Regulatory strategy for product development and life cycle management : A Review

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ABSTRACT

More effective drug development and manufacture are required due to the complexity of the pharmaceutical market today. Even in this extremely complicated environment, Product Lifecycle Management (PLM) offers the potential to increase the effectiveness and reduce the risk of pharmaceutical production.[1] From an initial idea to the final retreat, the product lifecycle management develops and oversees a company's product-related intellectual capital. It helps the pharmaceutical sector by extending the life of patents and improving pricing tactics.[2] Among the key applications of product lifecycle management are increased patient compliance, revenue growth, extended clinical benefits, cost advantages, life extension exclusivity, and quicker market launch.[3] Less difficulties, lower costs, higher yields, personnel equipped to make wise decisions, and audits that make everyone more accountable are all advantages that leaders are actively pursuing through the implementation of PLM.[4-6]

Keywords : Product development, Life cycle management, Drug discovery, Regulation bodies, Intellectual property rights

WHAT IS DRUG DISCOVERY PROCESS

The process of discovering new drugs is a lengthy one that can last up to 13 years. Typically, screening for potentially active compounds is the first step in the early drug discovery process. Following their discovery, these substances are tested for safety and efficacy. They must have a therapeutic effect on the intended ailment.

Only 1 out of every 5,000 medications typically reach the level of market approval. In addition, only 250 of the 5,000 to 10,000 therapeutic candidates advance to preclinical testing. We'll address a few frequently asked queries about the drug discovery process below.

The Center for Drug Evaluation and Research (CDER) of the FDA is charged with ensuring that the American people have access to safe and efficient medications. For small businesses and anyone who are unfamiliar with the process of developing and approving new drugs, this section's definitions and interactive charts offer fundamental information.[7-9]

Access to the world's safest and most cutting-edge pharmaceutical system benefits American consumers. In this structure, CDER serves as the primary consumer watchdog. The center's most well-known function is testing new medications before they may be commercialised. In addition to preventing quackery, the center's review gives clinicians and patients the knowledge they need to utilise medications responsibly. CDER makes sure that both brand-name and generic medications are effective and safe.

Before a medication can be tried in individuals, the medication organization or support performs lab and creature tests to find how the medication functions and whether it's probably going to be protected and function admirably in people. Then, a progression of tests in individuals is started to decide if the medication is protected when used to treat a sickness and whether it gives a genuine medical advantage.[10]

There are various stages which includes the process are:[11-12]

- Target Identification

- Target Validation
- Lead Identification
- Lead Optimization
- Product Characterization
- Formulation and Development
- Preclinical Research
- Investigational New Drug
- Clinical Trails
- New Drug Application
- Approval

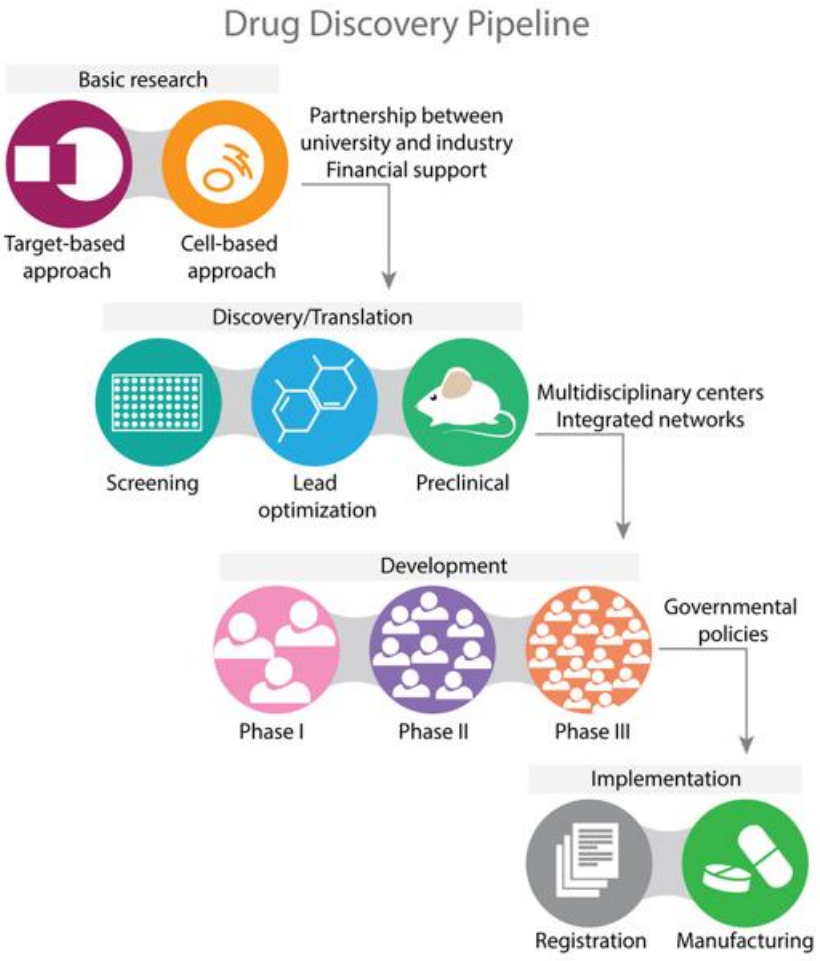


Figure 1 : Drug Discovery Pipeline

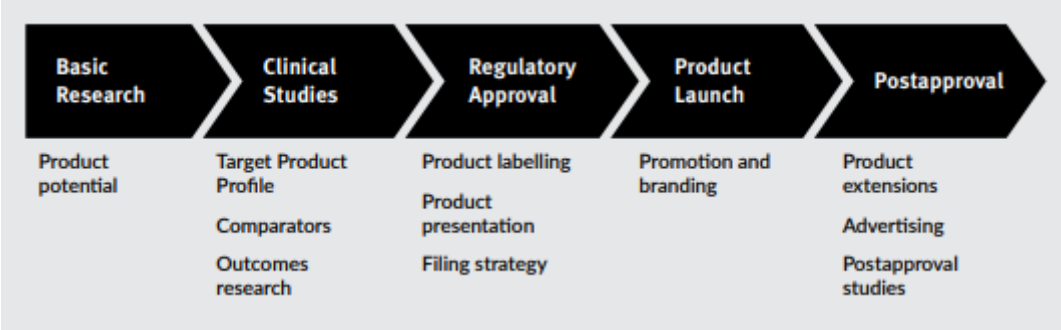
BACKGROUND INFORMATION ON MERS DISEASE

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a zoonotic virus that is transmitted from infected dromedary camels to humans. It is found in various countries in the Middle East, Africa, and South Asia. since 2012 a total of 27 countries have reported cases.[13]

BACKGROUND INFORMATION ON NITAZOXANIDE (ANTIVIRAL DRUG)

MERS is treated with nitazoxanide, an antiviral broad range drug. It lowers the generation of pro-inflammatory cytokines and inhibits the expression of viral N protein in peripheral blood mononuclear cells. It is being tested in clinical trials for the treatment of MERS, a viral respiratory infection.[15]

REGULATORY STRATAGIC PLAN



As a regulatory science expert, I put out the development plan for the antiviral drug Nitazoxanide, from filing an IND to submitting a New Drug Application to the USFDA.

Discovery, preclinical development, and clinical trials are the three stages of drug development. An Investigational New Drug application must be filed before clinical trials may begin.

The important steps in the discovery of Nitazoxanide are:[16-19]

- Identification of target: investigating, prioritizing, and screening of target takes place
- Validation of target: characterization of the target's role played in the disease.
- Identification of lead: screening and prioritizing of potential therapeutics
- Optimization of Lead: The product's actions are screened and characterized.

Following the identification of a lead molecule, a preclinical development program is launched, which includes API manufacturing, formulation studies, safety studies, and pharmacokinetic investigations.

Preclinical research is carried out to ensure that the medicine is both safe and effective. It entails putting medications (Nitazoxanide) through rigorous testing in animals to guarantee that they are safe for human trials. In these investigations, any adverse events or toxicities are noted and documented, allowing the medicine to progress to the next stage of clinical trials.

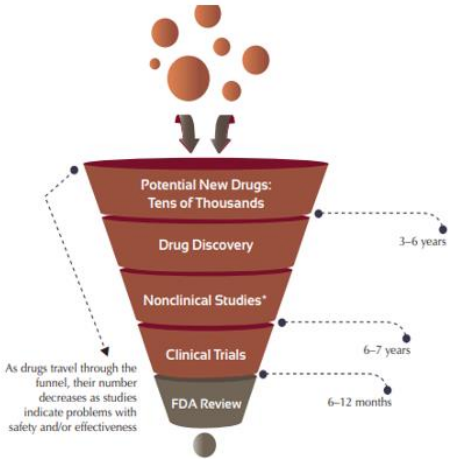


Figure 2: Drug Regulatory Process

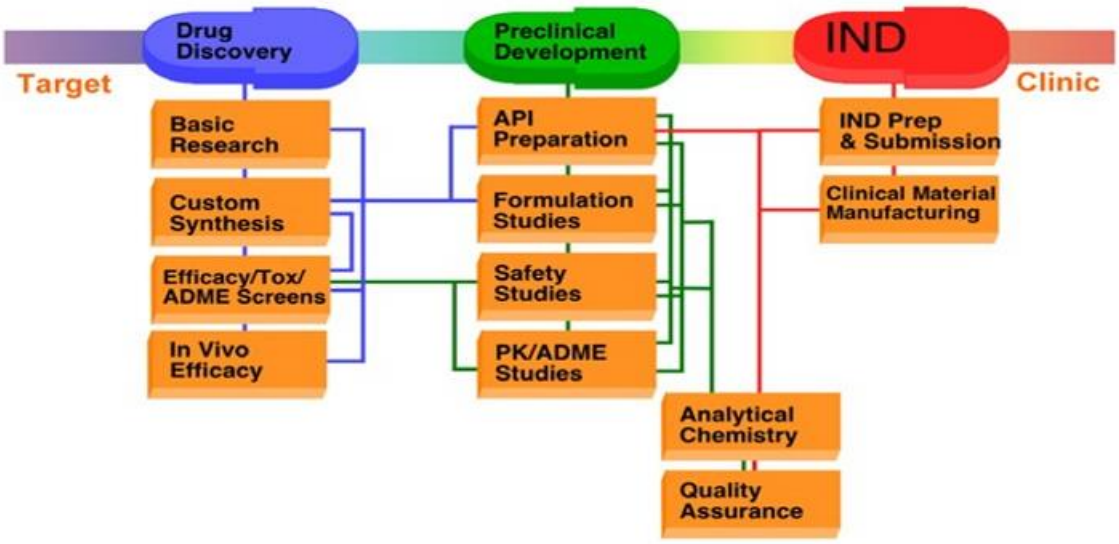


Figure 3: FDA Review Process

PRE-CLINICAL REQUIREMENTS FOR AN INVESTIGATIONAL NEW DRUG APPLICATION:[20-23]

- Pharmacological studies

Before a drug is administered to humans, it must first be identified how it affects the body. As a result, pharmacological research is carried out. Pharmacodynamics, on the other hand, determines the drug's interaction with the body to assess the effects of the drug on a specific response to assess potency, therapeutic index, effectiveness, and safety margins. It includes Nitazoxanide's primary and secondary pharmacodynamics.

- Pharmacokinetic Studies

It is described as the study of a drug's ADME (Absorption, Distribution, Metabolism, and Excretion) kinetics, which examines how a medication interacts with the human body after delivery. Analytical methodologies and validation reports are also included, as well as pharmacokinetic drug interactions.

- Toxicological Studies

The MTD (maximum Tolerable Dose) and NOAEl (No Observable Adverse Event Level) in rats and nonrodents are determined in this study. Toxicology research includes single-dose, repeated-dose, genotoxicity, carcinogenicity, local tolerance, and reproductive and developmental toxicity.

Components of Preclinical development include:

- Target product Profile

It is an essential tool for determining desired features of Nitazoxanide and provides a framework to ensure that the preclinical development program supports the intended clinical trial design and therapeutic use.

It consists of market size, dose route, clinical use, drug target, mechanism of action, bioavailability, CMC profile, storage conditions, stability profile, etc

- Regulatory Authority Meetings

Interaction with regulatory agencies occurs to obtain feedback on present information and also to know further development process. For such interactions regulatory authority meetings were conducted. For marketing the drug

in USA regulatory professionals interact with FDA Regulatory meetings with EMA is also periodically organized to determine the safety and efficacy of the drug. Major elements to be considered during meetings are:[25-27]

- Benefit-risk evaluation of study reports
- Reviewing of clinical reports before entering into the next phase
- Analysis of clinical design
- Certain committees do technical reviews

Figure 4 : Quality Targeted Product Profile

CLINICAL RESEARCH

Researchers conduct clinical trials to determine the safety, efficacy, and toxicity of newly discovered drugs. It includes 5 phases:[28]

Phase 1 Trials

- The main objective of phase 1 trials is the determination of the safety and tolerance of newly discovered drugs in healthy humans.
- Majorly called first in man studies
- These tests are conducted in a small population of fewer than 100 humans
- Pharmacokinetics, Pharmacology, Bioavailability, Bioequivalence studies are conducted and the data obtained is collected and further evaluated.
- Once the phase 1 trials are completed, the drug is sent for the next step of trials

Phase 2 Trials

- Phase 2 trials are focused on the determination of the safety and efficacy of a drug for a specific disease or a patient with a target disease.
- Also known as Pilot or Pivotal Phase
- Includes hundreds of patients
- Safety, efficacy, pharmacokinetics, drug-drug interactions, bioavailability, drug-disease interactions are determined
- If the drug passes this phase efficiently then the drug is sent for phase 3 trials

Phase 3 trials

- The main goal is to confirm therapeutic efficacy to justify the drug's marketing approval.
- Conducted in a large population of hundreds to thousands of people with multiple treatments consisting of control groups that are standards, typically for long term data collection
- If the drug complies with all the tests it is sent for FDA approval. Once the FDA approves then it is released into the market and distributed to larger populations.

Phase 4 Trials

- Helps in the determination of adverse effects, pharmacoeconomic, epidemiologic, and quality of life data.
- Essentially called Post Market Surveillance
- Thousands of people from the marketed groups typically participate in phase IV trials.

FDA DRUG REVIEW

A drug developer can apply to sell a drug if early tests and preclinical and clinical research FDA evaluates the reports of any adverse effects found during the post-market survey and takes required steps, such as recalling the medicine from the market due to its significant side effects.[29]

1. Isolation and Refinement of the indications

Every drug possesses some kind of risk. the main objective of the FDA is to ensure that drugs reaching the market are compliant with the safety standards and are efficient. The process by which FDA receives this data is by Investigational new drug application.[30-32]

Indications for a drug product can be identified by

- **Target Identification:** The goal of target identification in clinical pharmacology is to determine the effectiveness target of medicine, pharmaceutical, or another xenobiotic.
- **Target Validation:** Validating the target is the first step in developing a novel drug, which can take anywhere from two to six months. The technique comprises a range of approaches to demonstrate that drug effects on the target can provide a therapeutic benefit while preserving a reasonable safety margin.
- **Lead Identification:** H2L, or lead generation, is a stage in early drug development in which small molecule hits from a high throughput screen (HTS) are examined and subjected to minimal optimization to identify potential lead compounds.
- **Lead Optimization:** The process of lead optimization culminates in the discovery of a preclinical candidate.

With the support of effective pharmacokinetic and pharmacodynamic study design, analysis, and interpretation, the mechanism of drug action and identification of pharmacokinetic features can be determined. In the translation of in vitro chemical potency to in vivo, PK/PD models are critical.

The basic goal of the drug development process is to find effective and safe doses. Pharmacokinetic and pharmacodynamic features can be introduced early in the drug development process to construct a good clinical development strategy. This data can be modified through an iterative process to build a powerful forecasting tool that is based on efficacy requirements. It also assists the project team in comprehending the mechanism of the pharmacological action and selecting the best compound.

The use of PK and PD modeling in drug research decreases the use of animals, saves time, and allows for the estimation of therapeutic indexes and the prediction of dose ranges in clinical trials. These models enable the logical integration of data from multiple clinical investigations based on medication and illness knowledge. It also aids in the long-term decrease of resource investment. Upon direct assessment of new compounds with limited knowledge on it might be a major risk causing wastage of major resources and efforts. Validation of PK/PD models in comparison to established models is essential to achieving desired results.[33]

It is critical to isolate and refine a drug's indications to advance the drug's development and ensure that it reaches the market safely and effectively, allowing it to treat a variety of diseases with fewer adverse effects.

2. Benefit-Risk Assessment

It is an important aspect of the FDA's regulatory examination of new pharmaceutical drugs and biologics marketing applications. This assessment can be used to determine any uncertainties, adverse effects, or benefits. It can also be used as a means of communication.

The benefit-risk evaluation is established by determining the drug's essential advantages and dangers. Important benefits are assessed across studies in a development program using primary and secondary clinically important endpoints. The risk, in terms of frequency and severity, is unwanted side effects that are necessary due to their clinical and public health applications.

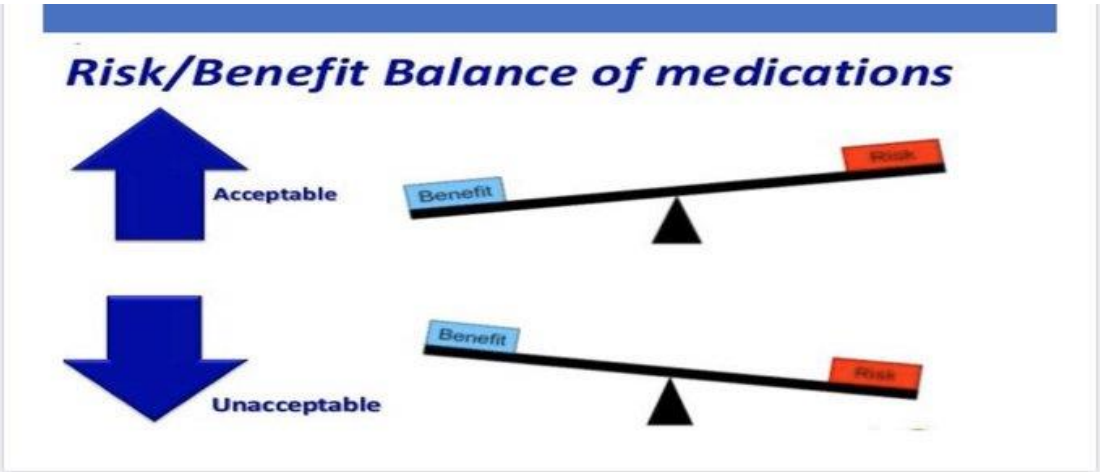


Figure 5 : Risk and Benefits of Medications

The benefit-risk analysis should be conveyed to the target audience. The identification of the primary advantages and hazards linked with Nitazoxanide is made possible by comprehensive data and analysis. Various sources give data on the benefits and hazards of various populations, which must be presented to the target audience. To communicate the clinical importance of the primary benefits and dangers, as well as the ensuing benefit-risk assessment, summary tables or graphs might be provided.[34]

When designing a product and assessing risks and advantages, strict guidelines should be followed. For a medicine to be recognized as safe for human use, the benefits must outweigh the hazards. For evaluating a product's risk profile and reducing medical errors, post-marketing surveillance is crucial.

RANDOMIZED CONTROLLED TRIALVs ADAPTIVE STUDY DESIGN

A randomized controlled trial is regarded as the gold standard for designing clinical investigations is the trial. Its goal is to reduce bias while evaluating new treatments by randomly assigning individuals to various groups, treating them differently, and comparing the results.

(i) Well blended RCT: the gold standard for clinical trials

(ii) Blinded RCT: evaluates safety and efficacy of medical drug products and also provides information on adverse effects.

RCT are further classified into:[35]

- Simple randomization
- Block randomization
- Stratified randomization
- Unequal randomization

RCTs give the most solid scientific data and decrease bias, but they are costly and time-consuming.

The adaptive study design There are several stages to it. Clinical trials are conducted and data is analyzed for effective results based on fresh knowledge at each stage.

Modifications incorporated in the clinical trial are:

- Dosage
- Sample size
- Patient selection criteria
-

These studies assist in the rapid development of therapeutically effective medications. It lowers the number of patients in a trial and the overall number of clinical studies. It's useful for clinical safety and efficacy studies that are well-controlled. Adaptive design can help with early-stage research, exploratory trials, and future trials to meet post-marketing obligations.

Because of the following reasons, as a regulatory expert, I believe that an adaptive platform architecture should be employed for performing clinical research to support an NDA filing for the medicine Nitazoxanide:

- It offers clinical data more effectively.
- Clinical trial efficacy has improved.
- This results in a better knowledge of the impacts of the investigational product.
- Today's human subject research is more aligned with basic ethical principles

The capacity to include prospectively planned chances for adjusting research design features and assumptions based on interim data analysis is a key benefit of adaptive design. Such changes must be planned ahead of time in the protocol, and any interim analyses must account for statistical bias.

DOSAGE FORMS AND ADMINISTRATION

Nitazoxanide tablets for oral use

Nitazoxanide for oral suspension

JUSTIFICATION OVER DOSAGE DESIGN

Bioequivalence research in vivo using PK endpoints:[36]

1. Type of research: Fasting Design: In vivo single-dose, two-treatment, two-period crossover

500 mg potency

Subjects: Nonpregnant, nonlactating females and healthy men from the general community.

2. Study Type: Fed

In vivo single-dose, two-treatment, two-period crossover design

500 mg potency

Subjects: Nonpregnant, nonlactating females and healthy men from the general community.

Analytes to be measured (in suitable biological fluid): Tizoxanide in plasma

Bioequivalence based on (90 percent CI): Tizoxanide

COMPLETE PRESCRIBING INFORMATION CONTENTS

The label must remain on the container and be readable throughout its lifecycle, which includes distribution, storage, and usage. The label's printing must also be legible during the course of this lifecycle.[37]

- Indication and applications
- Administration and dosage
- Dose formations and strengths
- Contradictions

- Harmful reactions
- Drug interactions
- Application in specific populations
- Ten overdosage
- Description
- Clinical pharmacology
- Nonclinical toxicology
- Clinical research studies
- How supplied/storage and handling
- Information on patient counselling
- Information about the manufacturer

GUIDANCE OVER DEVELOPMENT

- Regulatory (e.g., plans for submitting proprietary name requests, plans to postpone or waive specific studies, development plans with other FDA centers (e.g., the Center for Devices and Radiological Health for combination goods), application of an accelerated review process program)
- Clinical/statistical (e.g., planned clinical trials to establish efficacy vs a placebo) placebo or to demonstrate noninferiority to active control, outcome validity, and endpoints, trial size, enrichment strategies, and so on)
- Safety (for example, safety problems discovered in nonclinical investigations and early clinical trials, Immunogenicity, the extent of the total safety database, and concerns about specific substance populations, post-approval pharmacovigilance programs, risk assessment, and risk mitigation techniques (REMS), plans for human factors investigations, and difficulties with abuse evaluation potential)
- Clinical pharmacology and pharmacokinetics (for example, dosage selection and population, application in animals) particular demographics
- Nonclinical pharmacology, pharmacokinetics, and toxicology (for example, genetic toxicity, reproductive and developmental toxicology, carcinogenicity, mechanism of action)
- Product quality (for example, analytical similarity evaluation, anticipated shelf life, and stability) research, delivery systems, drug substance/product characterization, and facility compliance having strong manufacturing processes, comparability of clinical trial lots with commercial lots) Children's health (e.g., proposed paediatric development plan, dosing)[38]

REGULATIONS AND INTELLECTUAL PROPERTY

Enforcing IP rights about such items ensures, at least, that the products' origin is recognized and that they are genuine, whereas counterfeit products frequently fail to meet required safety requirements. This is especially true for trademarks, but patent licensing contracts, for example, may include quality assurance terms as well. Enabling indirect exploitation: When a firm protects its goods (or processes, etc.) with intellectual property rights, it may earn money not just from direct exploitation (by that company), but also from indirect exploitation by other parties through licensing arrangements. This increased indirect income can occasionally outweigh the profits from direct exploitation, especially since they do not necessitate more internal production capacity.[39]

Intellectual Property (I.P.)

- Laboratory Procedures
- Intellectual Property Ownership
- The Patent's Commercialization
- Taking Care of the Protected
- The Three-Way Conversation: Concentrate on the Invention
- Invention Licensing
- Commercial Conversations
- Development Financing
- Patents in the Future

Managing IP and IPR is a multifaceted process that necessitates a variety of activities and methods that must be by national laws as well as international treaties and standards. It is no longer just motivated by a national vision. Market demands, market reaction, the expense of turning IP into a commercial endeavor, and so on all have a significant impact on IP and its related rights. In other words, trade and commerce factors are critical in IPR management. Distinct types of IPR need different treatment, handling, planning, and tactics, as well as the participation of individuals with diverse subject expertise, such as science, engineering, medical, law, finance, marketing, and economics.

Depending on its field of expertise, each sector should have its own IP rules, management style, strategies, and so on. The pharmaceutical sector is actively developing an IP strategy. Given the greater likelihood that certain IPRs are invalid, antitrust law must intervene to guarantee that invalid rights are not unlawfully asserted to build and perpetuate illegitimate, if limited, monopolies within the pharmaceutical business. Many issues remain unresolved in this setting[40].

CONCLUSION

Pharmaceutical organizations are increasingly aiming for a single picture of their complete product development lifecycle with the capacity to view and trace every product detail throughout the whole process. Agile Product Lifecycle Management gives pharmaceutical companies the ability to centralise and manage product information even while addressing some of their most pressing requirements, such as accelerating time to market, reducing overall operating and production costs, and achieving quality standards like QbD.[41] Companies can finally reap the rewards of cross-functional collaboration where product information is transparent, facilitating product governance both internally and externally, by offering a unified perspective of the product(s) across the business (i.e., compliance with regulatory agencies). Pharmaceutical firms are attempting to have an united perspective more and more. When implemented correctly. These show how transformational features can enhance the "lab to launch" process and foster a culture of continuous improvement within the business based on the maxim "think big, start small, grow fast."[42]

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