding Members: 50 (June 1945)
4. No. of Members Today :193
5. Compare: No. of Member Countries in FIFA (Soccer): 211
6. No. of Member Countries in FIBA (Basketball):215

Aims:

- Maintain world peace & security
- Cooperate internationally to solve international economic, social, cultural & humanitarian problems.
- Promote respect for human rights and basic freedom

European Union

1. Formed in 1993
2. Headquartered in Brussels, Belgium
3. No. of Members Today: 28
4. Total Population: 503 million
5. Association of Southeast Asian Nations (ASEAN)
6. Background
7. Founded in August 1967 in Bangkok
8. Headquartered in Jakarta, Indonesia
9. Total Members: 10

Founding Members

Indonesia, Malaysia, the Philippines, Singapore & Thailand

"The ASEAN Emblem represents a stable, peaceful, united and dynamic ASEAN"

"The colours of the Emblem represent the main colours of the state crests of all the ASEAN Member States."

"The blue represents peace and stability. Red depicts courage and dynamism, white shows purity and yellow symbolises prosperity."

"Stalks of padi represent the dream... for an ASEAN comprising all the countries in Southeast Asia, bound together in friendship and solidarity."

"The circle represents the unity of ASEAN."

Newer ASEAN Members

- 1984: Brunei
- 1995: Vietnam
- 1997: Laos & Myanmar
- 1999: Cambodia

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Aims

Promote economic, social & cultural development of the region
Protect the peace & stability of the region
Provide opportunities for member countries to discuss & resolve differences peacefully ASEAN Guiding Principles
Non-Intervention in Domestic Affairs
ASEAN Guiding Principles
Consensus & Consultation (musyawarah and mufakat)
"Agree to Disagree"
Collectively, these principles are known as the "ASEAN Way"

MEMBER ECONOMIES

- Australia
- Philippines
- Papua New Guinea
- Brunei
- Canada
- Singapore Thailand
- Chile
- Peru
- Indonesia
- Japan
- South Korea
- United states
- Taiwan
- Russian
- Vietnam

NOTE - India is observer of APEC since 2011 and has applied for membership.

- Hong Kong
- China
- Malaysia
- New Zealand Mexico.

APEC's Pillar I
APEC's First Pillar: Trade and Investment Liberalization

- APEC's Second Pillar: Trade Facilitation
- APEC's Third Pillar: Economic and Technical Cooperation

INDIA and APEC

- APEC's activities cover a wide variety of disciplines.

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- It would provide India with an opportunity to socialize with the developed economies of the Asia-Pacific region.
- It is one of the missing link in 'India's Act East Policy'.
- APEC will provide India a perfect platform to integrate in global economies.
- With APEC membership, India's chance to get into FTAAP and TPP brightens.
- FTAAP: FREE TRADE AREA OF THE ASIA PACIFIC OR TPP: Trans-Pacific Partnership

APEC & PHARMA

- Harmonizing Regulatory Practices Across APEC: Good Clinical Research Inspection Global pharma necessitates harmonized regulation.
- Multinational drug companies conduct clinical research and trials in many countries and market the resulting products around the world. And in each country the companies face a different regulatory environment.
- (APEC RHSC Vision 2020)
- In 2010, the RHSC established under APEC's Life Sciences Innovation Forum (LSIF) advocated for regulatory convergence in pharmaceuticals for improved public health and economic development.
- Regulatory Convergence: Regulations for greater regulatory cooperation and does not necessarily require the regulations to be "harmonized".
- Ultimate AIM for APEC economies to achieve the maximum level of regulatory convergence feasible by 2020.
- The East African Community (EAC) is an intergovernmental organization composed of six countries in the African Great Lakes region in eastern Africa

It includes

- Burundi
- Kenya
- Rwanda
- South Sudan
- Tanzania
- Uganda

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The EAC aims at widening and deepening co-operation among the partner states and other regional economic communities in, among others, political, economic and social fields for their mutual benefit

The Treaty for Establishment of the East African Community was signed on 30th November 1999 and entered into force on 7th July 2000

The Republic of Rwanda and the Republic of Burundi acceded to the EAC Treaty on 18th June 2007 and became full Members of the Community with effect from 1st July 2007.

Quick Facts about EAC

Motto: "One People One Destiny"

Area: 1.82 million Sq. m

Population: 145.5 million (2015)

First Established: 1967

Dissolved: 1977

Re- Established: 7th July 2000

Headquarters: Arusha, Tanzania

Aims and Objectives

The EAC aims at widening and deepening co-operation among the Partner States in, among others, political, economic and social fields for their mutual benefit.

Governance

East African Court of Justice

The East African Court of Justice is the judicial arm of the community.

East African Legislative Assembly

The East African Legislative Assembly (EALA) is the legislative arm of the community. The EALA has 27 members who are all elected by the National Assemblies or Parliaments of the member states of the community.

EAC Organs

The main Organs of the EAC are

- Summit
- Council of Ministers

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- Co-ordinating Committee
- Sectoral Committees
- East African Court of Justice
- East African Legislative Assembly
- Secretariat

1. Introduction:

Therefore, the Ministerial Committee for Food Safety of the GCC countries proposed the importance of collective coordination and establishing of laws (regulations) of laws in food safety. The importance of the Guide comes as part of the efforts of GCC States to standardize and facilitate the import procedures and to complete the inspection of imported food consignments based on the degree of health risk without prejudice to the obligations of Member States towards the WTO Agreements and compatible with the best international practices in this area.

Development of GCC Guide for Control on Imported Foods

- 2007 : Initiated work on GCC Food Control Guide.
- 2011 : On-going consultation process to develop Guide. First (English) draft notified to WTO.
- 2014 : Second draft notified to WTO.
- 2015 :Guide translated to Arabic
- 2015 :Experimental Application of guide for 1 year.
- 2016 :Technical meeting in Dubai discuss all exporters concerns. Over 90% of comments were accepted
- 2016 :Third notification sent to WTO.
- 2017: GCC Countries will start applying the guide.

2. Scope:

This Guide describes principles and regulatory requirements to be applied by the exporting country and the importing GCC countries in assuring the safety and suitability of shipments of imported food. Specific attestations for animal and plant health certification are also provided in the Guide.

1. All GCC food standards and technical regulations are available at GSO website: www.gso.org.sa
2. The GCC food imports Guide tackles food suitability issues related to ethnic/religious considerations such as Halal food and labeling issues, which are considered as legitimate factors.
3. Foods imported for personal use are not subject to the requirements in this guideline and are allowed where the packaging is intact and provides sufficient information to allow entry e.g. name and number of food establishment in the country of origin.

3. Definitions:

The following words and expressions shall, unless the context otherwise requires, have the meaning hereby assigned to them

Fitness for human consumption: Food that is fit for human consumption according to its end use as specified by the technical regulations of the GCC, or approved alternative equivalent measures.

- **Food:** Any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of food but does not include cosmetics or tobacco or substances used only as drugs.
- **Food control:** Mandatory, regulatory activity, carried out by the competent control authorities, for the purposes of protecting the health of consumers and to ensure the safety of food during all stages of food chain.
- **Food Inspection:** Examination of food or food safety systems by the competent authorities in the importing country, for the purposes of control of production inputs, processes and final products through all stages of food chain, to verify their conformity to the technical regulations of the GCC, or approved alternative equivalent measures.

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