Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

https://doi.org/10.55544/jrasb.1.3.22

Quality Risk Management Approach for Drug Development and Its Future Prospectives

Dr. Muthukumar Subramanian[1], Dr. Keshamma E[2], Deepika Janjua[3], Devinder Kumar[4], Roshan Kumar[5], Purabi Saha[6], Rakesh Kumar Gupta[7] and Shuaib Rao[8]

[1]SRM Institute of Science & Technology, Tiruchirappalli Campus, Deemed to be University, Tamilndu, INDIA.

[2]Associate Professor, Department of Biochemistry, Maharani Cluster University, Palace Road, Bangalore-560001, INDIA.

[3]Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun -248007, Uttarakhand, INDIA.

[4]Assistant Professor, Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmcy, Bela, Punjab, INDIA.

[5]Research Scholar, Department of Pharmacology, Dev Bhoomi Institute of Pharmacy and Research, Dehradun-248007, Uttarakhand, INDIA.

[6]Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun -248007, Uttarakhand, INDIA.

[7]IIMT College of Pharmacy, Knowledge Park III, Greater Noida, Uttar Pradesh 201310, INDIA.

[8]Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun -248007, Uttarakhand, INDIA.

[4]Corresponding Author: devinderkumar1994.dk@gmail.com

www.jrasb.com || Vol. 1 No. 3 (2022): August Issue

Received: 13-07-2022	**Revised:** 03-08-2022	**Accepted:** 13-08-2022

ABSTRACT

These days, finding new marketing authorizations, guaranteeing regulatory compliance, and keeping labour costs competitive are extremely tough. Many pharmaceutical companies also struggle to deal with local regulatory issues and stay up with changes in key pharmaceutical markets. Regulations are thoroughly reviewed before being given to the RA department. This team compiles the most critical prescription information for global approval and marketing. This category accepts both new and revised product submissions. This is mostly handled by the RA department. RA's job is to provide feedback on proposed or disputed legislation. This is a proactive measure. The ICH framework allows for more early intervention. Regulators have a wide range of responsibilities. In the US, the FDA must register and clear the goods with the export company's regulatory professional.

Keywords- FDA, Regulatory Affairs, ICH, Pharmaceutical Companies, New drug Approval (NDA).

I. INTRODUCTION

Its department has the responsibility of acquiring FDA permission for new pharmaceutical items and keeping it so the product could be sold indefinitely. The project plan is the link between the regulatory agency and the project team, ensuring that the regulatory authority's requirements are appropriately predicted. RA is tasked for keeping up with important new laws, rules, and regulations. As a result, regulators expect corporations to interpret rules and recommendations. Staff from the RA help project managers understand and apply the rules. Concerns about guidelines, clinical research, and formulation formulation must be aired with authorities early in the process. [1]Most companies prioritise new initiatives based on a TPP. The RA professional's work determines what data should be on the product's "label." RA is also a member of the project

Journal for Research in Applied Sciences and Biotechnology
www.jrasb.com
ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 166-177
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team can help create the programme. Regulations are meticulously reviewed before being handed to the RA department for review. This team also draughts core prescription information used for global approval and marketing. Filings for new products and modifications to existing items are included. This obligation occupies a large chunk of the RA department's job. The RA's role is to provide input on proposed or debated legislation. [2]This is a proactive action. In the ICH context, there is more chance to influence early in the process. Regulators ensure the safety and efficacy of healthcare products globally. Regulatory professionals include individuals in charge of ensuring regulatory compliance, writing submissions, clinical affairs, and quality assurance. The regulatory professional of an export company must first obtain product registration and clearance from the country's health agency, such as the FDA in the US or the EMA in the EU.[1,2,3]

- Food and cosmetics are among the many products regulated by regulatory specialists.
- The following are examples of pharmaceuticals:
- veterinary goods, in vitro diagnostics, biologics & biotechnology, nutritional products, cosmetics
- Premarket approvals, manufacturing, labelling, and advertising, as well as postmarket surveillance, are all part of the regulatory professional's job description and responsibilities.

Role of regulatory Authority and Company

A regulatory agency is a government-created enforcement organisation tasked with monitoring and implementing workplace health and safety regulations. Establishing and enforcing safety standards is the responsibility of the regulatory authority.

Don't overstep your authority[2,3]

In order to benefit from third-party benefits, one must refrain from accepting them in order to promote the company's performance, exercise independent judgement, and use reasonable care, skill, and diligence.

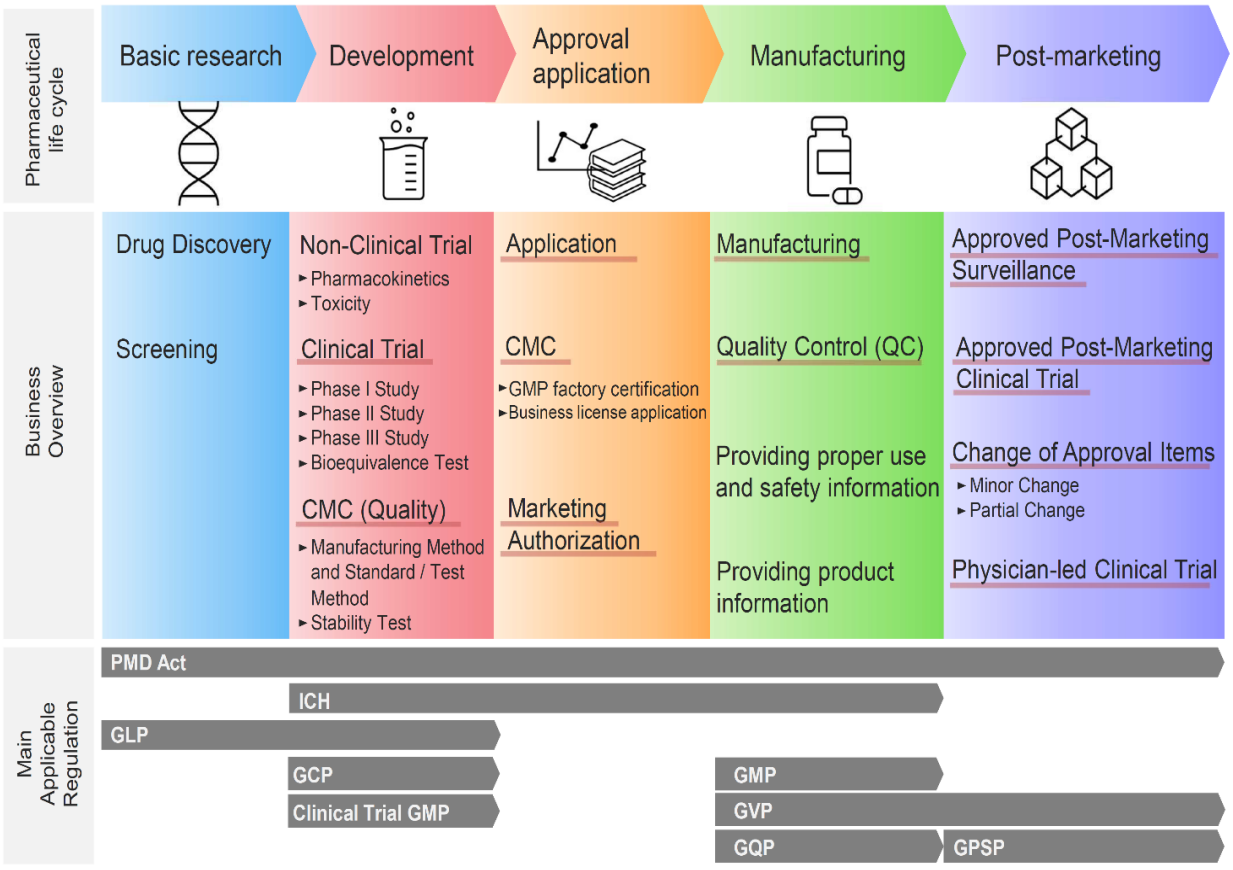

Figure 1: Role of Regulatory Affairs

II. HISTORY

Several tragedies in the 1950s, such as the sulfanilamide elixir, the vaccination disaster, and the thalidomide tragedy, led to a significant increase in the number of laws governing drug quality, safety, and efficacy in the United States. [4,5]More stringent requirements for things like marketing authorizations and GMPs have resulted as a result of this (GMPs). Let's take a look at what transpired in the United States, Europe, and India over the past few days.

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

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USA [4-8]

The first large-scale production of glycerine occurred between 1818 and 1840, when chemical manufacturing factories began to spring up in the early 18th century. Pharmacists and doctors, on the other hand, synthesised medicines in pharmacy laboratories. In response to the vaccination disaster, the Biologics Control Act of 1902 banned the production of all but the most basic of narcotics, such as opium. Biological items, such as serum, vaccine, toxin, and viruses, were to be licenced and labelled with the manufacturer's name, address, licence number, product identity, and expiration date (Figure 2). From the Import Medications Act of 1848 to the Biologics Control Act of 1902, the federal government took steps to prevent food, drugs, medicines, and liquors from being tainted or mislabeled. This statute made it illegal to ship tainted food and pharmaceuticals across state lines. Preservatives such as formaldehyde, copper and borax were prohibited from being used in food and medications under this rule. The 1906 Food and Drugs Act is better known as the Wiley Act, after Dr. Harvey W. Wiley, who coined the name for the law. Alcohol, cocaine, heroin, morphine, and opium were among the substances that had to be labelled under this rule. [6]This was the first comprehensive national food and drug safety law (Figure 3). As a result of the Federal Food and Drugs Act of 1906, the Food and Drug Administration (FDA) was eventually established (FDA). In 1927, the Bureau of Chemistry was reformed into the Bureau of Chemistry and Soils and Food, Drug, and Insecticide Administration, which was originally employed to control food safety. After a reorganisation, the present Food and Drug Administration (FDA) was established in 1930. FDA commemorates 1906 as the year it was founded because that was the year it was founded at its very roots.

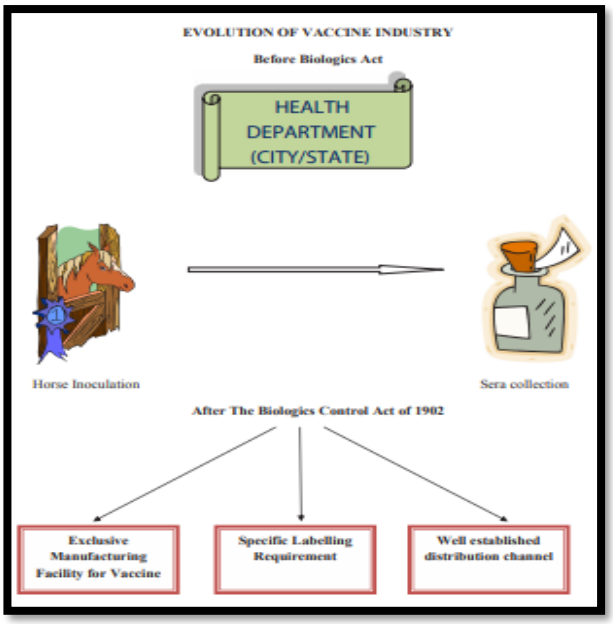

Figure 2: Evaluation of Vaccine Industry

Figure 3: Dr. Harvey W. Wiley (last third from right) with chemistry department staff

EU [5-7]

The fundamental goal of European healthcare regulations is to keep hazardous items off the market. Only a few other factors contributed to the highly regulated and technologically advanced pharmaceutical sector. Then came postwar health insurance. As the cost of pharmaceuticals is shifted from individuals to commercial and governmental health insurance systems, pricing is becoming more transparent. CJD cases began to rise in the UK in the early 1990s. Humans can get bovine spongiform encephalopathy (BSE), also known as "mad cow disease." This illness was suspected to be caused by consuming BSE-infected beef. Based on this incident, legislation relevant to BSE and TSE free use of materials has been implemented.

India [8,9,10]

The Poisons Act 1919 was passed to control cheap drugs. This statute prohibits the sale or possession of poisons. Poisons must be stored safely, labelled and packaged properly, sold in maximum quantities, and examined annually. Dangerous Drugs Act 1930 replaced the Poisons Act. This law regulates opium plant growth, production, ownership, import, export, transshipment, and sale. It repealed the Dangerous Drug Act of 1930 and the Opium Act of 1878. This era saw the enactment of the following laws:

The Drug & Cosmetic Act of 1940 regulates pharmaceutical import, manufacture, distribution, and sale. There are no exceptions to this law.

The Drugs and Cosmetics Act regulates the manufacture of Ayurvedic drugs for sale, not consumption, usage, or possession.

The Pharmacy Act of 1948, last revised in 1986, governs the profession in India.

b) 1960-1970: Global businesses dominated the market, with few Indian producers. India's pharmaceutical industry was just taking off. Lack of patent protection reduced emphasis on pure R&D. Prices were high and supply were low due to the market's reliance on imports.

b) 1970-1980: The government took over drug regulation and issued few laws and rules.

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The Indian Patent Act of 1970 established the country's patent system. Based on this, only Drug substance manufacturing procedure and method could be patentable. This act prohibited product patents. It came into force on April 20, 1972. This new law replaced the 1911 Indian Patents and Designs Act and took effect immediately.

The Drug Prices Control Order (DPCO) was designed to keep drug costs low. Local businesses have began using reverse engineering to make things and pharmaceuticals since the Indian Patent Act 1970 authorised product patents. The lower cost of these new treatments made several cheaper and more easily available alternatives to the high-priced imported new pharmaceuticals. This increased exports to countries including Russia, Africa, China, and South America. 2) Non-patent export of bulk drugs.

From 1980 to 1990, industry invested in developing API techniques and manufacturing facilities. The government has also aided exports. The Narcotic Drugs and Psychotropic Chemicals Act of 1985 regulates narcotic drugs and substances.

Between 1990 and 2000, the local pharmaceutical market grew substantially, as did globalisation. Businesses have begun their own study. After joining the Paris Cooperation Treaty in 1999, India adopted product patents on January 1, 2005. (PCT). f) 2000-2010: The period of Innovation and Research. During these years, innovative research, patenting of pharmaceutical formula, procedure, indication, and enterprise mergers began.

• Patent Amendment Act 2005: This act provides that if a patent application is filed before January 1, 2005, the manufacturer can market the product after that date without infringing the patent, if the manufacturer has made significant investment in manufacturing the product before January 1, 2000.

ICH guidelines are divided into four categories [11-14]

a. Q1-Q14 Quality Guideline A more flexible approach to pharmacological quality is based on Quality System Practice (GMP) risk management.

b. Concerns about carcinogenicity, genotoxicity, and reprotoxicity have been documented in the ICH safety guidelines (S1-S12). The most prevalent reason for drug discontinuation is QT interval prolongation.[12]

c. Efficacy E1-E20 Efficacy work is involved with the design, conduct, safety, and reporting of clinical research. It also includes new drugs developed by biotechnological methods and more focused therapies using pharmacogenetics/genomics.

d. Guideline M1-M13 Those are the topics that cross over into Quality, Safety, and Efficacy. That is, the ICH medical language, the Common Technical Document, and the creation of Electronic Standards for Regulatory Information Transfer (ESTRI) (ESTRI).

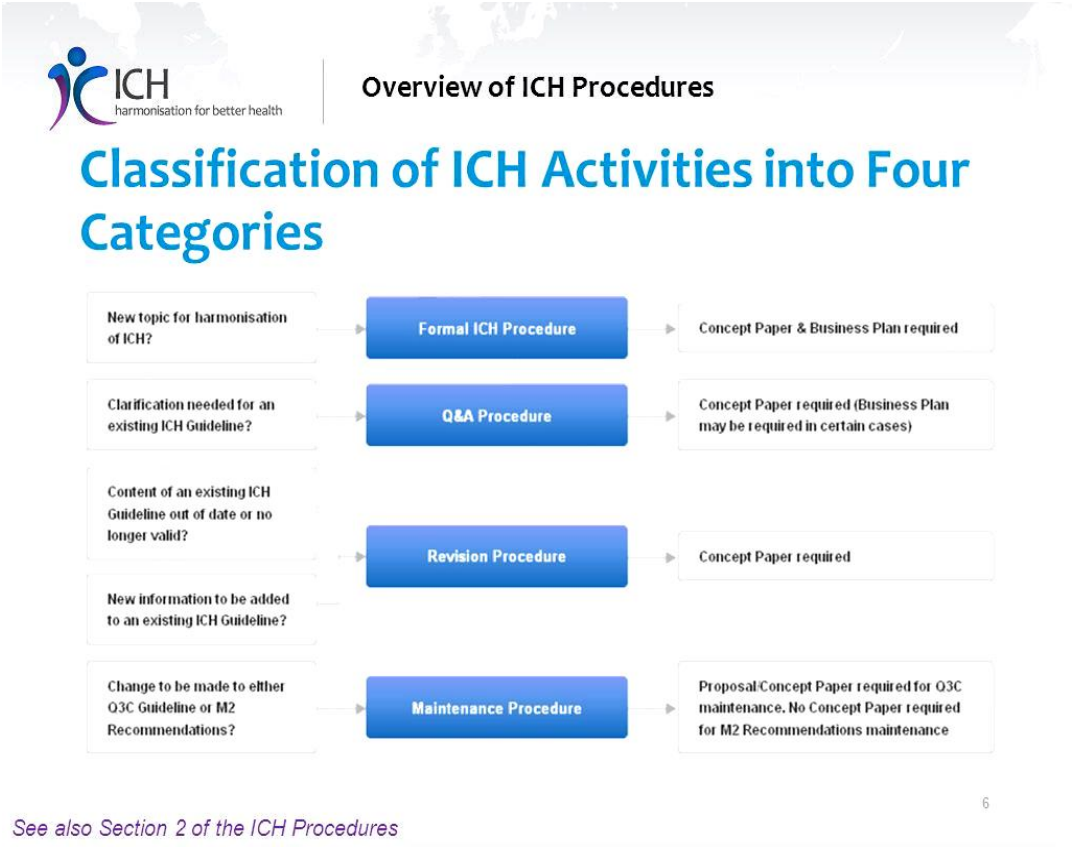

Figure: 4 Classification of ICH activities into Four Categories

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

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Drug Appproval Process [16,17]

A drug's FDA approval means that the drug's advantages outweigh its known and potential dangers for the targeted demographic. The drug approval process follows a framework that includes:

• Reviewers examine the risks and benefits of the drug against the current treatment landscape and the target condition. For example, while the hazards of a non-life-threatening sickness are undesirable, they may be tolerable for a life-threatening condition

• Clinical data benefit and risk assessment: FDA reviewers assess clinical data benefit and risk, taking into account any uncertainties that may arise from defective or incomplete data. To ensure that a first trial's results are not due to chance or prejudice, the FDA normally requires two properly conducted clinical trials. In some cases, especially when the disease is rare and multiple studies are not feasible, one clinical trial's findings may be sufficient. The evidence that the drug will help the target group should outweigh the hazards

Any drug has some level of danger. An FDA-approved drug label discusses the benefits and risks of a drug, as well as how to detect and manage risks. Hazard mitigation requires extra effort at times. As a result, a drug maker may need to develop a Risk Management and Mitigation Strategy (REMS) (REMS).

However, the FDA's risk-benefit studies and [18]findings are not always clear-cut. The FDA review committee may come to different conclusions than the medicine developer after analysing the same data. As a science-led agency, FDA uses the best available research and technology to make judgments.

Quicker Authorization

In some cases, a new drug's approval is rushed. Accelerated Approval is available for new medications that cure serious or life-threatening illnesses and outperform conventional therapies. This strategy enables for the approval of drugs that show a therapeutic benefit on a "surrogate endpoint" that occurs earlier but is not as robust as the regular endpoint used for approval. This approval approach is especially useful when a medicine's effects must be investigated over a longer period of time. Post-market clinical trials are required to validate and describe the drug's benefit.

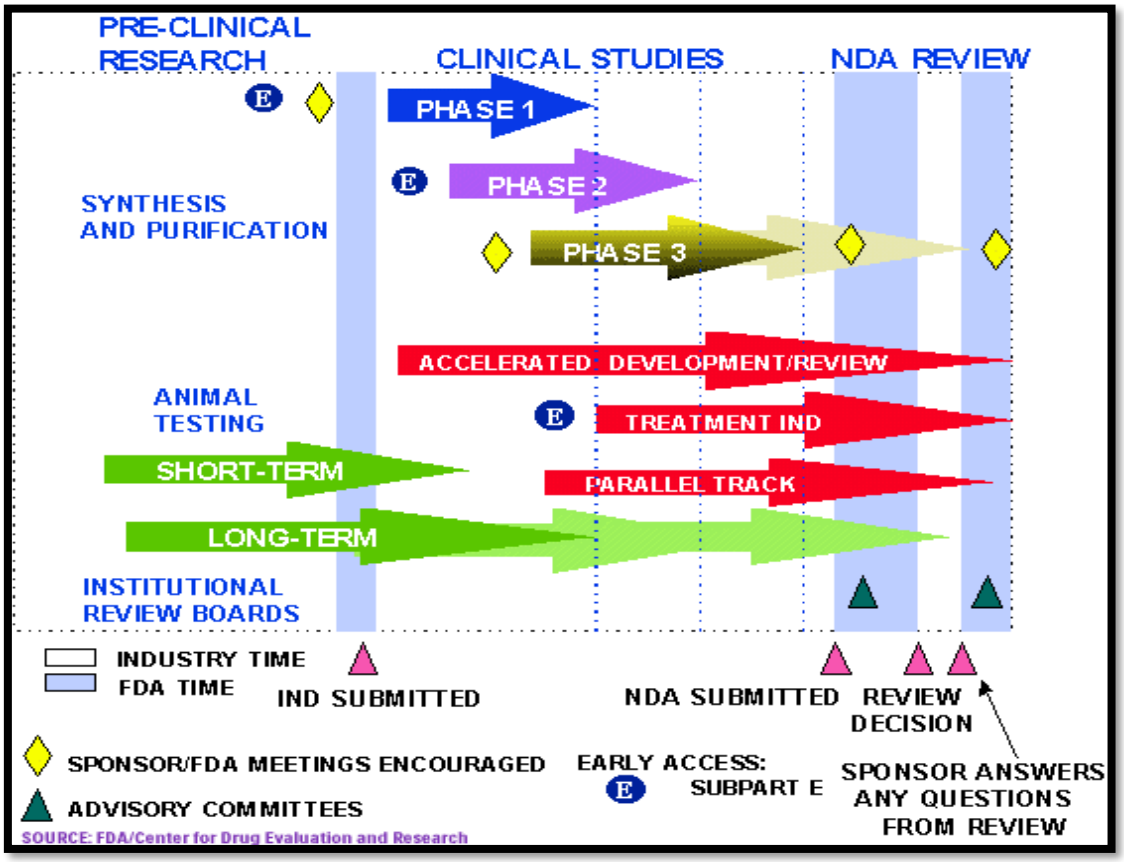

Figure 5: Drug Appproval Process

Since its beginning in 1992, the Rapid Approval process has authorised numerous life-saving therapies that have significantly influenced disease progression. Examples include various antiretroviral drugs that were quickly approved and later changed the therapeutic paradigm. This approach has also helped bring a number of cancer-fighting drugs to market.

Guidance For New Drug Application [19,20,21,22]

The EPA's guideline materials reflect current thinking on a topic. These resources were prepared for

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

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FDA review staff and can be used by applicants and sponsors for application processing, content, evaluation/approval, and design, development, manufacturing, and testing of regulated products. [20]They also set policies and procedures for inspection and enforcement of the Agency's regulations. Because they are neither regulations nor laws, they cannot be enforced administratively or judicially. Alternative strategies are legal if they meet the necessary statutory and regulatory standards.

The New Drug Application has supervised and controlled new medications in the US for decades (NDA). Before any new medicine may be sold in the US, it must be approved by the FDA. The NDA application is how pharmaceutical companies ask the FDA to approve a new drug for sale in the US. The NDA includes data from animal and human clinical trials for an Investigational New Drug (IND). [22]

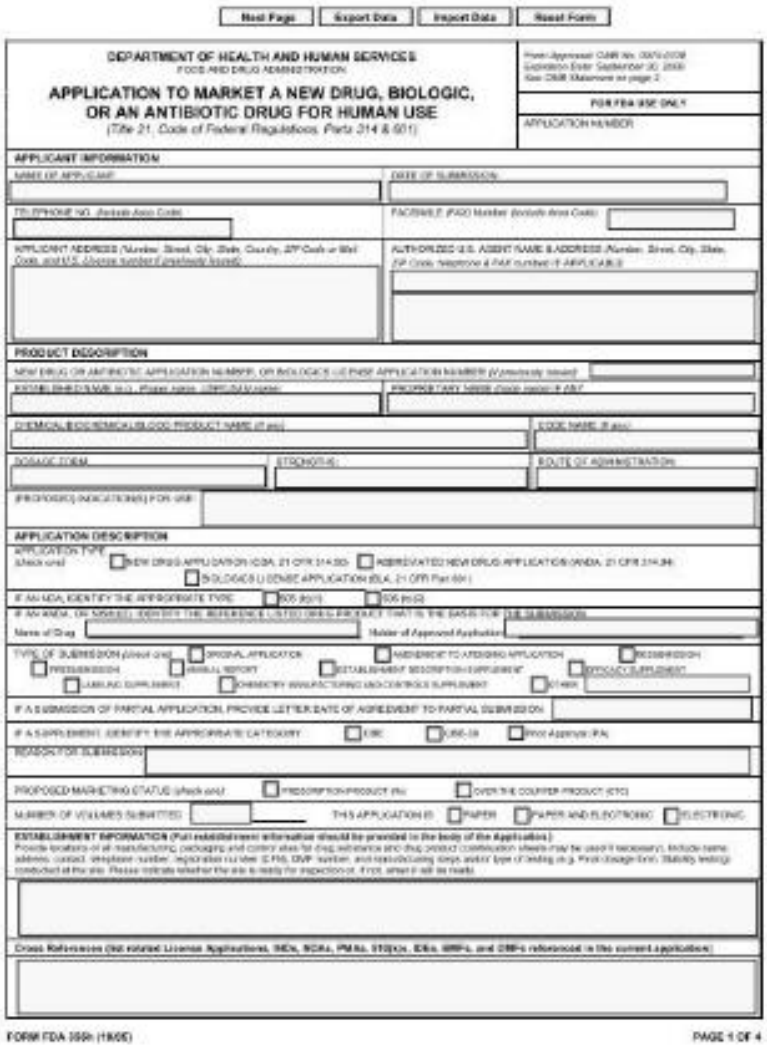
• Whether the medicine is safe and effective for the suggested use(s) and whether the benefits of the treatment outweigh the risks.

Concerns about the drug's intended labelling (package insert).

A drug's identity, strength, quality, and purity must be maintained by manufacturing processes and quality controls.

An NDA is expected to include all aspects of a drug's life cycle, from development and testing to human and animal studies to packaging and distribution.

India's drug policy is overseen by both the central and state governments. It is the responsibility of CDSCO to approve new drugs, conduct clinical trials in the country, set standards for drugs, monitor the quality of imported drugs, coordinate the activities of state drug control organisations, and provide expert advice to ensure uniformity in the enforcement of the Drugs and Cosmetics Act. This essay will describe the New Drug Approval Process in India.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

PRODUCT DESCRIPTION

APPLICATION DESCRIPTION

ESTABLISHMENT INFORMATION

FORM FDA 356h (10/05)

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Figure 6: Application form for new drug Process in Market

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

https://doi.org/10.55544/jrasb.1.3.22

On March 19, 2019, India issued G.S.R. 227 (E) which covers all new pharmaceuticals, experimental innovative medications for human use, [24]clinical trials, bioequivalence studies, bioavailability research, and Ethics Committee. These rules are called the New Medicines and Clinical Trial Rules, 2019.

Examining the Indian legal definitions of "Drug" and "Novel Drug" can help us better understand the clearance period for new pharmaceuticals.

Figure: 7 drug License Online Process

The Drugs act Act of 1940, section 3(a) defines this medication as:[23-25]

1. All drugs for internal or external use in humans or animals, including formulations used to the skin to repel insects like mosquitoes;

2. The Central Government may prescribe items (other than food) to exterminate rodents or insects that bring disease to humans or animals. These are ii substances.

3. empty gelatin capsules, which are designed to be used in medication;

4. equipment designed for internal or external use in diagnosing, treating, mitigating or preventing sickness or disorder in humans or animals, as determined by the Central Government in consultation with the Board.

Rule 2 (w) of the 2019 New Drugs and Clinical Trial Rules states:

1. One that has not been utilised in the country in any substantial way except as provided by law and rules made thereunder, and has not been approved by the Central Licensing Authority as safe and effective with respect to its claims.
2. A medicine's indication, method of administration, dosage, and dosage form must be approved by the Central Licensing Authority before it may be sold (ii).
3. Indication, route of administration, dosage, and dosage form are all proposed to be changed in a fixed dose combination of two or more medications authorised separately for specified claims and proposed to be combined for the first time.
4. This includes any medicine approved by the CLA in modified or sustained release form, or in a novel drug delivery technology.
5. living modified organism (LMO), monoclonal antibody, stem cell derived product, gene therapy product or xenografts
6. Except for pharmaceuticals listed in subclauses (iv) and (v), the Central Licensing Authority must consider new drugs for four years after they are licenced (v).

If the proposed drug substance or drug product falls under the New Drug definition, the firm must follow multiple regulatory procedures. Major elements affecting regulatory processes include:[26]

1. The type of drug substance or medicinal product is a significant aspect in determining the approval process. Novel drugs are defined as those that are made from recombinant Deoxyribonucleic Acid (r-DNA), live modified organisms (LMO), monoclonal antibodies, stem cell derived products, gene therapy products or xenografts. As a result, any manufacturer wishing to market any of these drugs must conduct extensive non-clinical and clinical studies to demonstrate their safety and efficacy.
2. The type of formulation factors in influencing the approval process. Modified or sustained release

ISSN: 2583-4053

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https://doi.org/10.55544/jrasb.1.3.22

medication forms or unique drug delivery technologies licenced by the Central Licensing Authority are always considered new drugs. So, before applying for a Marketing Authorization, every company must complete clinical trials and/or BA-BE investigations.

3. Drugs already approved in the US: The New Drugs and Clinical Trial Rules, 2019 provide that a drug is considered new for four years after the Central Licensing Authority approves it. During this time frame, a producer who desires to create a novel medicine for sale and distribution must also file a CT-21. This category will be studied closely as a model for new drug approval.
4. IND: INDs involve extensive research and testing, both clinical and non-clinical. Phase I clinical trials are followed by Phase II and Phase III. On the basis of these data, regulatory bodies will decide whether or not to grant a Marketing Authorization.
5. Orphan Medications: Different standards can be relaxed for orphan drugs, but the Central Licensing Authority must approve. In such cases, a pre-submission meeting with CDSCO officials is advised to discuss and agree on the pathway.
6. New compounds, combinations, dosage forms, indications, dose, and delivery methods Before applying for a Marketing Authorization, a company must complete clinical trials and/or BA-BE investigations.
7. Notably, the dossier requirements include CMC, non-clinical, clinical, and administrative information.
8. As an example, let us imagine a drug that has been approved in India as a new drug but is still regarded a new drug because the Central Licensing Authority has not awarded it a four-year extension

Let's imagine a corporation wants to create a new drug that has just been approved by the Central Licensing Authority and hasn't been produced in four years. The path is as follows:

1. Apply for CT-11 or CT-14: A-B-E, or testing, analysing, and evaluating, is allowed under CT-11 and CT-14. CT-11/CT-14 The API approval status distinguishes CT-11 and CT-14. If API is obtained from a permitted source, permission is sought on CT-11; if obtained from an unapproved source, permission is sought on CT-14. The SUGAM portal is used to apply for CT-11 and CT-14.
2. To get Form 29 from the State Licensing Authority, the manufacturer must first obtain CT-11 or CT-14, if appropriate. Form 29 allows the creation of medications for research, testing, or analysis.
3. Making trial batches and collecting data: After receiving Form 29, a producer purchases API and other materials and makes trial batches. The Second Schedule of New Drugs and Clinical Trial Rules, 2019 requires all CMC data to be generated.
4. After that, a contract is formed with a Clinical Research Organization to conduct BA-BE studies for the company. Assembling and sending the BA-BE research protocol and its associated paperwork to the product manufacturer
5. CT-21 application: A corporation applies online to CDSCO. The Sixth Schedule of New Drugs and Clinical Trial Rules, 2019 requires all required information to be uploaded along with the application fee.
6. In case the regulatory body finds all the documentation sufficient, they may award CT-07 (permission to conduct BA-BE research on new medicine). Any queries must be resolved prior to granting CT-07. CRO can start BA-BE study after receiving NOC.
7. Tested by the Indian Pharmacopoeia Commission in Ghaziabad. This is followed by a letter from the regulatory authorities requiring the producer get an analysis at the Indian Pharmacopoeia Commission in Ghaziabad. The manufacturer must then send the medicine sample for testing.
8. Upload additional data: After receiving the BA-BE research report and sample testing report, the manufacturer must upload them to the CDSCO portal
9. After data assessment, CT-23 is issued. So long as the regulatory authority is satisfied with the findings, it may grant CT-23 a licence to manufacture pharmaceutical formulations of novel drugs for sale or distribution.
10. SLA licence: After receiving CT-23, the drug maker must apply for a product permit on Form 25 or 28 from the State Licensing Authority.

Future Prospective Drug Regulatory

The pharma sector is shifting rapidly. The pharmaceutical sector is plagued by cost pressures and employee discontent. Recent trends show that obtaining new marketing authorizations, maintaining regulatory compliance, and assuring competitive personnel costs are becoming increasingly difficult. In addition, many pharmaceutical companies see the inability to handle local regulatory issues and monitor regulatory changes in important pharmaceutical markets as a substantial hindrance. Due to tighter market and trading conditions in the pharmaceutical business, more pharmaceutical and biotech decision-makers are considering outsourcing regulatory affairs services. This article explains why regulatory outsourcing is worthwhile, what duties are commonly considered for outsourcing, and what the future holds for RA outsourcing. The outsourcing of regulatory affairs services is already increasing proportionally, but a significant and sharper expansion of this set of services is anticipated in the future. This service's growth pattern parallels the growing need for clinical research outsourcing. Pharmaceutical companies would likely choose flexible collaboration and knowledge, which only regulatory affairs professionals can deliver. A completely standardised regional or worldwide level outsourcing will enable pharmaceutical businesses centralise regulatory affairs operations. The regulatory affairs service delivery model would be restructured to ensure worldwide coverage and uniform governance.

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 166-177

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III. CONCLUSION

In this post, we'll look at the benefits of regulatory outsourcing, as well as some of the tasks that are frequently outsourced. Regulatory affairs outsourcing is already on the rise, but this service offering is expected to grow significantly and rapidly in the near future. As the demand for clinical research outsourcing grows, so does this service. Regulatory affairs specialists are likely to be preferred by pharmaceutical businesses because of their ability to provide flexible collaboration and knowledge. Pharmaceutical companies can streamline their regulatory affairs operations by utilising a regional or global outsourcing model that is fully harmonised. Regulator affairs service delivery model would be changed to guarantee global coverage and consistent governance.

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