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Principles of Drug Discovery and Development

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Abstract. *Finding new treatments is a drawn-out, intricate process that draws on a variety of scientific fields and methods. There are two separate stages to this process. Target selection and the identification of possible lead compounds by high throughput screening and/or in silico screening techniques are included in the discovery phase. Ultimately, lead optimization yields a clinical candidate. The goal of the second phase, which is also known as the development phase, is to ascertain whether a candidate molecule has any clinical value for patients. Data from clinical trials intended to evaluate a candidate compound's safety and effectiveness are used to support regulatory approval. To introduce the important issues discussed in the remaining portion of the work, this chapter gives an outline of the procedure*
***Keywords**: Drug discovery, NDA, ANDA, SNDA, Post marketing surveillance.*

1. INTRODUCTION

The history of drug discovery is lengthy, going all the way return to dawn of human mankind. In prehistoric days, remedies arise frequently found by accident either as a result of observing nature. They usually, though not always, included components that were taken from plants or animals, and they were utilized for both bodily and spiritual healing. In the early 1900s, modern drug discovery research began to be conducted. These days, the creation of a new medication typically begins with basic research, frequently carried out in academic settings, that identifies a macromolecule (large sized molecule, such as alleles or amino acid), a malfunctioning signal transduction, or a biochemical process that appears accustomed to be connected to a medical condition (pre-discovery stage). Investigational team typically try to find the so-called typically proteins which is connected to the illness state at this point. Researchers must also identify therapeutic drugs that alter the disrupted target's function in order to improve health or lessen symptoms before the target can be designated as a therapeutic target. But identifying the proper target is really difficult. Moreover, medications work specifically on the intended therapeutic target in people in addition to interacting with other, unwanted (and frequently unknown) targets.

The search for therapeutic agents is the next step in the process. After that, possible medications are examined in a variety of non-human model to determine their security and identify bio-active compound. After that, human study can begin to determine the medication's safety and effectiveness in the patients who have the highest benefit-to-risk ratio. Regulatory bodies then receive the studies, evaluate the supporting documentation, and make a determination regarding market approval. The medication can then be administered to patients and put on the market if the review is positive. Following approval, studies keep an eye out for any potential negative effects that the novel medication may have in the road. This final stage, commonly known as a "phase 4" clinical trial, is frequently referred to as drug safety studies. The entire process of finding and developing new drugs takes years, several different disciplines, and a lot of money. It also means the creation and application of enormous volumes of data, which are often collected using various high-throughput technologies. To speed up some phases of the process and learn more, various tests and the assessment of the data can be automated using computer-assisted approaches and reduce mistakes [1].

2. CLINICAL RESEARCH PROCESS

The drug discovery process is in fig 1**.**

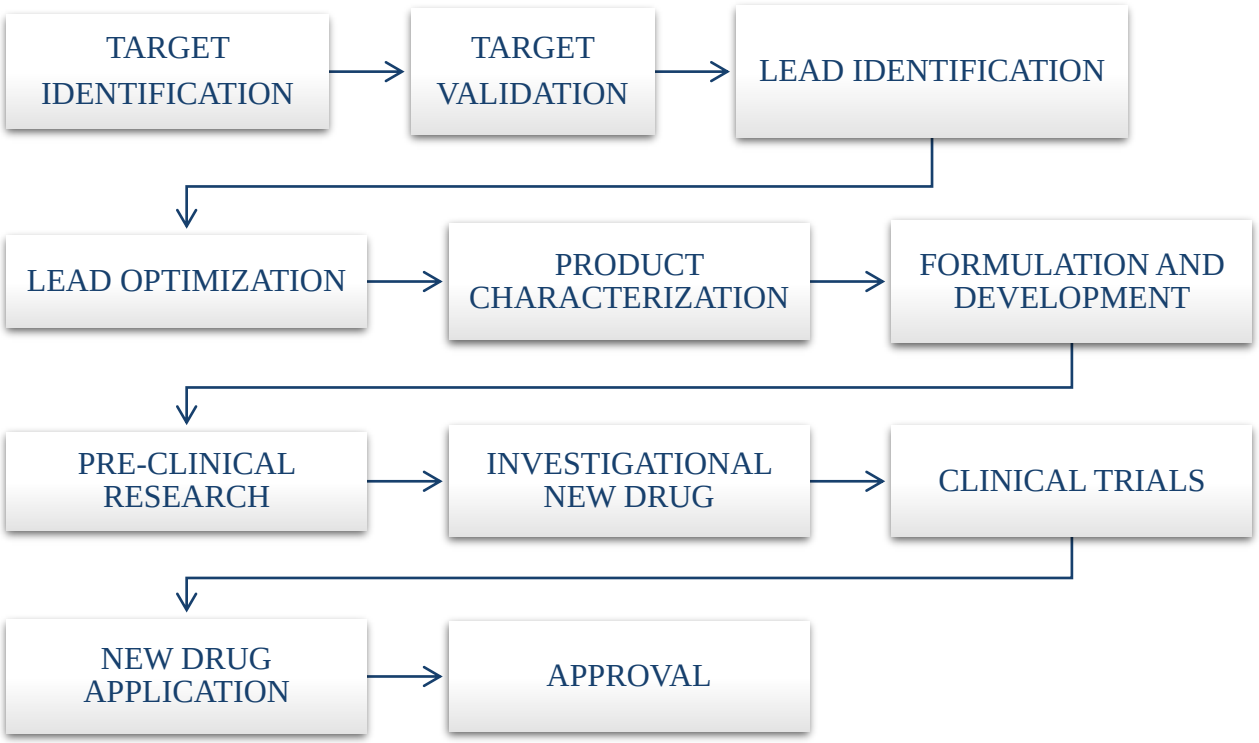

FIGURE 1. Drug discovery process

Target discovery: Isolating a potential therapeutic target's function and contribution to the disease is the first step in target identification (gene, nucleic acid, protein). Following target identification, the molecular pathways connected to the target are analyzed. An optimal objective should be safe, effective, and satisfy commercial and clinical needs [2].

Target validation: The process of certifying the intended biological target, such as nucleic acid, is known as target verification. Finding the structural activity relationship (SAR) of the small molecule's analogs is one method of target validation.

Lead identification: A synthetically stable, practicable, drug-like molecule that exhibits appropriate particularity, compatibility, and exclusivity for the target binding site in primary and secondary testing is referred to as a chemical lead. This calls for defining the structure-activity link, assessing the viability of the synthetic process, obtaining preliminary data on in vivo effectiveness, and engaging the target.

Lead optimization: The process of creating a treatment candidate following the identification of a lead chemical is known as lead optimization. To give an indication of how carbon framework and activity are connected to target interrelations and metabolic processes, a prospective medication must undergo an iterative synthesis and characterization procedure.

Manufactured product's characterization: A unique drug molecule is identified by its dimension, form, durability, frailty, usage, toxic potential, and biological response when it has promise therapeutic action. Characterizing the compound's mode of action is aided by early pharmacological research phases.

Composition and advancement: The physicochemical properties of active pharmaceutical ingredients (APIs) are ascertained during the pharmaceutical formulation stage of drug development in order to generate a bioavailable, stable, and ideal dosage form for a certain administration technique.

Pre-clinical testing: In the pre-clinical stage of the drug development process, the safety and effectiveness of the drug are assessed in animal models with the aim of predicting human outcomes. The pre-clinical studies also need

to be approved by the relevant regulatory agencies. Regulatory agencies will only approve drugs that have been shown to be both safe and effective, also have an ethical and safe trialing process to guarantee. An essential set of technical requirements for appropriate preclinical drug development has been defined by ICH. Pre-clinical experiments can be carried out using either general pharmacology or toxicology methods.

Investigational new drug application [3]:

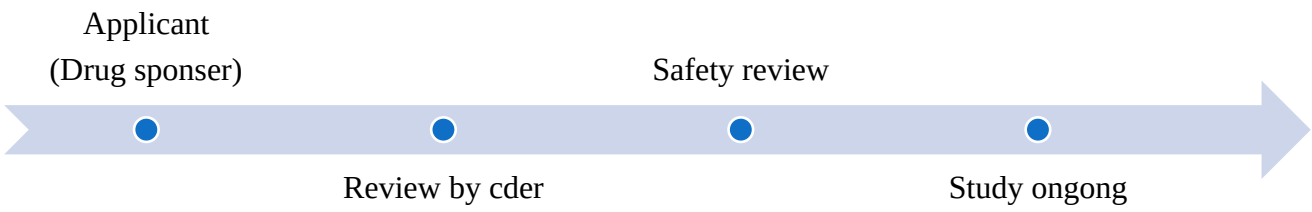

FIGURE 2. Investigational new drug application process

New drug application:

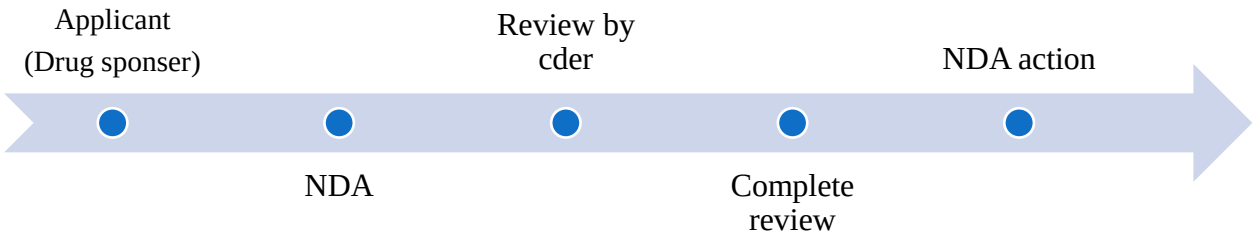

FIGURE 3. New Drug Application Process

New drug approval:
To launch a new drug in Indian market any person / organization need to get authorization from national drug regulatory agency of India (CDSCO) [4].

3. DEVELOPMENT OF INFORMATION CONTENT FOR IND

A sponsor developing a new drug must apply for an Investigational New Drug exemption from the FDA to ship the drug across state lines for clinical trials. This is required to verify that the drug is safe for early human trials and may offer therapeutic benefits. The FDA oversees this process to protect human subjects in early-stage clinical studies.

There are three Types of INDs:

- **Investigator IND:** Submitted by a physician who conducts the study
- **Emergency Use IND:** For urgent situations needing immediate experimental drug use
- **Treatment IND:** For experimental drugs showing promise in treating serious conditions.

There are two IND Categories:

- **Commercial:** For drugs intended for market.
- **Research (Non-commercial):** For academic or exploratory studies [5].

The IND application must cover:

- **Animal studies:** Effects and toxicity in animals.
- **Manufacturing:** Production and quality details.
- **Clinical protocols:** Trial plans and testing information.

Guidance documents for INDs:

CGMP for Phase 1 Investigational Drugs: Recommendations for applying CGMP standards to early-phase clinical trials.

Exploratory IND Studies: Guidance on conducting early-stage studies to explore drug safety and efficacy. Content and Format of INDs for Phase 1 Studies: Instructions on the information and structure required for IND submissions for Phase 1 studies of new drugs.

Bioavailability and Bioequivalence Studies: General considerations for studies assessing how drugs are absorbed and work in the body.

IND Exemption for Cancer Studies: Guidelines for using lawfully marketed drugs for cancer treatment under IND exemption.

Drug Master File (DMF): Provides confidential details about drug manufacturing and processing to the FDA.

Immunotoxicology Evaluation: Recommendations on assessing the impact of drugs on the immune system during toxicology studies.

IND Development Process [6]**:**

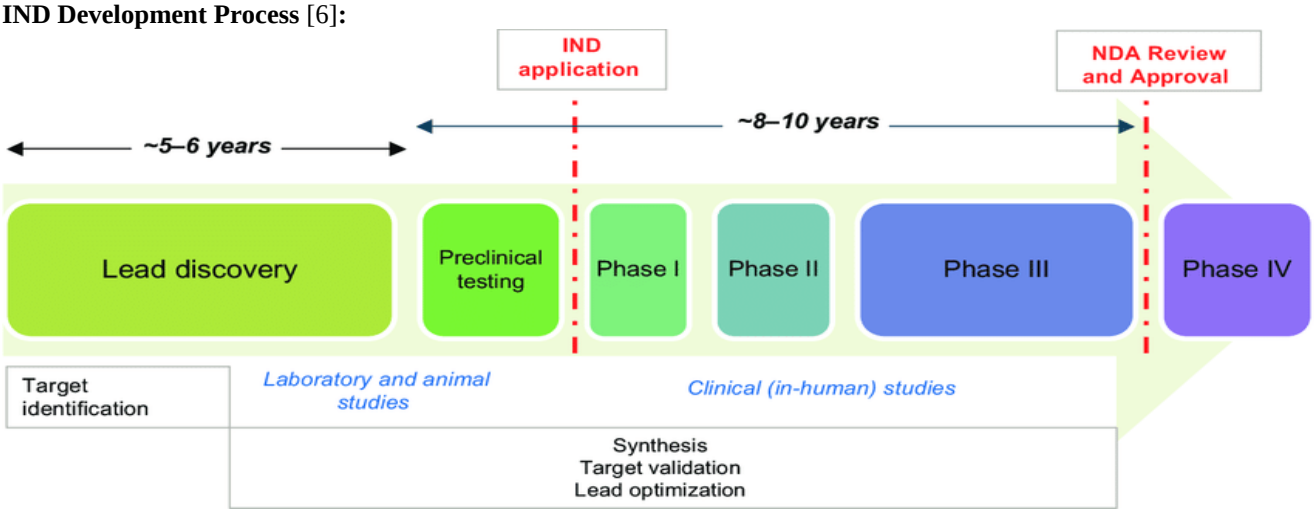

FIGURE 4. Clinical process

Preclinical Research: Comprehensive laboratory and animal research is conducted to get preliminary evidence on the safety and biological activity of the medicine before submitting an IND application [7].

IND Application: The sponsor submits an IND application, together with preclinical study data, drug formulation and production details, and a clinical trial schedule, to the regulatory body (the FDA in the U.S., for example).

FDA Review: The regulatory agency reviews the IND application to assess whether the proposed clinical trials are safe to proceed. This review typically includes an evaluation of the drug's preclinical data, the trial design, and the safety monitoring plan [8].

Clinical Trials: Upon approval of the IND, clinical trials are conducted in stages:

- **Phase 1:** In a small sample of healthy volunteers or patients, safety, dose, and pharmacokinetics are tested.
- **Phase 2:** Assesses safety and adverse effects on a broader patient population.
- **Phase 3:** Monitors side effects in a sizable patient population and verifies efficacy.

Post Market Surveillance [9]**:** After successful clinical trials and regulatory approval, the drug is marketed, and its safety is continually monitored through post-marketing surveillance and reporting of adverse effects.

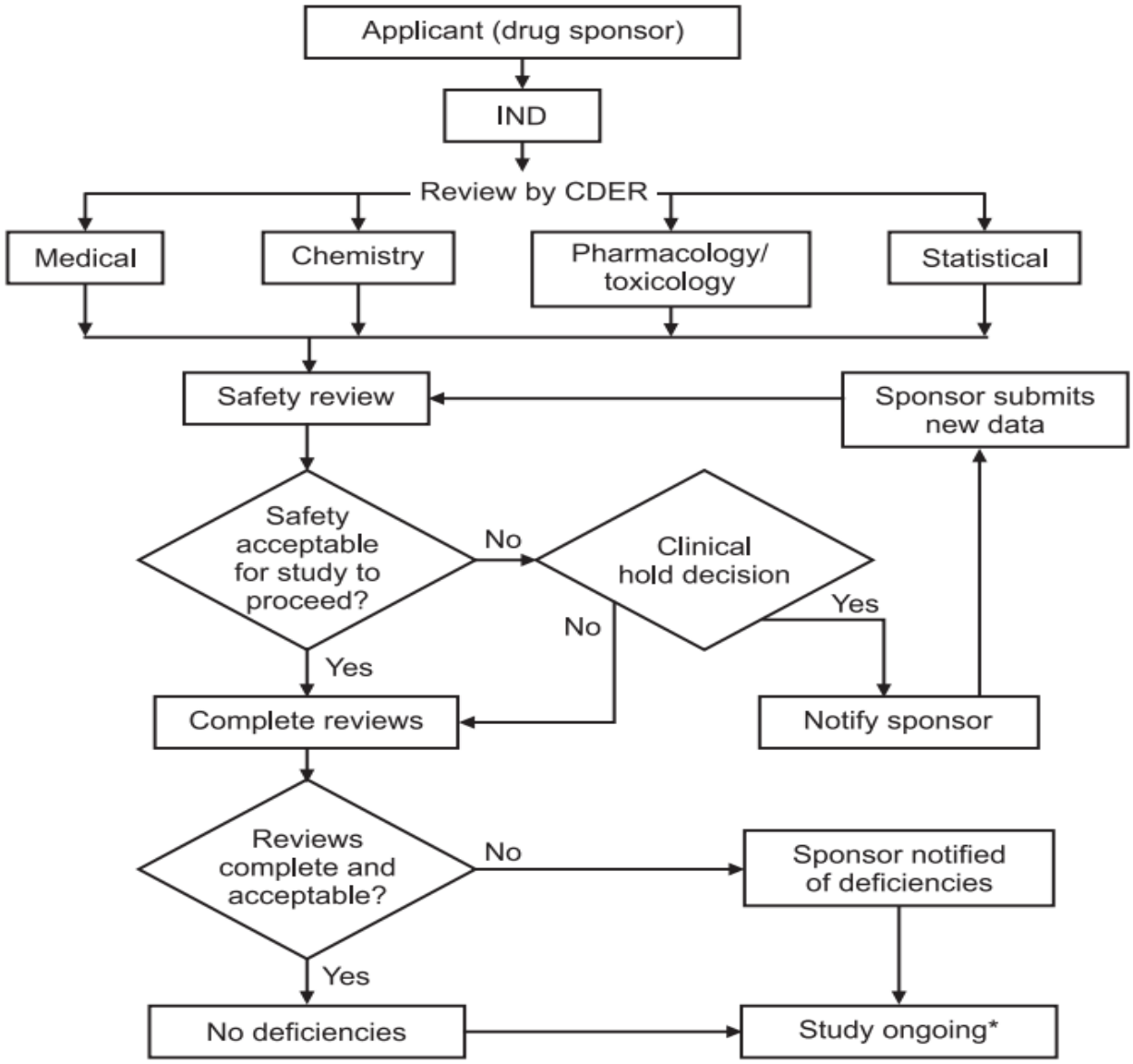

FIGURE 5. Schematic Presentation of Investigational new drug application process

4. NEW DRUG APPLICATION

Pharmaceutical companies formally request FDA approval for a new medication to be sold and marketed in the United States by submitting an NDA application. Data from animal studies and clinical trials conducted during the Investigational New Drug (IND) phase are included in the NDA. The main goals of NDAs are to evaluate the drug's quality, safety, efficacy, and labeling.

The goal of the NDA is to supply FDA reviewers with adequate information to make important decisions, including:

- Evaluating whether the medication is safe and successful for its planned purposes and whether its advantages justify any potential risks.
- Assessing whether the drug's suggested labeling (package insert) and its content are suitable.
- Maintaining the drug's identity, potency, integrity, and cleanliness in accordance with the manufacturing procedures and quality control methods employed [10].

The application process for marketing a novel medication, biologic, or antibiotic for use in humans is governed by Form FDA-356h.

An NDA's contents and format [11]:

NDA Contents and Structure: As stated in this section, New Drug Applications (NDAs) and their supplements must follow the prescribed format, which includes all pertinent information specific to the given submission. Each

NDA must be signed in triplicate: one for filing, one for archival purposes, and one for review. The review copy is organized into five or six sections of technical and scientific data, as well as the cover letter, application form, overall summary, index, and individual review sections. The archival copy acts as a reference and contains material that is not included in the review copy. An application form, an index, a summary, five or six technical sections, drug samples, case report forms, patient data tabulations, and labeling—which may contain any required Medication Guides listed in part 208 of this chapter—are usually included in a novel chemical entity's NDA.

Code of Federal Regulations (CFR):
The CFR consists 50 titles covering various categories regulated by federal laws. All food and drug regulations are located in section 2, and the FDA interprets the Federal Food, Drug, and Cosmetic Act and associated acts within their portion of Code of Federal Regulation. 21 CFR-Part-314 contains the applications for FDA approval of new medicines and antibiotics. The documents, which offer guidelines on the processing, content, evaluation, and approval of applications, are meant for FDA review personnel as well as applicants and sponsors. The NDA paperwork must comprehensively cover the drug's entire development history, including details from clinical trials, ingredient composition, animal research outcomes, The way the medication works, as well as how it's made, processed, and packaged. The FDA's Center for Drug Evaluation and Research (CDER) published rules in 1997 that let sponsors electronically submit NDAs using the Common Technical Document, which is made up of five modules. Additionally, there are three types of FDA approval processes: Fast Track approval, Accelerated approval, and Priority Review for NDAs [12].

5. ABBREVIATED NEW DRUG APPLICATION (ANDA):

In order for a generic medicine to be approved, it is necessary to submit a new drug application (ANDA) to the Food and Drug Administration (FDA) in the United States. The following are important details to be aware of regarding ANDA.

1. GOAL: Manufacturers are able to market a generic drug that is identical to a previously approved brand-name drug in terms of dosage form, strength, method of administration, quality, performance characteristics, and intended use through the ANDA system.
2. BIO-EQUIVALENCE: To gain approval for a generic medication,

Those seeking approval must show that their product is as effective as the original drug. This suggests that the amount of active components in the generic drug must enter the patient's bloodstream in the same amount of time as the active ingredients in the brand-name drug.

3. Cost and Time Efficiency: ANDAs do not need the submission of clinical (human) and pre-clinical (animal) data to demonstrate safety and efficacy, in contrast to New Drug Applications (NDAs). This significantly reduces the cost and time required for approval.
4. Regulatory Framework: The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments, regulate the procedure. By establishing the bioequivalency standard, these modifications made it possible to approve generic medications without having to conduct expensive clinical trials again [13].
5. Submission Requirements: ANDA submissions need to be made electronically (eCTD) and contain a number of forms and records attesting to the submission's adherence to FDA guidelines [14].

Because the ANDA procedure eliminates the need for redundant clinical trials, generic medication approvals can happen more quickly and at a lower cost. The applicant must prove scientifically that their generic medication is bioequivalent to the reference listed drug (RLD) rather than starting additional clinical trials. This implies that the generic medication needs to enter a patient's bloodstream with the same quantity of active components in the same length of time as the brand name medication.

6. SUPPLEMENTAL NEW DRUG APPLICATION

A supplemental new drug application is submitted to make modifications to a product for which an authorized new drug application has previously been filed, according to regulatory perspectives. Supplemental new drug applications are those that are presented for an already authorized New Drug Application (NDA) and pertain to any modifications to the packaging, labeling, doses, ingredients, or additional indications. It goes by the acronym SNDA. To guarantee that the product still satisfies the initial requirements, CDER must approve any significant NDA modifications (such as those involving ingredients or packaging). What's important Pharmaceutical businesses can enhance the usefulness of their products, keep them current with new scientific discoveries, and make the required modifications in response to changing patient requirements and medical expertise through the supplemental new drug application (SNDA) procedure. Therefore, it is essential to ensuring that medicines that

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Examples of such modifications include: • Increasing the medicine's approved indications (additional uses). • Changing the suggested dosage or method of administration. • Including fresh safety or efficacy information that wasn't in the first NDA. • Changing the medication's label. [15] For instance, to reinforce confirmation that the medication will have the character, strength, quality, and immaculateness that it professes to have, the support might try to add another determination or test strategy or make changes to the office, methods, or controls. The sponsor may decide to eliminate a regulatory analytical method, develop a brand-new regulatory analytical method, or relax the specifications' restrictions for a drug substance and/or drug product. Furthermore, the support might need to broaden the termination date of the medication item founded on information got under a new or on the other hand amended solidness testing convention that has not been endorsed in the application or to lay out another strategy for going back over a group of the medication item that neglects to meet the requirements. It ought to be noted, notwithstanding, that in an SNDA, the support is expected to portray the change completely in each condition laid out in a supported application beyond the already existing variation in the application [16].
Process of Submission The cycle for presenting a SNDA by and large includes: Meetings before submission: The company may meet with the FDA to talk about the changes it wants to make and get advice. Preparation of the Application: The business creates a comprehensive document with information about the proposed changes and both clinical and nonclinical data. FDA Review: The FDA looks over the application to make sure that the changes that are being proposed are safe and work. This can include meetings with warning councils, if important. Decision: The FDA will decide whether or not to approve the changes. Whenever endorsed, the progressions will be integrated into the medication's naming and use [17].

7. SUPAC GUIDELINES

The US Food and Drug Administration (FDA), the US Pharmacopoeia (USP), and the American Association of Pharmaceutical Scientists (AAPS) collaborate to create the SUPAC guidelines. The guideline examines manufacturing processes, compositional modifications during scale-up, and post-approval modifications in the pharmaceutical industry. The phrase "scale-up" in pharmaceutical technology refers to the growth in batch size from small to big scale during the transfer of a pharmaceutical product from small scale (research) to the manufacturing scale, along with a rise in simultaneous production outputs. Generally speaking, the process of increasing the batch size is known as "scale-up." This procedure is necessary for a thorough analysis and understanding of the product, which must be produced on a bigger scale.
Scale-up and post-approval changes, or SUPAC, are modifications to the manufacturing process, equipment, composition, and site that are implemented after approval. It is crucial to confirm that the process being used can produce products of the right quality and that there are no changes to the product's chemical or physical characteristics following scale-up. It outlines the three stages of modifications, each of which is tested for bioequivalence, in vitro dissolution, manufacturing and controls, and chemistry[18].

Levels

1. Modifications that are not expected to have a discernible effect on the performance and quality of the formulation
2. Modifications that might significantly affect the performance and quality of the formulation
3. Modifications that could significantly affect the performance and quality of the formulation

Scale-up and Post Approval Changes, or SUPAC for short, are criteria governing modifications made during the post-approval stage of medication manufacture. These rules are applicable in the event that:

1. equipment or manufacturing processes Details.
2. components or composition.
3. production facility.
4. increasing or decreasing the batch size.

8. BULK ACTIVE CHEMICAL POST APPROVAL CHANGES

"The global industry of bulk drug manufacturing directly affects every facet of pharmaceutical development. Industry frequently has to alter its production process for a number of reasons, including those related to the economy, the environment, and other factors. The FDA and business community both understand how critical it is to examine the effects of these changes from a solid scientific foundation. The basic idea behind the current FDA initiative to develop new guidance on Bulk Actives Post Approval Changes may be found in this quote from the introductory remarks in the brochure announcing the "American Association of Pharmaceutical Scientists FDA Workshop on Drug Substance Manufacturing Changes: Global Perspective," held March 25–27, 1997 in Arlington, Virginia [19].

The industry anticipates that the FDA will take into account the following significant ideas that the PhRMA BACPAC II Working Group highlighted when creating the new BACPAC II guidance:

- Determining a filing category based on a rational evaluation of risk might be made simple with the use of a decision-tree technique.
- Site, specification, and process modifications are the three different categories of changes.
- A sufficient estimate of risk necessitates a quality review both before and after the modification.
- A prior approval supplement, or PAS, is necessary for any modification for which a comparable or greater level of quality cannot be guaranteed.
- Current scientific concepts, including validation, allow for an adequate assessment of the impact of changes in analytical procedures.

There is always a chance that altering a pharmacological substance's manufacturing process will have an unfavorable effect on the material's physical characteristics or the kind or quantity of contaminants it contains. It is well accepted that changes made closer to the conclusion of the drug substance production process, as opposed to the beginning, have a higher chance of unfavorable outcomes. Additionally, some types of modifications—such equipment or site modifications—are thought to be less likely than others to have unfavorable effects (like changing the synthetic route).
But figuring out how much danger comes with a certain alteration is not something that can be done easily.

Depending on whether the drug substance synthesis is documented in an application or in one or more master files, one or more entities may be responsible for reporting modifications of the kind outlined in this guideline. Anytime someone who holds the master file makes a BACPAC I adjustment, they have to tell all those who will be impacted as well as record the change in the master file and allow users to access it. To ensure the quality of the pharmaceutical product, the notice must include all necessary information and indicate the source of the advice that was followed in order to make the alteration.

A master file modification is required, for instance, if the owner of the master file makes changes to the site for an intermediate other than the final intermediate. The drug product applicant shall then explain the adjustment in the next year's annual report (i.e., notice). The yearly report to the drug product application or the modification to the master file provide the information needed to support the site update [20].

9. POST-MARKET SURVEILLANCE

A series of actions carried out by manufacturers to gather and assess data from medical products that have been put on the market and determine whether any action is necessary are known as post-market surveillance. In order to make sure that medical devices remain safe and effective and that action is taken if the risk of using the device longer than its useful life justifies the expense, post-market monitoring is an essential tool. Examining post-market surveillance data might also point out areas where the medical device can be improved [21].

History:
Serious medication responses were seen in many individuals in the 1960s. Phocomelia—limb deformities—are brought on by thalidomide. The optic nerve that was noted in Japan, subacute myelooptic neuropathy damage brought on by clioquinol

- For this reason, the joint commission on prescription

  Drugs Use was founded in 1976 and was mostly supported by the pharmaceutical business, with the obligation to create a post-marketing monitoring system to identify, measure and explain the expected and adverse effects of marketed medications.

Need for Post- Marketing Surveillance:

- The main goal of post-marketing monitoring is to gather data regarding the effects of drugs in normal drug usage situations.
- Because very large clinical trials have limitations, rare adverse events might not be found in prelicensure investigations.
- More patient and data access is possible. Considering the variety of data sources, creative methods of obtaining important information have a lot more potential than relying just on one source.

Types of Post Marketing Surveillance:

1. Spontaneous Reporting Systems

This is the commonly used PV system, which is also known as "voluntary" reporting. Reporters must be informed and driven to document and submit their observations in order for there to be spontaneous reporting.

All practicing healthcare professionals and community members should receive training on how to raise awareness of the reporting culture and the appropriate things to report—such as what, where, when, how, and to whom. The highlighted limits of spontaneous reporting, particularly the underreporting, would be addressed through subsequent training on adopting procedures. As such, precisely estimating the danger associated with a suspected substance is difficult. Furthermore, there is prejudice in the reporting of the cases that are reported. The quality variety of the reported details that were submitted and the missing data are two more constraints [22].

2. Cohort studies

Cohort studies monitor a certain patient population over an extended period of time. There is no blinding or randomization involved in this method's patient group assignment. Cohort studies typically look ahead and track the cohort.

• Patients using the medicine of interest are gathered and monitored as a group.

• A second patient group (the control group) with identical medical conditions Individuals may obtain alternative treatment and who are not taking the medicine however, who otherwise match the cohort as nearly as feasible, maybe studied concurrently as well [23].

3. Active Surveillance

Data from a simulated or real-world environment are actively gathered as part of this research methodology. A more realistic picture of the device's true performance can be obtained through surveys, interviews, patient feedback, and regulatory complaints. In order to gather firsthand input from people who use the product, the EU-MDR Post-Market Clinical Follow-up report, or PMCF, requires end-user survey data. This is an example of active surveillance.

In order to ensure that the outcomes of this technique are pertinent to the requirements of a clinical trial as specified by the Medical Device Regulation (MDR), which went into effect in May 2021, it is crucial to formulate clearly defined research questions. This kind of research offers more detailed information about a device's functioning than passive surveillance, but it is more costly and time-consuming [24].

10. PRODUCT REGISTRATION

Cosmetic Product Registration:

Cosmetic products are classified into 4 major categories:

- Skin products, (i.e, facemasks, fragrance powder, perfumes, shaving cream, face creams)
- Hair and scalp products, (i.e, soaps, conditioners & shampoos, hair colors)
- Nail and cuticle products, (i.e, chemical thinner, nail polish, bleach, hair removal creams)
- Oral hygiene products, (i.e, toothpaste, mouthwash, mouth sprays)

There are two types of cosmetic registration processes:

1. For manufactures
2. For importers.

The new amendment which came into effect on December 15, 2020. In this rule, at first, the term, 'New Cosmetic' was introduced, which means a makeup product that includes a unique component that has never been used before or that no national or international literature has approved for use in cosmetics. These new regulations simplify the procedure for registering cosmetic imports. The duty of periodically issuing the notification has been assigned to the Central Licensing Authority (CLA) and the State Licensing Authority (SLA).

Registration Process

- First, the relevant form will be submitted through the online Sugam portal on CDSCO.
- The necessary documents will be attached & uploaded.
- The declaration for compliance as per D&C Act 1945 will also be submitted.
- Document scrutinization & review will be done by the SLA and CLA.
- In the case of the manufacturer, an inspection will be conducted by the SLA.
- In the case of the importer, the Central Licensing Authority will be directly involved.
- After the inspection, the inspector will submit the audit report to the concerned authority.
- After the authority will review the report, they will grant the license.

11. MDA REGISTRATION

Compared to other countries,India imports medical devices more frequently. Providing a steady market opportunity for global Medical device manufactures under the guidelines, that is IMDR 2017 issued by CDSCO [25].

Process to obtain an MDR CDSCO license [26].

- Through the Ministry of Health's online Sugam portal, the first pertinent form will be submitted.
- Required documents will be attached.
- Declaration for compliance with QMS will be aptly submitted.
- Document scrutinization will be done by the SLA and CLA.
- In the case of Class B devices, an inspection will be conducted by Notified body within 90 days of submission of the application.
- An audit report will be submitted to SLA/ CLA and a grant of the license will be provided after scrutinization of the reports.
- In the case of products under Class C and D, inspection will be conducted by competent officials.

Product registration in USFDA: The US Food and Drug Administration (FDA) requires companies to register their products before selling them in the United States. This registration process ensures that all products meet quality standards [27].

Electronic submission:
All registration and listing information must be submitted electronically, unless a waiver is granted.

Establishment registration:
An establishment registration SPL document must be created and submitted in order to register an establishment. This document should comprise of:

The name of the establishment and its Data Universal Numbering System (DUNS) or Dun and Bradstreet verification number should be included.

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