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Review Article

Regulatory Status of Microbes as Antibiotics: An Overview

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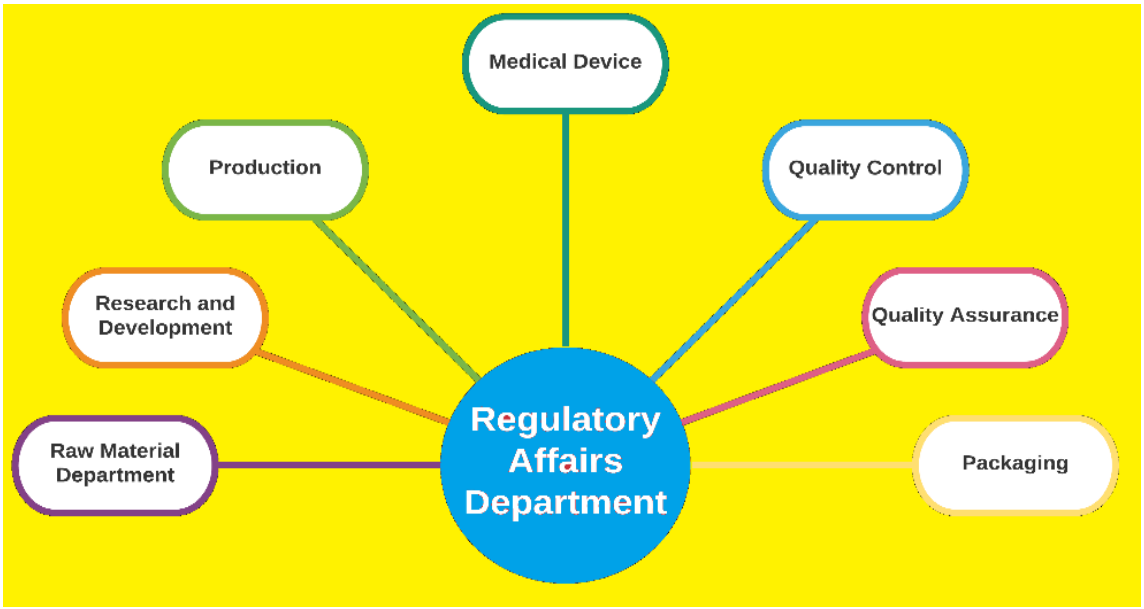
Abstract: Regulatory affairs (RA) play crucial roles in the pharmaceutical industry because they are concerned with the lifecycle of healthcare products, they offer strategic, tactical, and operational direction, and they support working within the law to hasten the development and delivery of safe and effective healthcare products to people all over the world. The purpose of regulatory affairs is to create and implement a regulatory strategy to guarantee that the combined efforts of the drug development team result in a product that is acceptable to international regulators while also standing out from the competition. Microorganisms play a vital role in every field of drug such as production of antibiotics, antifungal, anticancer, vitamins, vaccines and enzymes etc. These are some examples where microbial products are widely used. In the present work we will discuss various aspects where microorganisms widely used in production of drug and their regulations in US and India.

Keywords: Microorganisms**,** antibiotics, antifungal, Regulatory affairs (RA) & FDA.

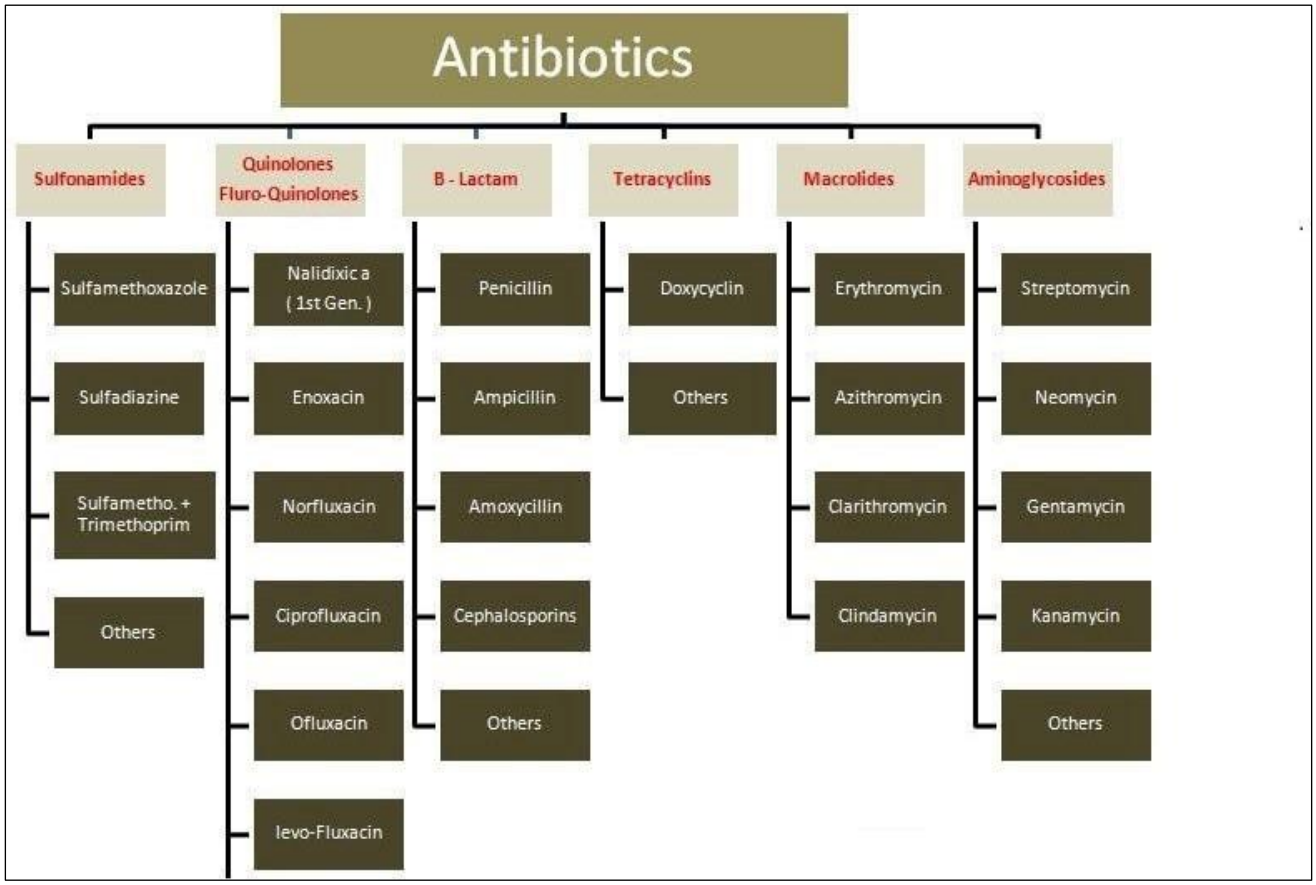
INTRODUCTION

Pharmaceutical regulatory affairs are important participants in the development of new drugs because they keep open lines of communication between pharmaceutical firms and regulatory organisations like the FDA in the United States, the TGA in Australia, the MHRA in the United Kingdom, and the MCC in South Africa, to mention a few [1]. Regulatory affairs are also responsible for ensuring that the company's operations, from non-clinical research to advertising and promotion, are carried out in compliance with the rules and regulations set forth by regulatory authorities.

Microorganisms play a vital role in production of number of antibiotics such as Beta lactam, Aminoglycoside, Fluoroquinolones, Macrolides, Glycopeptide and miscellaneous antibiotics. Antibiotics are low molecular-weight (non- protein) molecules produced as secondary metabolites, mainly by microorganisms that live in the soil. Most of these microorganisms form some type of a spore or other dormant cell, and there is thought to be some relationship (besides temporal) between antibiotic production and the processes of sporulation. Among the molds, the notable antibiotic producers are penicillium and cephalosporium, which are the main source of the beta-lactam antibiotics (penicillin and its relatives). In the bacteria, the actinomycetes, notably streptomyces species, produce a variety of types of antibiotics including the aminoglycosides (e.g. streptomycin), macrolides (e.g. erythromycin), and the tetracyclines. Endospore-forming bacillus species produce polypeptide antibiotics such as polymyxin and bacitracin [2-4].



Role of Regulatory Affairs in Health care



List of antibiotics and their primary mode of action [2]

	Examples	Biological source	Spectrum (effective against)	Mode of action
1.	Penicillin G, Cephalothin	Penicillium notatum and Cephalosporium species	Gram-positive bacteria	Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly
2.	Ampicillin, Amoxycillin		Gram-positive and Gram-negative bacteria	Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly

	Examples	Biological source	Spectrum (effective against)	Mode of action
3.	Clavamox is clavulanic acid plus amoxicillin	Streptomyces clavuligerus	Gram-positive and Gram-negative bacteria	Suicide inhibitor of beta-lactamases
4.	Aztreonam	Chromobacter violaceum	Gram-positive and Gram-negative bacteria	Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly
5.	Imipenem	Streptomyces cattleya	Gram-positive and Gram-negative bacteria	Inhibits steps in cell wall (peptidoglycan) synthesis and murein assembly
6.	Streptomycin	Streptomyces griseus	Gram-positive and Gram-negative bacteria	Inhibit translation (protein synthesis)
7.	Gentamicin	Micromonospora species	Gram-positive and Gram-negative bacteria esp. Pseudomonas	Inhibit translation (protein synthesis)
8.	Vancomycin	Streptomyces orientales	Gram-positive bacteria, esp. Staphylococcus aureus	Inhibits steps in murein (peptidoglycan) biosynthesis and assembly
9.	Clindamycin	Streptomyces lincolnensis	Gram-positive and Gram-negative bacteria esp. anaerobic Bacteroides	Inhibits translation (protein synthesis)
10.	Erythromycin	Streptomyces erythreus	Gram-positive bacteria, Gram-negative bacteria not enterics, Neisseria, Legionella, Mycoplasma	Inhibits translation (protein synthesis)
11.	Polymyxin	Bacillus polymyxa	Gram-negative bacteria	Damages cytoplasmic membranes
12.	Bacitracin	Bacillus subtilis	Gram-positive bacteria	Inhibits steps in murein (peptidoglycan) biosynthesis and assembly
13.	Amphotericin	Streptomyces nodosus	Fungi	Inactivate membranes containing sterols
14.	Nystatin	Streptomyces noursei	Fungi (Candida)	Inactivate membranes containing sterols
15.	Rifampicin	Streptomyces mediterranei	Gram-positive and Gram-negative bacteria, Mycobacterium tuberculosis	Inhibits transcription (eubacterial RNA polymerase)
16.	Tetracycline	Streptomycesspecies	Gram-positive and Gram-negative bacteria, Rickettsias	Inhibit translation (protein synthesis)

MICROBIAL PRODUCTS AS ANTIFUNGAL DRUG [5, 6]

Microorganisms play a vital role in production of number of antifungal drugs such as Amphotericin, flucytosine, fluconazole, itraconazole, echinocandin, voricnazole, posaconazole and isavuconazole etc. Antifungal are the drugs that treat fungal infections by acting on the synthesis of the fungal cell membrane, cell wall components, membrane permeability, synthesis of nucleic acids and on the mitotic spindle function of the fungi during cell division.

MICROBIAL PRODUCTS AS VACCINE PRODUCTION [7, 8]

Microorganisms play a vital role in preparation of number of vaccines such as Killed, Attenuated, Toxoid, Subunit, Conjugate and Valence vaccine. A vaccine is a biological preparation that improves immunity to a disease. It contains an agent resembling a disease-inducing microorganism– a bacterium, virus or toxin – that activates the body's immune system. White blood cells – APCs, B cells, and T-cells – recognize, destroy and "remember" this version of the pathogen. That way, the immune system can quickly recognize and destroy this harmful microorganism later. A vaccine is essentially a pathogen-imposter.

Bacterial Vaccine [8]

Disease	Organism	Vaccine
DIPHTHERIA	Corynebacterium diphtheriae	Inactivated exotoxin
TETANUS	Clostridium tetani	Inactivated exotoxin
MENAGITIS	H influenza Neisseria meningitidis	Polysaccharide protein Conjugate
PNEUMONIA	Strep pneumoniae	Polysaccharide protein conjugate
WHOOPING COUGH	Bordetella pertussis	Acellular components- inactivated toxin
PLAGUE	Yersinia pestis	Inactivated exotoxin
	Bacillus anthracis	Inactivated exotoxin
	Mycobacterium tuberculosis	Live attenuated BCG
	Vibrio cholerae	Inactivated bacteria

Viral Vaccine [8]

DISEASE	VIRUS TYPE	CONSTITUENTS
SMALLPOX	Variola virus	Vaccinia virus
POLIO	Picorna virus	oral: live attenuated Parenteral: inactivated
HEPATITIS A	Picorna virus	Killed virus
HEPATITIS B	Hepadna virus	Recombinant antigen
INFLUENZA	Orthomyxo virus	Inactivated virus
MEASLES	Paramyxo virus	Live, attenuated virus
MUMPS	Paramyxo virus	Live, attenuated virus
RUBELLA	Toga virus	Live, attenuated virus
CHICKEN POX	Varicella zoster	Live, attenuated virus
RABIES	Lyssa virus	Inactivated virus

Microorganism derived anticancer agents [9]

Compound	Microorganism source	Use in cancer
Actinomycin	Streptomyces spp.	Sarcoma and germ cell tumors
Bleomycin	Streptomyces verticillus	Germ-cell, cervix and head and neck cancer
Daunomycin	Streptomyces coeruleorubidus	Leukemia
Doxorubicin	Streptomyces pneuceticus	Lymphoma, breast, ovary, lung and sarcomas
Epirubicin	Streptomyces pneuceticus	Breast cancer
Idarubicin	Streptomyces pneuceticus	Breast cancer and leukemia
Mitomycin C	Streptomyces caespitosus	Gastric, colorectal, anal and lung cancer
Geldanamycin	Streptomyces hygroscopicus	Experimental
Rapamicin	Streptomyces hygroscopicus	Experimental
Wortamannin	Talaromyces wortmanni	Experimental

DRUG DISCOVERY AND DEVELOPMENT PROCESS [13-15]

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drug. The new drug approval is of two-phase process - the 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 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 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 (populations) should also be monitored.

Drug approval process in United States [14]

The United States Food and Drug Administration (FDA) is an agency within the Department of Health and Human Sciences. FDA is required by US Federal Food, Drug, and Cosmetic Act to regulate drug products in the United States.

FDA approval process [14]

	Preclinical Testing		**Phase 1**	**Phase 2**	**Phase 3**	
Subjects	Laboratory And animal studies		20-100 Healthy volunteers	100-300 Patient volunteers	1000-3000 Patients volunteers	
Purpose	Assess safety & biological activity	**FILE IND**	Determine safety & dosage	Evaluate effectiveness & side effects	Verify effectiveness & monitor adverse long-term use	**FILE NDA**
Time course	Year 1-2		Year 3	Year 4-5	Year 6-8	
New Drugs Passed	100%		70% of INDs	33% of INDs	27% of INDs	

The regulation of drug products is the responsibility of the Office of Medical Products and Tobacco, which comprises the following:

- **Centre for Drug Evaluation and Research (CDER).**
- Centre for Biologics Evaluation and Research (CBER).
- **Centre for Devices and Radiological Health.**

Centre for Drug Evaluation and Research (CDER)

CDER: CDER oversees the research, development, manufacture, and marketing of synthetic small molecule drugs. CDER is also responsible for the regulation of certain biologic therapeutic products. Most of these drugs are large protein-based molecules generated by hybridoma or recombinant DNA technology. These products are the following:

a. Monoclonal antibodies for in vivo use.
b. Cytokines, growth factors, Enzymes, immunonomodulators and thrombolytics.
c. Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant version of these products.
d. Non-vaccine therapeutic immunotherapies.

Centre for Biologics Evaluation and Research (CBER)

CBER regulates certain nontherapeutic biologics which are not regulated by CDER. They are as follows:

a. Allergenics.
b. Blood and blood products.
c. Cellular and gene therapy products.
d. Tissue and tissue products.
e. Vaccines.
f. Xenotransplantaion.

FDA Processes and Controls [16-17]

The application regulations for drug are codified in Title 21 of the US Code of Federal Regulations (CFR). These regulations promulgate FDA's requirement in many aspects of drug clinical research, manufacturing, and marketing.

Document number and Description [18]

Document Number	**Description**
21 CFR50	Protection of Human Subjects
21CFR56	Institutional Review Board
21CFR58	GLP for Nonclinical Laboratory studies
21CFR210	cGMP Practice in Manufacturing, Processing, Packaging or Holding of Drugs
21CFR211	cGMP For Finished Pharmaceuticals
21CFR312	IND Application
21CFR314	NDA Application
21CFR600	Biological Products: General
21CFR610	General Biological Products Standards

Investigational New Drug (IND) application [18]

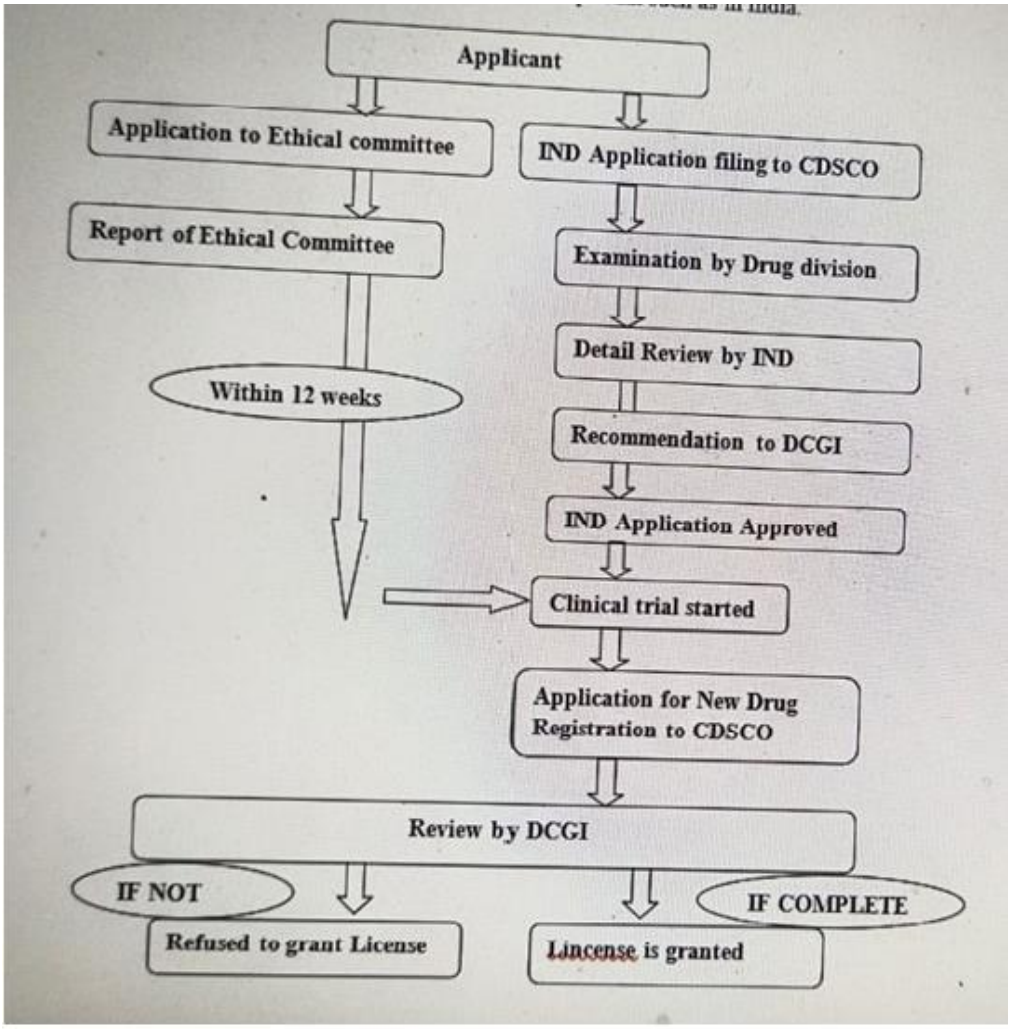
It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials. A firm or institution, called a Sponsor, is responsible for submitting the IND application.

A pre - IND meeting can be arranged with the FDA to discuss several issues:

- The design of animal research, which is required to lend support to the clinical studies.
- The intended protocol for conducting the clinical Trial.
- The chemistry, manufacturing, and control of the investigational drug.

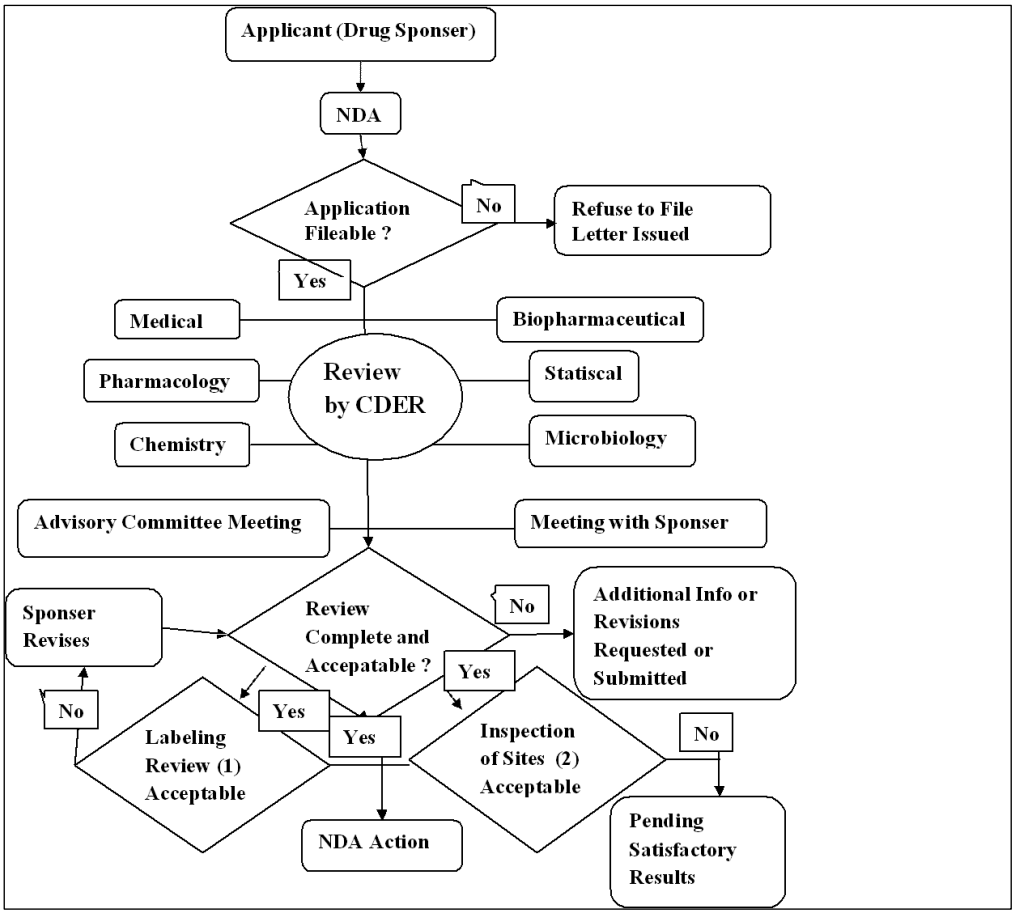
PART 312 -- INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A -- General Provisions
Subpart B -- Investigational New Drug Application (IND) Subpart C -- Administrative Actions.
Subpart D -- Responsibilities of Sponsors and Investigators. Subpart E – Miscellaneous
Subpart F -- Drugs for Investigational Use in Laboratory Research Animals or in Vitro Tests.



Investigational new drug application (IND) Process

New Drug Application (NDA) [18]



Refuse to File Letter Issued

New Drug Application (NDA) Process [18]

Drug Approval Process in India [17-18]

When a company in India wants to manufacture/import a new drug it must apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it must conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format. But a provision is there in Rule - 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health, he may grant permission for import of new drugs basing on the data of the trials done in other countries. Similarly, there is another provision in Rule - 122A which says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

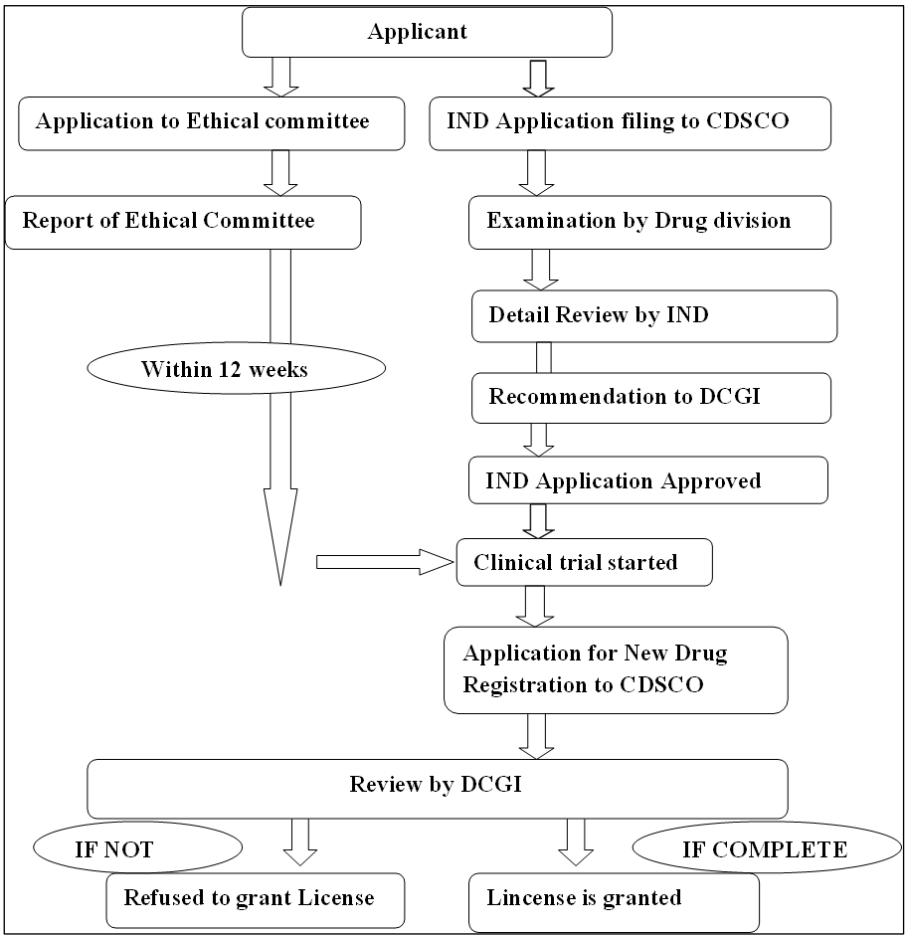
Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials. Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials.

Procedure for New drug approval in India

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. The changes

include, establishing definitions for Phase I–IV trials and clear responsibilities for investigators and sponsors. An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. On healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, If the new drug substance is not marketed in any other country. The new drug registration (using form # 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of about 12-18 months. After the NDA approval, when a company can distribute and market the product, it is in Phase IV counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan, it is mandatory that the dossier prepared in CTD format, however, in some countries it is optional such as in India.



Flow chart of drug approval process in India

SUMMARY AND CONCLUSION

The study given in this article focuses on microbes, which are significant to and have a significant influence on our daily life. Every area of medication manufacture, including the creation of antibiotics, antifungals, anticancer, vitamins, vaccines, and enzymes, depends heavily on microorganisms. Regulation and guidelines are

required for the use of microorganisms in the pharmaceutical industry. There are several phases in the drug research and development process, including drug discovery, drug development, clinical trials, and marketing application. The United States Food and Drug Administration (USFDA) is the regulatory body that oversees the use of medications including antibiotics, antifungals, and cancer treatments in the USA include vitamins and vaccinations. The research, development, production, and marketing of drugs are overseen by the Centre for Drug Evaluation and Research (CDER). After conducting preclinical research, the applicant submits an IND application in accordance with the FDA approval process. After successfully completing phases 1, 2, and 3, the applicant submits an NDA application to request medication marketing permission. The Central Drugs Standard Control Organisation (CDSCO) is the regulatory body that oversees drug regulation in India.

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