A REVIEW ON DRUG DEVELOPMENT TEAMS

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ABSTRACT

Drug development has advanced from workbench chemical synthesis to an automatic and in a few instances digital process where in big numbers of systems may be simulated, synthesized, evaluated and in maximum instances discarded. To identify the behaviour that distinguish the performing drug development teams. The results of the study describe the specific behaviour and strategies used by the teams. These findings suggest a preliminary road map of actions for team members, leaders, and managers. The reader is invited to consider how the outcome of this research might provide benefit for cross-functional teams in other organizations.

KEYWORDS: Validation, Pharmacokinetics, Authorization, Evaluating, Clinical Research.

INTRODUCTION

Drug development teams are multidisciplinary group of experts that work together to discover, develop and bring new medications to market. These teams consist of scientists, researchers, medical doctors, regulatory experts project managers and other professionals with specific expertise in different aspects of the drug development process.

Drug development teams are typically assembled by pharmaceutical companies or research organizations to efficiently and effectively navigate the complex process of developing a new drug. They collaborate closely throughout the entire drug development life cycle, from initial research and discovery to clinical trials, regulatory approval, and commercialisation.

The primary goal of a drug development team is to ensure the safety and efficacy of a new medication, while also maximising its potential for success in the market. This involves conducting extensive research and preclinical testing to identify promising drug candidates, designing and conducting clinical trials to evaluate their safety and effectiveness in humans.[1]

STAGES OF DRUG DISCOVERY AND DEVELOPMENT INCLUDE:

- Target identification
- Target validation
- Lead identification
- Lead optimization
- Product characterization
- Formulation and development

- Preclinical research
- Investigational New Drug Application (INDA)
- Clinical trials
- New Drug Application
- FDA Review
- Approval
- FDA Review
- Approval

Target identification and its role in drug discovery:

Identifying the biological origin of a disease, and the potential targets for intervention, is the first step in drug discovery of a medicine. Target identification is the process of identifying the direct molecular target for proteins or nucleic acid. In clinical pharmacology, target identification is aimed at finding efficacy target of a drug /pharmaceutical or other xenobiotic. Target identification and mechanism of action studies play an important role in molecule discovery. A excellent goal desires to be efficacious, secure meet scientific and industrial desires and, above all be "druggable" target is accessible to the drug molecule, be that a small molecule or larger biological And upon binding, elicit a organic reaction which can be measured each in vitro and in vivo. Target identity may be approached through direct biochemical methods, genetic interactions, or computational inference. Combinations these approaches may be required to fully characterize of small-molecule action. The discovery and improvement businesses are made from the fundamental scientists and chemists who created the brand-new molecule. This organization synthesizes drug materials for "drug screening", pharmacology, and toxicology studies, and additionally prepares medical supplies. Members in this group include Biochemists, Pharmacologists, System biologists, Cell biologists, Immunologists and Bioinformaticians, in addition to synthetic, medicinal, analytical, and computational chemists, Biotechnologists and Therapeutic region specialists.

Target validation and its role in drug discovery

New target validation is the basis of completely new drug exploration and the initial step of drug discovery. New drug target validation might be of great help not only to new drug research and development but also provide more insight into the pathogenesis of target related diseases. Basically, the target validation process might include six steps:

1. Discovering a biomolecule of interest.
2. Evaluating its potential as a target.
3. Designing a bioassay to measure biological activity.
4. Constructing a high-throughput screen.
5. Performing screening to find hits.
6. Evaluating the hits.

The drug discovery process starts with the identification, or growing evidence of, biological targets that are believed to be connected to a particular condition or pathology. Information supporting the role of these targets in disease modulation can come from a variety of sources. Traditionally, the targets have been researched and largely discovered in academic laboratories, and to a lesser extent in the laboratories of pharmaceutical and biotechnology companies. Basic research into understanding the fundamental, essential processes for signalling within and between cells and their perturbation in conditions has been the basic approach for establishingpotential targets suitable for drug intervention.

Members in the group include includes Biochemists, Pharmacologists, System biologists, Immunologists, Bioinformatics. Bioinformatics is assuming an increasingly important role in the target validation process by analysing and integrating the datasets from these experimental studies and by making predictions about target function based on mining of genomic, transcriptomic, and proteomic data.

Lead identification and its role in drug discovery

During the early stages of drug discovery for a certain disease, the underlying molecular mechanisms behind the disease are studied. These studies include identifying the cellular and genetic factors involved in the disease, followed by the identification of potential targets. In order to ensure that the biological target is involved in the disease, *in vitro* (isolated cells) and *in vivo* (animal models) tests are performed. This is also known as the target validation stage. Modern target validation often involves a combination of *in vitro*, *in vivo*, and *in silico* (performed with a computer) studies. The results of the target validation stage can assist in lead compound identification.

Lead compounds **are** chemical compounds that show desired biological or pharmacological activity and may initiate the development of a new clinically relevant compound. Lead compounds are typically used as starting points in drug design to give new drug entities. Drug design strategies can be used to improve the compound's pharmacodynamic and pharmacokinetic properties.

The main approach to hit discovery is high throughput screening (HTS); assays that are used to screen an entire compound library against a new drug's target. Knowledge-based screening (also known as focused-based screening) is another crucial aspect of hit discovery. This involves a thorough analysis of a chemical library consisting of smaller subsets of molecules with potential activity at the target site. Fragment-based screening and physiological screening processes may also be used to complement these approaches during the drug discovery process. In drug discovery, Structural bioinformatics enables the efficient analysis and interpretation of large-scale biological data, facilitating target identification and prediction of drug target interactions.[3]

Lead Optimisation and its role in drug discovery.

Lead optimization involves converting a lead series to a pre-clinical candidate. This multiparameter optimization exercise involves fine-tuning the lead structures and drug-like properties to match the desired target product profile.

This design-make-test-analyse (DMTA) process requires both medicinal and computational design strategies, the use of efficient chemical synthesis and pharmacokinetic, pharmacodynamic and safety profile optimization. Where appropriate, structural biology, CADD, cell biology and proteomics are among the tools used to improve understanding of thepotency, selectivity, and mechanisms of action.

In addition to optimizing the lead compound's safety profile, researchers must develop a clear understanding of the mode of action, nature of the target, and establish the biological relevance of the animal species in pharmacological studies as well as explore potential differences between animal models and humans.

Among the lead selection and optimization services we offer, they include:

- Evidence of target or pathway engagement in human systems
- Human dose predictions
- Patent filing
- Studies to maximize potency and selectivity plus minimize toxicity
- Generating a preclinical candidate adhering to agreed-upon criteria
- Lead optimization non-glp toxicology studies for expedited data

In drug discovery, Bioinformatics enables the efficient analysis and interpretation of large-scalebiological data, lead compound optimization and prediction of drug target interaction.[3]

Product characterisation and its role in drug development

Product characterization can be challenging throughout drug development because it requires advanced technologies and specialized expertise. Thus, it is vital to start product characterization early and use it throughout all phases of the drug manufacturing process. It is also essential to capture a biologic's activity profile from binding, affinity, and potency bioassays to have a better understanding of a drug's critical quality attributes.

The primary goal of product characterization is to ensure safety, purity, identification, and accurate potency. New biologic drugs are designed with a clear mode of action. Early investment in product characterization helps uncover whether the molecule in development meets established criteria and if the molecule can be manufactured at a large scale. This characterization work can identify problems as early as possible, essentially de-risking the development and manufacturing process and expediting product quality decisions at critical junctures.

Product development chemist conducts research analysis and experimentation for such purposes as product characterization process development.

Formulation and development and its role in drug discovery

Drug formulation is one of the most critical aspects of the pharmaceutical development process. If a drug cannot be delivered in a stable form that is acceptable to the patient, it is unlikely to find a sizable market, and it may not even go beyond Phase 1 Clinical trials.

Drug preformulation studies are the first step in formulation development. During this phase, we identify the chemical, physical, and mechanical properties of a drug to determine the inactive ingredients, or excipients, that should be paired with it. The goal is to create a formulation that is stable under a variety of conditions, from extreme cold to extreme heat.Adding excipients can change a drug's qualities and ensure an end-product that doesn't degradeduring shipment or storage.

Members in the group include involves pharmacologists, biochemists, microbiologist, physician, pharmaceutical chemists.[4]

Pre-clinical Research and its role in pre-clinical drug development team

in preclinical studies. These studies can either be 'invitro', Latin for "within the glass" and referring to studies using cell cultures studied outside of the body, or 'in vivo' Latin for "within the living", referring to studies that take place in the body. In preclinical studies, only animals are used for in vivo tests as this stage comes prior to human testing to ensure its safety.

For in vitro studies, cell lines are derived from either humans or non-human animals and are introduced to the new pharmaceutical under development within a Petri dish or test tube.In vitro studies have many benefits. The first, and most obvious benefit is that they do not cause harm to the animal or person that the cell cultures have been derived from, they are free of the drawbacks of animal testing. Other benefits of in vitro models include their relative cheapness in set up and running; they are also reliable and efficient, and produce robust results.

In vivo studies are able to address the major limitation of invitro studies, they are able to demonstrate the impact of a pharmaceutical on the body as a whole, rather than how it impacted isolated cells. This allows in vivo studies to better visualize potential interactions, which can improve its predictions of safety, toxicity, and efficacy. This helps scientists predict the impactof candidate drugs on human disease.

The Preclinical Development Team coordinates the company's activities in the area of preclinical studies of selected drug candidates. With its vast skills and experience, the Team can efficiently assess if molecules are ready for phase 1 clinical trials (known as first-in-human, FIH) and provide significant support for finished value-added dosage forms, allowing Adames to obtain regulatory approval for bringing new medicines to the Polish and international markets.

The Team's numerous tasks mainly include the assessment of a drug candidate's safety (toxicology studies), which is primarily aimed at estimating the MRSD in clinical trials. This assessment is a multi-stage process, starting with in vitro tests using a cell line panel and in vivo tests on animal models which are aimed at establishing the maximum tolerated dose, to proper toxicology studies as per the mandatory Good Laboratory Practice standards. In addition to general toxicology studies, the Team also coordinates genotoxicity, reproductive toxicology, local tolerability, hypersensitivity, and ecotoxicology studies depending on project needs.

Members in the group include a management-assigned project team leader and coordinator R A and QA professionals, clinical trial team, analytical chemists, manufacturing and marketing analysts.[5]

IND Application and its role in regulatory team

An Investigational New Drug Application (IND) is a request from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Clinical studies are often conducted to collect safety and effectiveness information in support of marketing applications for biologic and drug products. Unless exempted, the sponsor for a clinical study must obtain authorization from FDA for conducting the study by submitting an IND Application. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics Product License Application.

Regulatory affairs team developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines, and by the companies responsible for the discovery, testing, manufacture and marketing of these products wanting to ensure that they supply products that are safe and makea worthwhile contribution to public health and welfare.[6]

CLINICAL TRAILS

Phase 0: Clinical trial

According to the FDA a phase ‘0’ is designed to carry out before in phase 1, it has very limited human exposure receiving only sub-therapeutic dose and this means the volunteer produces a response (Pharmacological Action) than the toxic effect with less risk compared to conventional clinical trials in phase 1 in which administration continues if clinical benefit which means even phase ‘0’trials don’t have any therapeutic intention. With the ultra-sensitive accelerator mass spectrometry (AMS) it was possible to carry out clinical trials in human usingsmall dose to obtained pharmacokinetic data.

Phase 1: Safety and dosage

A Phase 1 clinical trial evaluates the best way to administer a drug, its frequency and dose, the maximum tolerated dose (MTD), and side effects. Tolerability, pharmacokinetics, and pharmacodynamics are evaluated. These studies determine, most importantly, if the treatment is safe. Trials usually include 20 to 100 patients and are monitored by the clinical researcher. Doses are increased if there are no severe side effects and patients are tested to determine if he or she is responding to the therapy. These escalation dose studies are used to determine the best and safest dose that can be administered and is a fraction of the dose that caused harm during animal testing. Unnecessary exposure of subjects to subtherapeutic doses while maintaining safety and rapid accrual is the primary goal of Phase I trial.

Phase 2: Efficacy and side effects

This is conducted by physicians who are trained as clinical investigators, and involve 100–500 patients selected according to specific inclusion and exclusion criteria. The primary aim is establishment of therapeutic efficacy, dose range and ceiling effect in a controlled setting. Tolerability and pharmacokinetics are studied as extension of phase I. The study is mostly controlled and randomized, and may be blinded or open label. It is generally carried out at 2-4 centres. The candidate drug may get dropped at this stage if the desired level of clinical efficacyis not obtained

Phase 3: Efficacy and adverse drug reactions monitoring

Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market

Phase 4: Post-Market Drug Safety Monitoring

This phase is also called as Post Marketing Surveillance Trials. They are conducted after a drug or device has been approved for consumer sale after approval regulatory authority. Pharmaceuticals companies have several objectives at this stage:

1. To compare a drug with other drugs already in the market;

2. To monitor a drugs long-term effectiveness and impact on a patient's quality of life; and To determine cost-effectiveness of the drug therapy relative to other available and new therapies. Phase 4 studies can result in a drug or a device being a taken off the market registrations of use could be placed on the product depending on the findings in the study.

Members in the group include associate investigators, site principal investigator, biostatistician, study coordinator, data manager, programmer, clinical trial pharmacist.[7]

Clinical research Team

Clinical research has the ultimate responsibility for testing drug products in humans: the monitoring of drug safety rests squarely on the shoulders of clinical research. Clinical trials must be science-based with proper statistical methodologies and have clinically relevant end points. Clinical research interacts directly with the FDA and is responsible for the generation of study reports with input from biostatisticians and regulatory affairs. Clinical research can also generate the publications necessary for the marketing of any drug product.

Roles:

- Participants are provided with information about the clinical trial.
- The content of the informed consent is explained.
- Reporting of adverse events or drug reactions.
- report suspected misconduct.
- Protect the integrity and confidentiality of records and data during the clinical study

Members in the group include physicians, clinical research associates, drug product production, QA, statisticians, research pharmacists, study coordinator participants.[7]

NDA

The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. Every new drug has been the subject of an approved NDA before commercialization in the U.S. since 1938. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.[8]

FDA review

Once FDA receives an NDA, the review team decides if it is complete. If it is not complete, the review team can refuse to file the NDA. If it is complete, the review team has 6 to 10 months to make a decision on whether to approve the drug. The process includes the following:

- Each member of the review team conducts a full review of his or her section of the application. For example, the medical officer and the statistician review clinical data, while a pharmacologist reviews the data from animal studies. Within each technical discipline represented on the team, there is also a supervisory review.
- FDA inspectors travel to clinical study sites to conduct a routine inspection. The Agency looks for evidence of fabrication, manipulation, or withholding of data.
- The project manager assembles all individual reviews and other documents, such as the inspection report, into an “action package.” This document becomes the record for FDA review. The review team issues a recommendation, and a senior FDA official makes a decision.[9]

FDA Approval and its role in legal team, Marketing team and Management team

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The role played by this team was In order for a drug to be financially successful, patent protection is a key element. The legal group must submit patents at the appropriate time and do all in its power to avoid lawsuits from potential competitors. The legal group also ensures that neither the FDA nor the other organization or company will challengeadvertising and promotional materials.

The marketing group has the ultimate responsibility for marketing and selling the drug. As a result, they need product, labelling that differentiates their drug from those already marketed. Marketing has to provide creative concepts for the prescribing physician, the patient, and the company's senior management. They also have to make sure that, budget goals arc met. It is not uncommon for the marketing group to have differences of opinion from both the clinical and regulatory groups within their own company, as well as with the FDA.

They co-ordinate with all the respective teams and responsible for successful completion of project in a time bound manner. [10]

CONCLUSION:

Drug development comprises all the activities involved in transforming a compound from drug candidate to a product approved for marketing by the appropriate regulatory authorities. These findings provide a preliminary road map for the actions that can be taken by the team leaders, team members and management to develop a high-performance team culture. The review presented here was conducted with cross-functional teams in a drug development setting. While we believe that many of the findings are generalizable to cross-functional teams in other contexts, similar research with product development teams in other industries would aid the identification of those strategies that are transferable to other environments.

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