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CLINICAL DEVELOPMENT AND THE DEVELOPMENT PROCESS INVOLVED IN BRINGING NEW MEDICINES TO THE MARKET

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ABSTRACT

There are multiple concerns involved in drug development process. The process involved has stage of development of drug molecule. This developed drug molecules are put forth to studies for proving its Quality, Efficacy and are validated for its procedural development upon a development of a drug molecule in a research laboratory. (Pharmaceutical Research Laboratory) it is evaluated for its therapeutic activity and are clinically tested and evaluated for its assigned activity. There are various drug regulatory agencies involved in this process and are based on continuous monitoring process that is called as ongoing monitoring. This monitoring are carried out by clinical experts such as: pharmacists and physicians. This clinical experts are involved in to assists the clinical safety data on a clinical safety evaluation of a drug molecule or an entity as an API. These studies are carried based on the guidelines that are accepted internationally. (ICH). One goal of such on-site monitoring is to ensure that you have the right information at right time and right place. Such on-site monitoring ensures that Healthcare is an excellent and most trusted industry that could provide and nurture mankind for its continuous advanced human health care to deliver valued and real outcome. Sustainability is a critical consideration and thus involves (OHDSI) in its safety monitoring process.

KEYWORDS: Clinical development, Drug Molecules, Formulation Safety, Regulatory Agencies.

1. INTRODUCTION

Research and development in the field of pharmaceutical involves the basic principle of developing new molecular entity for the betterment of healthcare in humans and veterinary sciences. Such development can be in the fields of:

i) Improvement of drug dosage forms.
ii) Improvement and development in the stability of drug in dosage forms.
iii) Improvement in shelf life.
iv) Improvement in the dosage regimen.
v) Development of the new dosage forms.
vi) Development of the new drug entity.

Bringing of a new medicine to the market involves extensive study based modelling in the field of research and pharmaceutical sciences. Such studies are based on the development of a new drug molecules or new drug entity called as pharmakon (drug). Pharmakon development traces its early development history as published in Luminare Majus as a recipe book of the apothecaries profession that was first published in the city of Nuremberg. It was later overcome by a book called Dispensatorium written by Valeria Cordus as Luminare Majus contains preparations older than a century.

1.1. Few of the early discoveries in drug material such as

i) Tobacco: (Plant Based Drugs.)
ii) Cascara: (Plant Based Drugs.)
iii) Ipecac: (Plant Based Drugs.)
iv) Cinchona bark: (Plant Based Drugs.)

Study of plant based drugs by medical Botanists such as Otto Brunfels and John Gerards led to a rapid pace of development in medicines. Such discoveries of plant based drugs can be found in the most famous work, 'The Materia Medica of Dioscorides' (40-90 AD).

'The Materia Medica of Dioscorides,' describes 600 plants of reputed medicinal value and also excipients and mineral substances expressing dogmatic opinions in Greek and also included synonyms used in various countries. It is also one of the cause to eliminate superstitious feeling among the people. Leading to this there were development of universities for further development of pharmakon in the West in Universities of England and Universities of Michigan in 1868.

Few of the reputed development are in the fields of germ theory of disease which was released by Louis Pasture's-rabies vaccine and Imilvon Behring's diphtheria antitoxin gave a directional change in the treatment of infection disease. Such development of new drug or new molecular entity are documented for its therapeutic effects, which include formulation safety and treatment of drugs of pharmaceutical importance. These document also describes: assay, limit tests and other necessary details for a stability of drug in formulation.

1.2. Documenting includes the following parameter

1) Title.
2) Structural Formula.
3) Molecular Formula.
4) Molecular Weight.
5) Chemical name.
6) Category.
7) Dose.
8) Usual Strength.
9) Description.
10) Solubility.
11) Storage.
12) Containers.
13) Standards.
14) Identification.
15) Acidity or alkalinity.
16) Clarity and Color of Solution.
17) Limits tests.
18) Loss on drying.
19) Assay.

1.3. Including Additional items for formulations

a) Labelling.
b) Uniformity of Content.
c) Disintegration and Dissolution - For Tablets and Capsules.
d) Particulate matter, pH, etc. - For Injectable.

1.4. Other Requirements Including a Requirements Lists

i) Apparatus.

ii) Chemical etc.

2. Developing New Medicines and bringing it to the Market

Developing of new medicines includes various parameter and clinical development which undergoes extensive testing to establish newer drug as a medicine or API. This trials are approved by testing and be approved by relevant regulatory agencies.

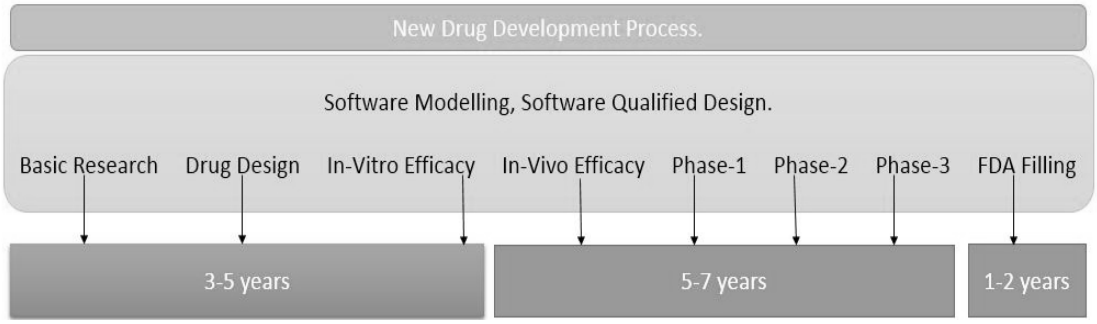

Figure 1: New Drug Development Process.

There are various stages included in the development process of drug or API. The first stage in the development process is pre-clinical research during which the drug is tested on animals for one to three years of time period. This includes various drug testing criteria of irrefutable manner. During this time period the data obtained is monitored for its Quality, efficacy, etc.

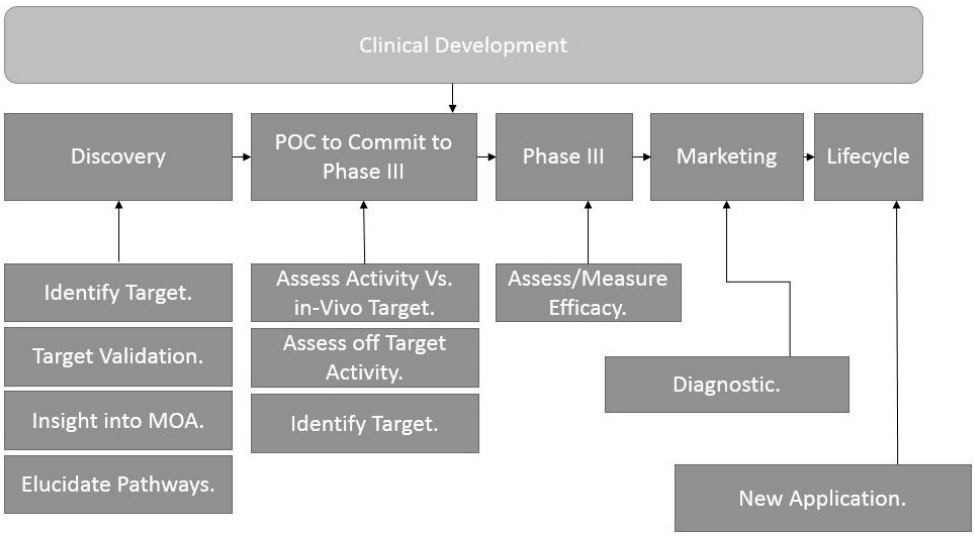

Figure 2: Clinical Development.

Bio analytical studies of the drugs is well documented for proving the safety of the newly established pharmakon.

"If the results indicate its safety for human testing, the product then undergoes its clinical tests in humans. "Only upon preliminary studies".

2.1. There are four phases included in clinical trials

1) Phase -I
2) Phase - II
3) Phase - III a-b
4) Phase IV

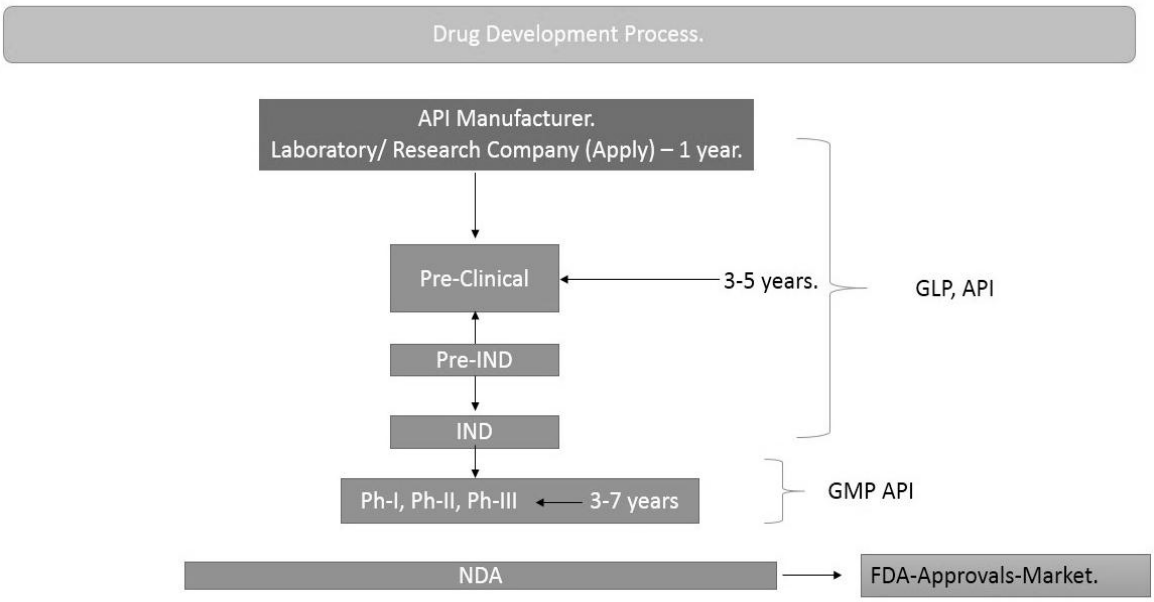

Figure 3: Drug Development Process.

Phase one is for basic safety and gaining of pharmacological data phase two is dose response relationship phase these focuses on regulatory approval producing clinical data: Safety, Efficacy, Packaging, Labelling and phase four to collect and analyse long term safety and evaluation data. All the phase are conducted according to a standard protocol based on guideline that are accepted internationally.

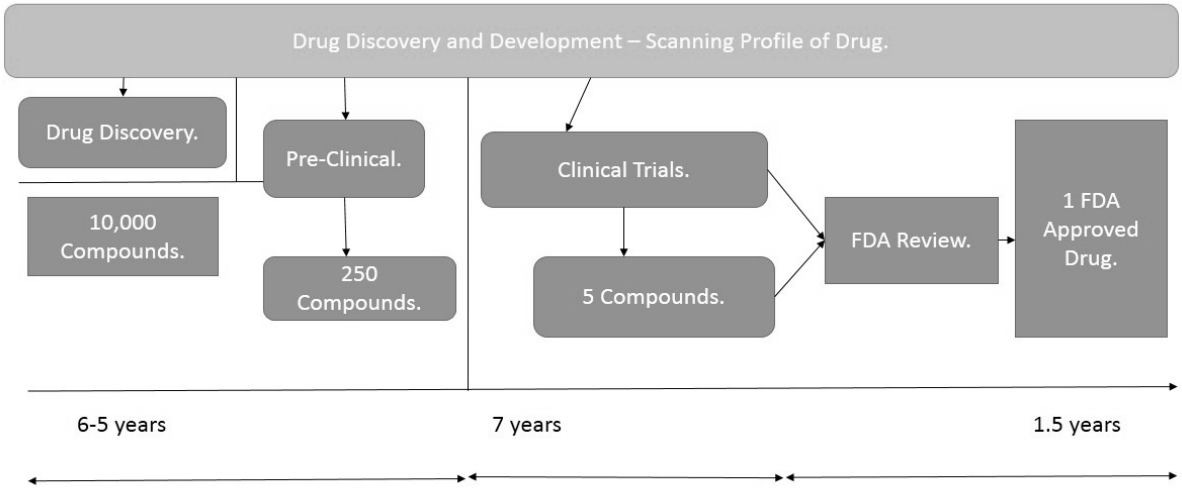

Figure 4: Drug Discovery and Development–Scanning Profile of Drug.

To conduct these phase of trial and obtain and monitor the clinical data and maintain it in repositories and on file for the verification. Such data requires early identification of risk levels and issues occurring during the study conduct and responsible for identification of risk which includes monitoring of site performance and make recommendation for timely corrective actions together as CAPA.

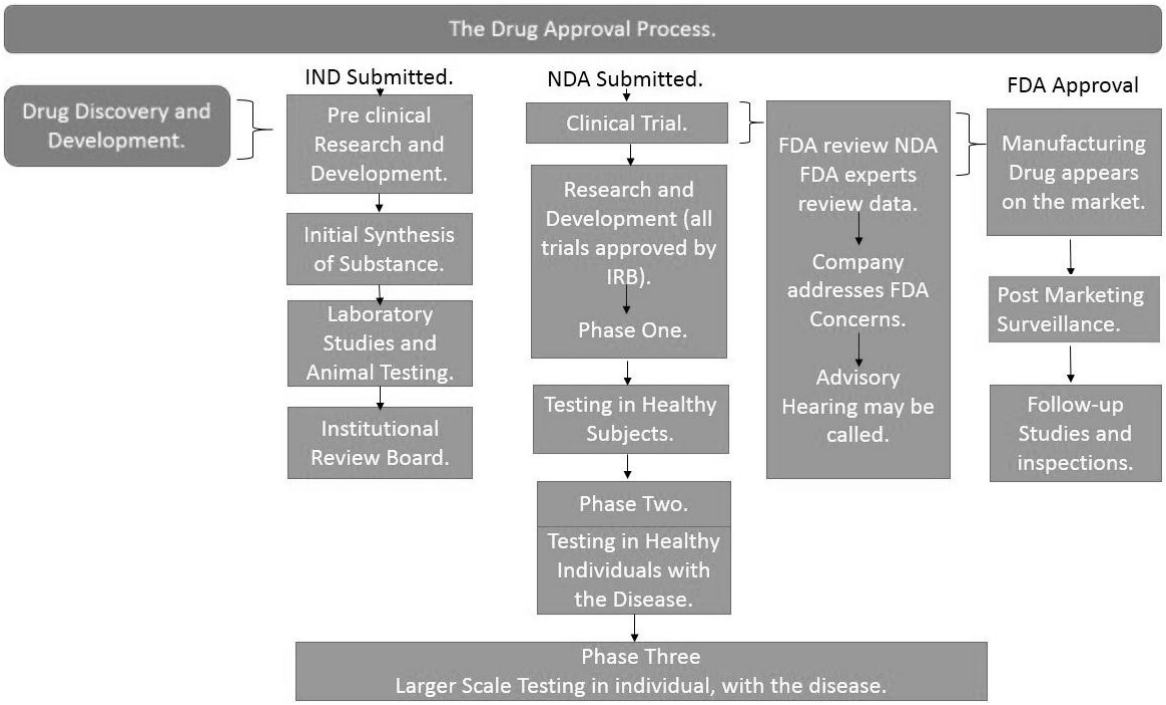

Figure 5: The Drug Approval Process.

So for the safety launch of IND the clinical evaluation is a critical and irrefutable element in the marketing of a new medicinal product.

This requires adequate and tailored clinical studies carried out in a positive way with suitable study management.

So, thus a clinical investigation requires dedicated management of resources documents and overall study progress. The study requires a hand on approach to maintain investigational data, operational management and onsite monitoring in the fields of study.

Onsite monitoring also include various parameters based on studies that explains hierarchy of individual monitoring.

2.2. Consideration of adverse events and pharmacovigilance and a valid case report

The discipline of pharmacovigilance has its improvements in the field with an immense transformation throughout the world over a past few decades.

There are regulatory actions that are been enacted across the countries for the pharmacovigilance legislations for the concerns of healthcare systems and patient safety.

This have led to:

1) Post Marketing Safety Studies.
2) Clinical Trail Safety evaluations.
3) Increasing Trends of e-Submission by Regulators.
4) Innovative Models in Pharmacovigilance Operations.
5) Health Benefit-Risk Assessment.

Thus, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines. This all comes together in the form of valid case which is reported by a valid reporter also known as an identifiable reporter or an identifiable patient and on a suspected product which had shown adverse drug events.

2.3. Adverse Drug Events (ADE)

Any untoward medical occurrence in a patient or clinical investigator subject administered with a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatments.

2.4. Adverse Drug Reaction

An adverse drug reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of distance or for the modification of physiologic function.

"Note that there is a report format of adverse drug reaction."

In the statement to consider, if an event is associated with anyone of the following it is considered to be serious.

A) Death.
B) Life threatening.
C) Hospitalization or prolongation of hospitalization.
D) Congential anomaly disability.
E) Medically significant.

2.5. Volume 9A

Volume 9A brings together general guidance on the requirement, procedures, roles and activities in the fields of pharmacovigilance for both marketing authorization holders and competent authorities of medical product for human use. It incorporate international agreements reached within the framework of the International Conference on Harmonization (ICH).

2.6. CSR

Monitoring data should also contain evaluation of CSR. A CSR includes patient demographies: Like age, gender, suspect product details: drug, dose, dosage form, therapy dates.

Reports on Congenital Anomaly/Birth defect.

Report on suspect that an exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Other serious (Important medical event): Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention. Treatment to prevent one of the other outcome. Example includes allergic condition requiring treatment in an emergency room.

A professional clinical study document should include following requirements.

i). Identifies the specific regulatory requirements to be addressed.

ii). Connect to the risk management activities/plan.

iii). Relates to the clinical claims.

iv). Verifies the need to collect additional/clinical data.

v). Addresses the relevant clinical research questions.

2.7. Specialized submission reports and professional study conduct should include:

i) Compiling Submission Package.

ii) Ethics Committee Submission.

iii) Competent Authority Submission.

iv) Regulatory and EC reporting and Maintenance.

v) Local Hospital Board Approvals.

vi) Submission Planning and Strategy.

vii) Study Amendments and Study Termination.

2.8. Clinical study management also includes support system for maintaining study details

1) Study Protocol.

2) Monitoring Plan.

3) Investigator's Brochure (IB).

4) Trial Reports.

5) Patient Information.

6) Recruitment Materials.

7) Training Slide Decks.

8) Scientific Publication.

9) Journal Manuscript and Abstracts.

10) Investigator Newsletters.

11) Promotional Materials.

12) Educational Materials.

2.9. Some of the commonly used Abbreviations are

ADE: Adverse Drug Event.

ADR: Adverse Drug Reaction.

AGM: Annual General meeting.

BPCA: Best Pharmaceutical for Children Act.

CDER: Centre for Drug Evaluation and Research.

CEVA: Clinical Event Validation and Adjudication.

CHMP: Committee for Human Medicinal Products.

CIOMS: Council for International Organisation of Medical Sciences.

CPD: Clinical Development Plan.

CPG: Consumer Packaged Goods.

CRF: Case Report form.

EMR: Electronic Medical Record.

FDASIA: FDA safety and Innovation Act.

GDD: Global Drug Development.

GRAAS: Global Regulatory Affairs and Safety.

IAPO: International Alliance of Patient Organization.

IBD: International Birth Date.

ICSR: Individual Case Safety Report.

IDE: Investigation Device Exemptions.

iPSP: initial Paediatric Study Plan.

KRI: Key Risk Indicators.

LS: Lifecycle safety.

MCC: Multiple Chronic Condition.

MDAE: Medical Device Adverse Event Reporting.

MedDRA: Medical Dictionary for Regulatory Activities.

NCDS: Non-communicable Disease.

OHDSI: Observational Health Data Sciences and Informatics.

PDCO: Paediatric Committee.

PeRC: Paediatric Review Committee.

PIP: Paediatric Investigational Plan.

PMDA: Pharmaceutical and Medical Devices Agency.

PPSR: Proposed Paediatric Study Request.

PREA: Pharmaceutical Research Equity Act.

PSN: Paediatric Site Network.

PSP: Paediatric Study Plan.

PSUR: Periodic Safety Update Report.

RFP: Request for Proposal.

RFQ: Request for Quotation.

RFT: Request for Tender.

RID: Regulatory Intelligence Database.

RWE: Real world Evidence.

SAE: Serious Adverse Event.

SAWP: Scientific Advice Working Party.

SMO: Site Management Organization.

SSAR: Suspected Serious Adverse Reaction.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

2.10. Process Validation

i) Successful process validation gives assurance about produced Drug Quality in which Drug should be fit for its intended use.
ii) Quality, Safety and Efficacy should be built into the product.
iii) Only if-process test and finished product tests can met give assurance of product quality.
iv) Every step of product manufacturing process should be controlled and assure that finished product passes all the test as per specifications.

2.11. So how should we proceed for process Validation as per US-FDA Guidelines of process validation as below

i) Stage 1 - Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
ii) Stage 2 - Process Qualification: During this stage the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
iii) Stage 3 - Continued Process verification: Ongoing assurance is gained routine production that the process remains in a state of control.

2.12. Source of variation which could play a role in compromising properly which will help in below study

Detect the variation.

Detect the degree of variation.

Detect and understand the impact of variation on process and ultimately on product.

Control the variation.

2.13. Types of process validation

2.13.1. Prospective validation

It is performed before production batches and during the product development. It gives clear idea about risk during production of particular product which helps in risk analysis. It also gives clear idea about critical steps in product manufacturing process.

Evaluate individual risk for each one.

Investigate the same.

Find potential cause.

Check for solutions.

Find out effects.

Set out effects.

All should cover in validation.

Which will give proper idea about validation which will help in actual production of product.

2.13.2. Concurrent validation

It comes when the first three batches of product being manufactured on production scale, very closely. It will give all data required for assessing the batch manufacturing on production scale. This data collected during the batch manufacturing will give precise and in depth idea about its fundamental and with the help of trend analysis and the test results manufacturing process time, stability, one can produce shelf life to extend at the same rate.

2.13.3. Retrospective Validation

Retrospective Validation is done with an ongoing process and process control which have not gone through concurrent validation process for this validation we can use historical data of manufactured batches with proper documenting evidence which shows process is working as it is intended to work because this type of validation is only accepted in well-established process. It cannot be performed when there is any change in API, vendor, formulation changes, manufacturing process change or equipment changes.

2.13.4. Re-validation

Re-validation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional do not adversely affect process characteristics and product quality (WHO).

It can be divided into two types,

A) Re-validation after any change that shows effect on product quality.

B) Second is periodic Re-validation carried out on specified schedule.

A. Re-validation after any change that shows effect on product quality

- Site to site transfer of product.
- Changes in the plant, the product, the manufacturing process, the cleaning process or other changes which cause direct and indirect effects.
- Change in batch size (Increase and decrease).
- Unexpected changes and deviation may be observed during self-inspection or audit, or during the continuous trend analysis of process data.

B. Second is periodic Re-validation carried out on specified schedules

- Equipment wear out may also cause gradual changes.
- Basis on review of historical data, trend should be evaluated.
- Some time it is done in-house like for 1st 3 batches of production year.
- Validation protocol should be as per WHO.
- A suggested scheme for the validation protocol and subsequent report concerning a particular process is shown below.

2.14. Detailed scheme of parts of validation procedure

Part 1. Purpose (the validation prerequisite).

Part 2. Presentation of the entire process and sub process flow diagram, critical steps/risk.

Part 3. Validation protocol, approval.

Part 4. Installation qualification, drawing. (IQ).

Part 5. Qualification protocol/report.

5.1 Sub process 1.

5.1.1 Purpose.

5.1.2 Methods/procedures list of manufacturing methods, SOPs, and written procedures as applicable.

5.1.3 Sampling and testing procedure, acceptance criteria (detailed description of, or reference to, established procedure, as described in pharmacopoeias).

5.1.4. Reporting.

5.1.4.1. Calibration of test equipment used in the production process.

5.1.4.2. Test data (raw data).

5.1.4.3. Result (summary).

5.1.5. Approval and Requalification Procedure.

5.2. Sub Process 2 (same as for Sub process 1).

Part 6: Product characteristics, test data from validation batches.

Part 7: Evaluation, including comparison with the acceptance criteria and recommendations (including frequency of re-validation/requalification).

Part 8: Certification (approval).

Part 9: If applicable, preparation of an abbreviated version of the validation report for external use, for example by the regulatory authority.

The validation protocol and report may also include copies of the product stability report or a summary of it, validation documentation on cleaning and analytical methods.

3. CONCLUSION

Researchers and pharmaceutical companies along with the regulatory authorities are focusing on the development of newer molecular entity or new drug that are to be investigated prior to its launch in the market. This assures the evaluation of safety data of on-site monitoring of the new drug molecule to be established as a new entity to be proven as a therapeutic equivalence or therapeutic importance. The safety evaluation studies include all the parameters that are to be produce during the time of request upon the regulatory submission. This data are monitored and maintained in a proper formats called as dossiers. These dossiers contains the study information of the newer molecular entity and has to be produced and maintained upon the request by regulatory authorities or agencies such as: US-FDA. Few of the regulatory authorities across the world are:

1) US-FDA
2) MHRA
3) EMA
4) EDQM
5) TGA
6) TPD, HPFB of Canada
7) AFSSAPS
8) BFArM
9) ANVISA

10) SWISSMEDIC
11) Spanish Agency of Medicines and Medical Product
12) CDSCO
13) HAS

Thus clinical monitoring in development of newer drug molecules and assessing clinical data found during the phases of study trial finds an important pathway, a key pathway in developing and producing newer drug molecules of therapeutic importance to the market. Conductance of post marketing surveillance in the field of study of the newly marketed drug also summon up the safety evaluation data that is found during the post marketing surveillance obtained from the larger number of population based on the report and valid case that is developed and obtained through the pharmacovigilance studies.

4. APPENDICES

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6. Conflict of Interest

Author declares no conflict of interest regarding publication.

7. REFERENCES

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