SIGNIFICANCE OF PHARMACEUTICAL RESEARCH IN AYRVEDA

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Abstract

The word pharmaceutical pertains to pharmaceutical industry and drugs which is prepared and dispensed in pharmacies for the medical treatment. Production and development of standard genuine new dosage design according to approved formula and processes prescribed in science falls within the scope of pharmacy.

Pharmaceutical research intends at mass production of medicines economically from standard raw material at low cost yet with improved standard of selectivity, pharmaco kinetics, clinical response of the drug etc. Preparations are classified into primary, secondary and tertiary dosage forms.

Globalisation of Ayurveda and industrialization of the Ayurvedic drug sector needs standardization and quality assurance of the in use drugs besides developing new drugs and formulation for more recent indications. Validation plays a pivotal role in this.

Key words: Pharmaceutical research, quality assurance and standardization

Introduction

The word pharmaceutical pertains to pharmaceutical industry and drugs which is prepared and dispensed in pharmacies for the medical treatment[1]. Production and development of standard genuine new dosage design according to approved formula and processes prescribed in science falls within the scope of pharmacy.

Pharmaceutical research intends at mass production of medicines economically from standard raw material at low cost yet with improved standard of selectivity, potency, efficacy, safety, durability, pharmaco kinetics, administration modalities, palatability and clinical response of the drug. Pharmaceutical preparations are mainly classified into primary and secondary. Primary preparation includes *swarasa ,kalka, kwatha, hima, phanta*, and their upakalapnas.Secondary preparations are *churna, vati ,avaleha ,thaila, grutha ,asava, arishta*[2] etc and modified tertiary dosage forms like haridragandam granules, ksheerabala 101 capsule etc

Stages of pharmaceutical Research

1. Research of different sources and selection of the raw drug
2. Extraction of active principles
3. Various drug manufacturing process
4. Scientific drug Evaluation like process monitoring and continuous improvement, system biology, pharmacoeconomics
5. Process control and Process validation
6. Scale up and tech transfer
7. Optimization techniques
8. Packing, preservation storage and shelf life
9. Standardization of formulation

Phases of Pre- clinical in pharmaceutical research

There are four phases in research studies. All these steps must be successfully completed and all results known before a new drug can be approved for public use.

- Phase I studies are done on healthy volunteers who agree to take the study drug to help the doctors determine how safe the drug is and if there are any side effects. Studies are also done to determine how the drug is absorbed, metabolized and excreted. Usually a small number of subjects (20-100) participate in Phase I studies. Approximately 70% of new drugs will pass this phase.
- Phase II studies measure the effect of the new drug in patients with the disease or disorder to be treated. The main purpose is to determine safety and effectiveness of the new drug. Usually several hundred patients participate. These studies are usually "Double-blinded, randomized and controlled". In controlled studies, the effect of the active drug is compared to the effect of a placebo. In double blinded studies neither the investigator nor the study subject knows who is getting active drug and who is receiving placebo medication. One third of studied drugs complete both Phase I and II.
- Phase III studies also use patients with the disorder to be treated by the new drug. These studies are done to gain a more thorough understanding of the effectiveness, benefits and side effects of the study drug. These studies use a large numbers of subjects, several hundred to several thousand. Of the new drugs that enter Phase III studies, 70 to 90% of drugs successfully complete this phase. If the results show a good effect and safety profile, the company will submit the data and request to FDA approval for marketing the drug.
- NDA (New drug application)-if the results of all the previous testing is positive then the pharmaceutical company files an NDA
- Phase IV-Once the NDA is approved and the drug is available post marketing studies are conducted to further confirm safety and efficacy during long term use.
- In case of ayurveda drug development, after preparing the medicine as per the guidelines, the drug should be given for laboratory analysis. If it fulfils all the criteria, then the submission of the sample, laboratory report and request for the drug approval is given to the drug controller. From there the drug is send to the selected centres for clinical study. After the completion of successful clinical study the drug can be introduced into the market.

Present challenges

Globalisation of ayurveda and industrialization of the ayurvedic drug sector, that needs standardization and quality assurance of the in use drugs besides developing new drugs and formulation for more recent indications. To address the issue of standardization of ayurvedic medicine, the department of AYUSH, Government of India has set up the ayurvedic pharmacopeia committee. This committee with the help of eminent scholars developed AFI Part 1 and Part 11, API Part 1 with 7 volumes and part 11 with three volumes. This work has set up standards for single herbs and multi ingredient formulation described in the ayurvedic texts.

The parameters involved in the source and selection of raw drugs

High quality of raw dugs to be used, spurious drugs or substitutes of low qualities to be rejected.

Time, Place, state and Method of drug collection

Raw drug standardization

Standardization of crude drug is a multi dimensional approach; various parameters regarding different characters are to be considered mainly

1. Origin, common names, scientific nomenclature and family
2. Synonyms and varieties
3. Geographical sources and history
4. Classical references regarding *rasa, guna, veerya, vipaka* etc
5. Cultivation, collection, preservation and storage
6. Macroscopical, microscopical and sensory characters
7. Chemical composition
8. Identity, purity, strength and assay
9. Substitutes and adulterants
10. Contaminations, chromatography, markers and toxicity component.

Extraction of active ingredients

Active ingredients are the chemical components of the drug usually alkaloid, saponine, tannin, glycoside etc, which are largely responsible for conferring its characteristic therapeutic properties. It plays a vital role in compounding the formulation for diseases. Currently extraction by Co2, usage of poly compound aqueous extraction, extraction through controlled pressure etc also exist.

Drug manufacturing process

This is one among the important vicinity in the field of pharmaceutics where the scope of research is abundant. Pharmaceutical processes are techniques which modify the natural products into therapeutically potent dosage from. Which are easily absorbable in the biological system by specific processing methods resulting in the assimilation of newer properties. This modification is brought about by Heating, boiling, reduction, purificatory procedures, churning, flavouring, quenching, fermentation, impregnation, preservation, tabletting, incineration etc. In order to achieve the quality product the manufacturing process should be controlled.

Packing and storage

The process by which the pharmaceutical products are suitably packed to retain their therapeutic effectiveness from the date of packing till they are consumed is called packaging. Which involves preparing the articles for transport, air tight and weather proof packing impervious to light, storage, display and use.

Stabilization of pharmaceutical products:

It is the capability of a particular product in a specific container to remain within the physical, chemical, microbiological, therapeutical and toxicological specifications. The substance which are used to control these stabilities are known as stabilizers. They are antioxidants and preservatives. Commonly used preservatives are benzoic acid sodium benzoate etc

Standardization [3]

It is the inevitable part of pharmaceutical research. Standardize means to modify something to have the best possible features and to bring uniformity in the products. Qualitative and quantitative assessment should be followed to prove the efficacy of the drug. A standard is a numerical value which quantifies the parameters to denote the quality and purity of a product. The criteria or the parameter which is considered for making the standard is intimately related to the factor which is responsible for the expected quality and purity of the material. Generally the acceptability of a products always established by prescribing a standard. So standardization becomes the most essential entity.

Acceptability of a product depends on:
Raw single drugs
Method of preparation

Finished product

Present day justification for ayurvedic standardization in pharmaceutics

1. Socio economic changes in ayurvedic practice, changes in physical constitution, environmental stressors
2. Evolutionary phenotypic and agronomic changes in plant species
3. Substitution of drugs due to non availability or scarcity
4. Proliferation of proprietary formulae over traditional generic formulae
5. Translating ayurveda with the help of contemporary methods, revalidating ayurvedic principles as per the present day needs.
6. Change in the prescribing pattern of traditional products
7. Modernization of manufacturing process and effective overseas marketing etc

Process standardization

Standardized product is the outcome of standard process. Hence it is important to standardize the process by observing all stages in the manufacturing of a product. The control over this can be achieved by adopting standard operating procedure and Validation protocol. The need of validation and standardization in ayurvedic dosage forms formulated according to the textual reference as we as proprietary is due to the commercialization, globalization and inclusion of ayurvedic drugs under the drugs and cosmetic act 1940 and its rules in 1945.

Standard operating procedures

Since last few years there has been an overwhelming demand for ensuring proper safety and better efficacy of various ayurvedic products. It has been increasingly felt that in addition to the clinical safety of a drug that is established by the manufacturer, other factors also affect the quality of a product. These factors are storage, handling of raw material at the vendors place and the storehouse of concerned pharmacy. Cross contamination possibilities, precautions during manufacturing, quality control laboratory procedures for testing the drug product and finally the storage and handling at the manufacturer's warehouse and stockist. If an activity is to be preformed, there should be documentary evidences to prove that the activity has been done. It was completed by required procedure and this was verified by a competent person. In this ground research is very crucial.

Standard operating procedure contains the relevant information about the activity or procedure to be performed. SOPs are tools to ensure the good manufacturing practices that are being allowed wherever applicable. In order to ensure that the best possible medicine is made available to the consumer it is imperative that it fulfils three critical parameters. "Right quality, Right quantity, Right price". Hence keeping the above factors in consideration in the present scenario research in validation and qualification is an essential part.

Validation and Qualification of a compound

Validation process and Qualification are prerequisites of GMP, it is essential for the manufacturer to prove that the critical aspects of their particular operations are in control. Significant changes in the facilities, equipments and processes may affect the quality of the product, so it should be validated.

First step to design the validation master protocol (VMP)

VMP is written plan stating how validation will be conducted including test parameters, product characteristics, equipments and decision points on what constitutes acceptable test results. It consists of two steps Qualification and process validation.

Qualification

Design qualification is of self designed instrument regarding its performance in the defied job the compliances of design with GMP should be demonstrated and documented.

Installation qualification establishes confidence that the process equipment and ancillary systems are capable of consistent operations within established limit and tolerance.

Operational qualification is the test that has been developed from knowledge of processes, Systems and equipments. Test which includes some conditions encompassing upper and lower operating limits. The completion of a successful OQ should allow the finalization of calibration, operating and cleaning procedures.

Performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of process.

Process validation

Process validation comprises mainly retrospective process validation and revalidation. FDA defines process validation is establishing documented evidences which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre determined specification and quality characteristics. Critical steps should be validated prospectively or retrospectively. It refers to the standardization of process from the consignment of new material received at factory till it goes out in the form of final product.

Types of process validation of ayurvedic drugs

Retrospective process validation: it is based on the long term professional experience and retrospective data of the running plant set up. Also useful to augment initial premarket prospective validation for new products or changed processes.

Revalidation: it is applicable to all preparations .e.g. Sneha preparation in steam jacketed vessel which is a new method that has to be validated.

But there are few constraints one has to consider while doing process validation for the ayurvedic pharmaceuticals-

Linguistic constraints: abstractive nature of literature with large number of synonyms, creating confusion .e.g. Manaparibhasha

Operational constraints: variability of the composition of drug described by various authors under same name – Pathabhedha

Lack of batch yield concept-quantity of gained product is not mentioned

Investigative constraints: Due to chemical complexity one has to do the analysis of final product regarding its bio efficacy while validating the process.

Thus process validation is the most important thing when an attempt is made to validate the existing process as it bridges the gap between tradition and technology. In 21st century, technological advancements are to be brought to the scenario of ayurvedic pharmacy. Process validation is one method with which we can ensure the Batch to batch consistency of the finished product. Thus the quality and the standard of final products are built up and maintained automatically.

Finished product standardization

It is employed by different physiochemical parameters and newer techniques like TLC, HPTLC, GLC, GC, GCMS etc

General parameters to conduct experiment[4]

Physico chemical parameters :Determination of Ph ,Specific gravity, Refractive Index, Foreign matter, Acid Value, Saponification Value, Iodine value, Loss on drying, Ash value, Acid insoluble ash, Water soluble ash, Alcohol soluble extractive, Water soluble extractives, Ether soluble extractives (fixed oil content), Volatile oil, Fatty oil estimation, alkaloid estimation, melting range, boiling range, optical rotation, disintegration test, uniformity of weight, total solids, peroxide value, unsaponifiable matter, detection of mineral oil (Hold's test), rancidity test (kries test)Viscosity, Ester value, Alcohol content, Fineness of particles, Reducing sugar, Quantitative inorganic analysis, Qualitative identification of Inorganic elements, volatile oils, etc.

Limit test for heavy metal: Test for arsenic and lead, Chemical Assay[5]

Heavy metals by AAS (Atomic Absorption Spectrophotometry):
Determination of Cadmium (Cd) by graphite oven method
Determination of lead
Determination of Mercury (Hg) by (Cold absorption method)
Inductively-Coupled Plasma Mass Spectrometry (ICP-MS):This method is used for determination of arsenic, cadmium, lead, mercury and copper in herbal medicinal preparations.[6]

Biological parameters: It is designed to evaluate the untested pharmaceutical product samples on living beings. The studies are carried out experimentally in initial stage. If it shows a positive result then the product is advocated for clinical study in humans

Microbiological parameters[7] include total viable content, total mold count, total enterobacterial and their count. Limiters can be utilized as a quantitative or semi quantitative tool to ascertain and control the amount of impurities like the reagents used during abstraction of various herbs, impurities coming directly from the manufacturing vessels, from the solvents etc. Usually medicinal plants containing bacteria and molds are coming from soil and atmosphere. Analysis of the limit of E.coli and molds clearly throws light towards the harvesting and production practices. The substance known as afflatoxins will produce serious side-effects if consumed along with the crude drugs.

Drug assay-It is the estimation of potency of an active principle in unit quantity of formulation. It may be chemical, biological and immunological

Other areas should be enlightened

Periodic examination for Prathinidhi dravyas and abhava dravyas . Importance of storage vessel, variety climatic condition, modification of kalpanas , equipments for the preparation (development of motorized automatic khalwas, modern machineries for size reductions, lehyam and arishtam filling machines, tablet and capsule preparation , pouch packing, blister packing instrument etc. Heating devises like puta, fuel of cow dung and other specific wood should be validated. Processes like *mardana, sodhana*, *jarana* ad *marana*[8]etc should be scientifically studied for understanding the principles lying at their base, then the force of frictions, pressure, rate and speed of revolutions and temperature of heat applied during these process and ultimate transformation caused by them in the raw material are keenly observed without losing their pharmacological and therapeutically effectiveness .

Scope of research in the field of standardization:
1. To rule out the state of uncertainty about the identification and use of raw drugs
2. To frame the best method of preparation,
3. To bring the uniformity in all the finished products,
4. To compact the toxicity allegations in order to protect the public concern,
5. To meet the demand of ever increasing urbanization,
6. To combat the adulteration etc

Scope of further Research:

Areas like reverse pharmacology, lead molecule and process patent . Reverse pharmacology is the TDD (Target Based Drug Discovery). Mechanism of action at multiple levels of biological organization and to optimize safety, efficacy and acceptability of the leads in the products based on relevant science.

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