STRATEGIC MANAGEMENT FRAMEWORK FOR OSD GENERIC DRUG DEVELOPMENT IN US AND EU MARKETS: A COMPREHENSIVE ANALYSIS AND IMPLEMENTATION STRATEGY

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

By

Akshay Narayan Shinde

Under the Supervision and Guidance of

Dr. Saurabh Kumar

2024

CERTIFICATE

This is to certify that **Mr. Akshay Narayan Shinde** in partial fulfillment of the requirements for the award of the degree of MBA (Pharmaceutical Management) from the IIHMR University, Jaipur has successfully completed his internship at Mankind Pharmaceutical Pvt. Ltd.

Vivek Kumar Pandey

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Mankind Pharmaceutical. Ltd

MANKIND RESEARCH CENTRE 191E IMT MANESAR

Place: Manesar Delhi

Date: 01/07/23

Preceptor/Head of the Department

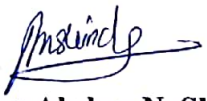
Mankind Pharmaceutical. Ltd

MANKIND RESEARCH CENTRE 191E IMT MANESAR

Arunkumar Maity
SVP- Project Mgmt

DECLARATION BY STUDENT

I hereby declare that this dissertation **"Strategic management framework for OSD generic drug development in US and EU markets: a comprehensive analysis and implementation strategy"** is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.



Name: Akshay N. Shinde

Date: 01/07/2024

IIHMR UNIVERSITY

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DR. SAURABH KUMAR BANERJEE
Faculty Guide
IIHMR University, Jaipur
Date: 1/7/2024

DR. MANTHAN D. JANODIA
School Dean
IIHMR University, Jaipur
Date: 01/07/2024

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141-3924700, 2791431- 32, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

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Vivek Kumar Pandey

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Mankind Pharmaceutical. Ltd

Apunkumar Mgt.
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MBA PM14

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DR. SAURABH KUMAR BANERJEE

Associate professor

School of pharmaceutical management

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ABSTRACT

Objective:

This thesis focuses on regulatory compliance, risk reduction, and timetable budgeting in order to improve project management strategies in the creation of generic oral solid dose (OSD) pharmaceuticals. It examines industry case studies and best practices, assesses risk mitigation techniques, makes sure regulations are followed, and suggests improvements for OSD drug development. It also evaluates the efficiency of the timeline budgeting method.

Methodology: This study used a mixed-methods approach to explore the integration of timeline budgeting within OSD generic medication development. A study of the research, case studies, and stakeholder interviews are all included. Validity and dependability are ensured through data analysis, which includes descriptive statistics for quantitative data and theme analysis for qualitative data.

Result:

The timetable and financial planning for creating generic oral solid dose (OSD) drugs for the US and EU markets are fully described in this thesis. From formulation to regulatory submission (EMA for the EU, ANDA for the US), it covers every step. It also includes risk identification, mitigation techniques, and useful tools for efficient development and approval."

Conclusion:

In particular, the study emphasizes rigorous formulation development, regulatory compliance through bioequivalency studies, and strategic planning for MAA and ANDA approvals. The study focuses on the methodical production of generic oral solid dose pharmaceuticals.

Keywords:

OSD generic drug development, project management, risk mitigation, budget estimation, timeline planning, cross-functional collaboration, key performance indicators (KPIs), regulatory filing.

ACKNOWLEDGEMENT

Project is like a bridge between theoretical and practical working. With this wiling, I joined the project **"Strategic management framework for OSD generic drug development in US and EU markets: a comprehensive analysis and implementation strategy"**. First of all, I would like to thank the supreme power the Almighty God who is obviously the one has always guided me to work on the right path of life. Next to him are my parents, I'm greatly indebted to them for support, love and encouragement at every stage.

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Akshay N. Shinde

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LIST OF ABRIVATIONS

USFDA	:	United States Food and Drug Administration
CTD	:	Common Technical Document
ANDA	:	Abbreviated New Drug Application
NDA	:	New Drug Application
GMP	:	Good Manufacturing Practices
GDEA	:	Generic Drug Enforcement Act
QOS	:	Quality Overall Summary
EU	:	European Union
CFR	:	Code of Federal Regulations
RLD	:	Reference Listed Drugs
EAS	:	Environment Assessment Statement
EPA	:	Environment protection act
OGD	:	The Office Generic drugs
SU	:	Scale up
AMV/AMT	:	Analytical Method validation/Analytical method Transfer
RA	:	Regulatory Affair
ARD	:	Analytical Research Development
FRD	:	Formulation Research and Development
EB	:	Exhibit Batch
CDER	:	The Centre for Drug Evaluation and Researches

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CHAPTER 1

INTRODUCTION

1.1. Background:

The development of generic OSD drugs for emerging markets requires meticulous planning and coordination across multiple departments. The role of a project manager in this context is critical to ensure the project's success within the defined budget and timeline. This paper examines the step-by-step process, from project initiation to the final submission for regulatory approval. A product made of generic drugs is defined as "a drug product that is comparable to a branded drug product or an RLD drug product in terms of intended use, quality and performance characteristics, dosage form, and route of administration." It can also refer to any drug that is offered either to the drug's chemical makeup rather than the marketing brand name it is sold under, or to its chemical name without any advertising. [2]

The active ingredient in generic drugs is the same as that in name-brand products. The US FDA states that the pharmacokinetic and pharmacodynamic properties of generic medications are identical to those of branded medications. [2]

When generic products are introduced to the market, competitive pressures usually lead to significantly reduced costs for both the brand-name product that was initially sold and its generic substitute. [2]

A generic medication may take a variety of times to reach the market. The majority of nations on earth grant 20 years of protection through patents. Nonetheless, a few of nations and areas, such as the USA and the European Union, may offer medicines an extra five years of protection (a process known as "patent term restoration"). [2]

The market for generic drugs is enormous and extremely profitable for everyone, including pharmaceutical corporations. This topic is based on the state of the generic medicine market today, the creation of generic drugs, budgeting and time management, risk management, the need for technical documentation, the requirements of regulations for the US and EU markets, and the different steps involved in the filing and approval of generic drugs. [3]

Because of the following factors, generic drugs are less expensive than innovative ones:

1. The identification and isolation of new chemical entities are free of cost.
2. Minimal the cost R&D
3. Because branded drugs have previously been approved as safe and effective, a minimum marketing expenditure is required. While brand-name drugs are still vital in medicine, generic versions are more affordable. [3]

According to our analysis, generic medicine markets in the US and Europe provide potential for cost savings. Regulators ought to facilitate the market entry of generic medications. The usage of generic drugs should rise, and payers and regulators should take action to encourage price competition among generic medication manufacturers. [4]

In 2023, the value of the worldwide generic medication market was projected to be USD 3, 20,307.22 million. Over the course of the forecast period, it is anticipated to increase from USD 343145 million in 2024 to USD 484209 million in 2029, at a CAGR (compound annual growth rate) of 7.13%.[5]

1.2 Importance of OSD Generic Drug Development

The development of OSD generics not only addresses market demands for cost-effective medications but also supports healthcare systems in providing accessible treatments to a broader population. This sector's growth is crucial for pharmaceutical companies aiming to expand their market reach and capitalize on global healthcare needs.

1.3 Importance of Timeline & Budgeting in OSD generic drug Development

Timeline budgeting plays a crucial role in ensuring the success and efficiency of pharmaceutical development projects:

a) Efficient Allocation of Resources: Allocation of persons, money, and time in such a way to complete the project according to deadlines and milestones.
b) Accounting and Predictability: Accurate time estimates and budget forecasts impose accountability and allow efficient tracking of progress during project execution.
c) Risk Management: In fact, cost and schedule control of the projects are much dependent on thinking ahead and minimizing probable risks as much as possible.
d) Faster Time to Market: Development schedules can be reduced, enabling a more competitive product position and shortened time-to-market.

1.4 Significance of Integrating Risk Mitigation Strategies

Risk mitigation steps in pharmaceutical development are basically inherent barrier and uncertainty management processes. The chosen methodologies matter a lot in safeguarding the success of the project and the welfare of patients. The key strategies include:

a) Risk identification: This is an all-inclusive assessment to discover all possible risks that may pertain to project budgets, schedules, or quality of the product.

b) Risk mitigation planning: These are proactive actions to either reduce or entirely eliminate an identified hazard before escalation.

c) Contingency planning: It involves the design of tactics to mitigate unforeseen adversities in case they may arise in any stage of the project flow.

d) Security and Compliance: Throughout the drug manufacturing process, it is very paramount to ensure the safety of the patients while adhering to the regulatory requirements.

e) Business Continuity: minimizing the effect on active initiatives for business continuity in order to maintain operational resilience.

f) Management of Risk: If efficient risk reduction techniques are enacted into projects, building resilience against threatened delays or failures reduces the expenses associated with these phenomena.

1.5 Objectives of the thesis

The following thesis seeks to advance understanding and better the application of project management techniques in generic oral solid dosage pharmaceutical development so as to meet three critical objectives: regulatory compliance, mitigation of risk, and timetable budgeting.

a) Analyze Timeline Budgeting: This is the first of the goals: utility regarding timeline budgeting for the development of medications within OSD—looking into how it might be able to help refine project scheduling, allocate resources more efficiently, and make the whole project more productive.
b) Risk Mitigation: The second objective assesses the extent to which risk mitigation strategies within OSD generic drug development are taken into consideration. Typical hazards are listed, how they can affect the outcome of a project is assessed, and practical techniques aimed at their reduction are considered.
c) Regulatory Compliance Verification: Ensure adherence to the legal and regulatory requirements of various markets. This objective confirms compliance with the related legal requirement to accelerate the process of product approval and market entry.
d) Analysis of Case Studies and Best Practices: The best practices and relevant case studies in the pharmaceutical business were considered in this thesis. These lessons and solutions give useful insights through practical examples of efficient timeline budgeting and risk reduction techniques.
e) Improvement Suggestions: Based on this study, this thesis suggests the inculcation of better risk mitigation techniques and facilitation of timeline budgeting procedures

within OSD generic medication development. All suggestions have, therefore, been targeted at enhancing the procedure and outcomes of project management.

1.6 Scope of the Thesis

a) Pharmaceutical Development Processes: Very related to this is an area on which the thesis works in great detail: the development process of generic oral solid dose medications. Beginning with the drug product's research and development, it covers all processes of product development, method development and validation, evaluation of bioequivalence, submission of regulatory filing, and implementation of post-approval commitments.
b) Timeframe Budgeting: This section will cover all concepts, practices, tools, and methods of pharmaceutical project management with regards to timeline budgeting. The result that the study is focusing on is how timeframe budgeting can lead to improved project outcomes and more effective resource management.
c) Risk Reduction Techniques: Detailed review of various risk-reduction techniques applicable for the manufacture of generic oral solid dose (OSD) products will be within the scope of work. This shall include the identification of potential risks associated with a project in advance, techniques relating to assessing such risks, risk response planning, and monitoring arrangements in order to minimize an exceedance of risk.
d) Submission details with a step-by-step approvals process in US (FDA) and EU (EMA).
e) Case Studies & Analysis Comparisons: Case studies assessments and comparative studies are part of the examples that will be included in the thesis about the subject, plus literature and business examples. The result of this comparison study will emphasize or demonstrate their efficiency and application upon some time-based budgeting and risk-reduction techniques.
f) Practical Recommendation: In this way, the thesis conclusion will be able to give pharmaceutical companies and other stakeholders involved practical recommendations on strategizing the development of generic oral solid dosage drugs. These are proposals with risk reduction and efficient scheduling at their core and thoughts for improved project management practices that reshuffle output and result in successful projects.

1.7 Challenges in Regulatory Approval

For OSD generics to be approved, regulatory agencies such as the European Medicines Agency (EMA) and the US FDA have requirements that must be fulfilled. These criteria require careful planning and execution throughout the drug development lifecycle and cover extensive evaluations of product quality, safety, and efficacy.

1.8 US FDA Criteria (Generic drug product)

According to the US FDA, generic pharmaceuticals must be pharmacologically comparable to innovator drugs if the active components are given in the same dosage form, at the same concentration, and with the same administration technique.[3] When potential bio-involution issues are absent, a generic medication functions biologically in the same way. [3] They have sufficient labeling and are regarded as safe and effective. [7] They satisfy the same standards of quality, strength, purity, and originality. [3] The FDA's good manufacturing practice requirements, which specify the same stringent regulations as innovator items, are followed during their manufacturing. [8] The word "bioequivalence" refers to a unique class of research in which two medications, or two formulations of the same medication, are contrasted to demonstrate that their PK/PD parameters and bioavailability are almost same.

1.9 European Medical Agency (EMA)

The primary duty of the regulatory agency, sometimes known as a decentralized body, is to safeguard and advance the health of the people and animals by assessing and supervising the use of medications for both human and veterinary purposes. One of the most respected regulatory frameworks in the world is found in the EU. [3, 25]

1.10 Various national regulatory bodies [3, 22, 23, 24]

1.10.1 USA

National Institutes of Health (NIH): Food and Drug Administration (FDA); Centers for Disease Control and Prevention: Office of Disease Prevention, National Science Foundation; Department of Health and Human Services (DHHS); National Library of Medicine; National Institutes of Health (NIH)

1.10.2 Europe

The European Directorate for the Quality of Medicines and Healthcare (EDQM), the European Medicines Agency (EMEA), Heads of Medicines Agencies (HMA), and EU Legislation - Eudralex

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of OSD Generic Drug Development

Oral solid dosage (OSD) generics play a crucial role in providing affordable healthcare solutions globally, particularly upon patent expiration of originator drugs. Regulatory approval for OSD generics in the EU (EMA) and US (FDA) requires rigorous demonstration of bioequivalence, stability, and manufacturing consistency (EMEA, 2008; FDA, 2019). Challenges include navigating complex regulatory landscapes and optimizing development timelines and budgets

2.2 Timeline Budgeting in Pharmaceutical Development

Timeline budgeting integrates project management principles with budget constraints to optimize resource allocation and scheduling (Archer & Ghasemzadeh, 2017; Berman, 2012). Benefits include improved cost control, enhanced decision-making, and reduced time-to-market (Garets & Davis, 2008). Challenges include accurately forecasting costs and timelines amidst uncertainties in regulatory approval processes and market dynamics (Kwak & Ibbs, 2000).

2.3 Pre-Formulation Investigation (PPIF) and New Product Development (NPD)

PPIF involves early-stage studies to understand drug substance properties and formulation challenges (Martinez & Amidon, 2002). NPD strategies focus on optimizing formulations and processes to ensure bioequivalence and stability (FDA, 2015). Effective PPIF and NPD are critical for laying the groundwork for successful OSD generic development (EMEA, 2012).

2.4 Formulation Strategies: AMD, AMV, AMT

Advanced formulation design (AMD) techniques, such as solid dispersion and microencapsulation, enhance drug solubility and bioavailability (Douroumis, 2012). Analytical method validation (AMV) ensures the reliability and robustness of analytical procedures used to assess the quality of pharmacological products (ICH, 2005). The FDA (2003) states that accelerated stability testing, or AMT, expedites the prediction of a drug product's shelf life under stressful circumstances.

2.5 Pilot Studies, Scale-Up (SU), and Exhibit Batch (EB)

Pilot studies bridge laboratory-scale formulations to commercial production, ensuring scalability and process optimization (Ghaderi & Hekmat, 2011). Scale-up (SU) challenges include maintaining batch uniformity and meeting regulatory standards (FDA,

2009). Exhibit batches (EB) refine manufacturing processes to ensure consistency in drug product quality (Ghaderi & Hekmat, 2011).

2.6 Pivotal Studies and Stability Data Generation

Pivotal studies demonstrate bioequivalence and therapeutic equivalence of OSD generics compared to reference products (EMA, 2014). Stability data generation follows ICH guidelines to establish drug product shelf-life and storage conditions (ICH, 2003). Rigorous study design and data analysis are essential for regulatory approval (FDA, 2017).

2.7 Regulatory Filings and Risk Mitigation Strategies

Regulatory filings require comprehensive documentation of data supporting product quality, safety, and efficacy (EMA, 2019). Risk mitigation strategies in pharmaceutical development include proactive risk assessment, contingency planning, and compliance with regulatory requirements (Mishra & Deshmukh, 2016). Effective risk management enhances project predictability and regulatory success (FDA, 2014).

2.8 Comparative Analysis: EU vs. US Requirements

The EU and the US have different regulatory requirements for OSD generic medication clearance, which affects documentation standards and approval timelines (EMA, 2018; FDA, 2020). Development methods and market entry are impacted by differences in post-approval responsibilities and bioequivalency study designs (FDA, 2018).

CHAPTER 3

METHODOLOGY

3.1 Research Design

Using a mixed-methods methodology, this study investigates the integration of timeline budgeting into OSD generic drug development processes. Mixed-methods research mixes qualitative and quantitative data collection techniques to create a comprehensive understanding of complicated occurrences (Creswell, 2014).

3.2 Data Collection Methods

Literature examination: To get information on OSD generic drug development, timetable budgeting methodologies, and regulatory requirements, a comprehensive examination of peer-reviewed journals, regulatory guidelines (EMA, FDA), and industry reports was carried out (Greenhalgh, 2018; Tranfield et al., 2003).

Case Studies: Based on their applicability to the stages of OSD generic drug development (formulation, pilot studies, and regulatory submissions), a number of case studies were chosen. Interviews with important stakeholders and document analysis were used to gather data (Yin, 2014).

3.3 Analytical Techniques

Data Analysis: Qualitative data from interviews and document analysis were analyzed using thematic analysis to identify key themes related to timeline budgeting integration and risk mitigation strategies (Braun & Clarke, 2006). Descriptive statistics were used for comparative examination of quantitative data from case studies.

3.4 Ethical Considerations

Ethical Approval: Ethical approval was obtained from the XYZ Ethics Committee prior to conducting interviews to ensure compliance with ethical standards in research involving human subjects.

3.5 Validity and Reliability

Validity: Triangulation of data sources (literature, case studies, interviews) and member checking during interviews were employed to enhance the validity of findings (Guba & Lincoln, 1989).

Reliability: Consistency in data collection methods, including standardized interview protocols and documented case study criteria, aimed to ensure reliability across different data sources.This detailed methodology ensures a comprehensive and systematic approach to the development of generic oral solid dosage forms, addressing all critical aspects necessary for successful drug development and regulatory approval.

3.6 OSD GENERIC DRUG DEVELOPMENT

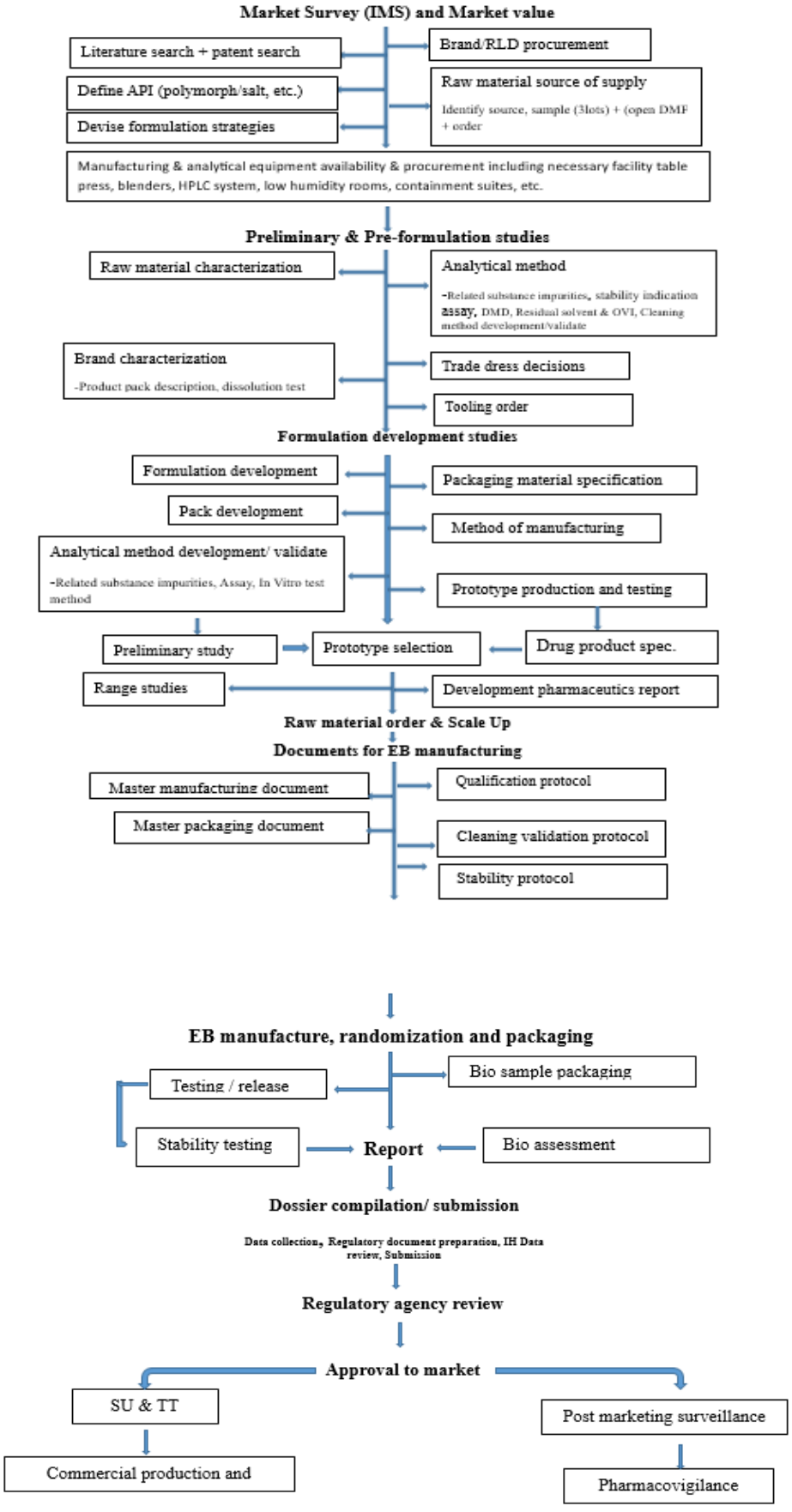

Figure-3.1: OSD Generic product development

3.6.1 Development Strategy:

The formulator needs to be aware of the unique legal requirements in each country where the medication is sold and planned to be filed before creating a generic version of the product. Compared to RLD drugs, this development employs a distinct methodology and strategy. The formulation of a generic medication must match that of its branded equivalent in terms of medicinal efficacy, safety, and performance characteristics. [6]

A great deal of scientific scrutiny and research are needed in the production of generic products for the pharmaceutical sector. The designated launch date must be met through careful strategic planning. [9]

Because different markets have distinct requirements, the formulation researcher must be aware of and conduct an analysis of the specifics of the products being developed as well as the target market. Before a formulation researcher may begin producing a product for the American market, it must pass the bioequivalency study of the novel product in the US and fulfill the USP method's physical and chemical requirements. It is not possible to commercialize a product created in accordance with US criteria in the EU/UK or vice versa. [10]

However, manufacturers of generic medications must demonstrate that the potency and quality of their formulations are bioequivalent to those of name-brand medications. While developing a unique medicine formulation, there are few limitations on excipients, manufacturing processes, and performance measurements. [11]

3.6.2 Examining Patent Restriction Issues:

An NDA outlining the parameters of "exclusivity" and "essential" patents for medicines that have been approved is developed when a medication produced with an NCE is submitted to the FDA for approval. This list can be found in the FDA's "Approved Drug Products under Evaluation of Therapeutic Equivalency," or "Orange Book." The inventor owns a monopolistic commercial license prior to the patent expiring. Thus, industry should definitely consider patent status and market share before selecting a generic product for development. [12]

3.6.3 Selection and characterization of the reference product

One of the most crucial requirements for the creation of generic medicines is, as previously stated, the bioequivalence of generic medications with listed drugs (RLD) [13]. By conducting a literature search of the US FDA database and using their NDA number, selecting a reference product for the US market is simple [14]. To determine the RLD for the EU market, the formulation investigator needs to consult a public assessment

report like UKPAR or EPAR. The European Medicines Agency EMA also helps with questions [15]. After the RLD of the pharmaceutical industry, all in vitro solubility tests of the respective substances, especially analyses, are carried out in the laboratory. The major goal of the formulation researcher is to analyze the reference drug's dissolution data and develop a generic qualitative and quantitative formulation that matches the dissolution profile, as the in vitro - in vivo correlation may be utilized to determine the percentage of predictability. [16].

3.6.4 Target Market Selection

The company's approach to developing a generic product, analyzing reference and generic products, choosing lot sizes, conducting stability tests, and other processes are all influenced by the target market selection. All excipients must meet USP quality standards, testing must be conducted using either our proprietary method or the USP method, and stability studies must be completed if the company intends to sell in the US. once more, given that a reference product from the EU that is authorized for use in the UK is used in the bioequivalency study. In this case, the dissolution profiles of the EU reference product and the UK reference product should be the only comparison that is shown. [1]

3.4.5 Feasibility of production:

Evaluating product profitability is always important in the pharmaceutical industry. The feasibility report characterizes the entire generic product development process. The maker of a generic product must have a facility for drug manufacturing, stability testing, and bulk production that is approved by the MHRA or GMP in order to register the product in the US, EU, or other countries. After that, the inspector also visits the factory before delivery and before delivery of documentation and other paper. [17]

3.7.1. Project Initiation:

3.7.1.1. Initial Steps:

Receipt of the Project Proposal Information Form (PPIF) from the Business Development (BD) department. After receiving the PPIF, coordination with all relevant departments to gather necessary inputs. Sharing the PPIF with the sourcing team to get the cost of API and RLD.

Distribution of PPIF to Analytical Research & Development (ARD), Formulation Research & Development (FRD), Packaging, Plant, Clinical Research Department (CRD), and Regulatory Affairs (RA) for comments.

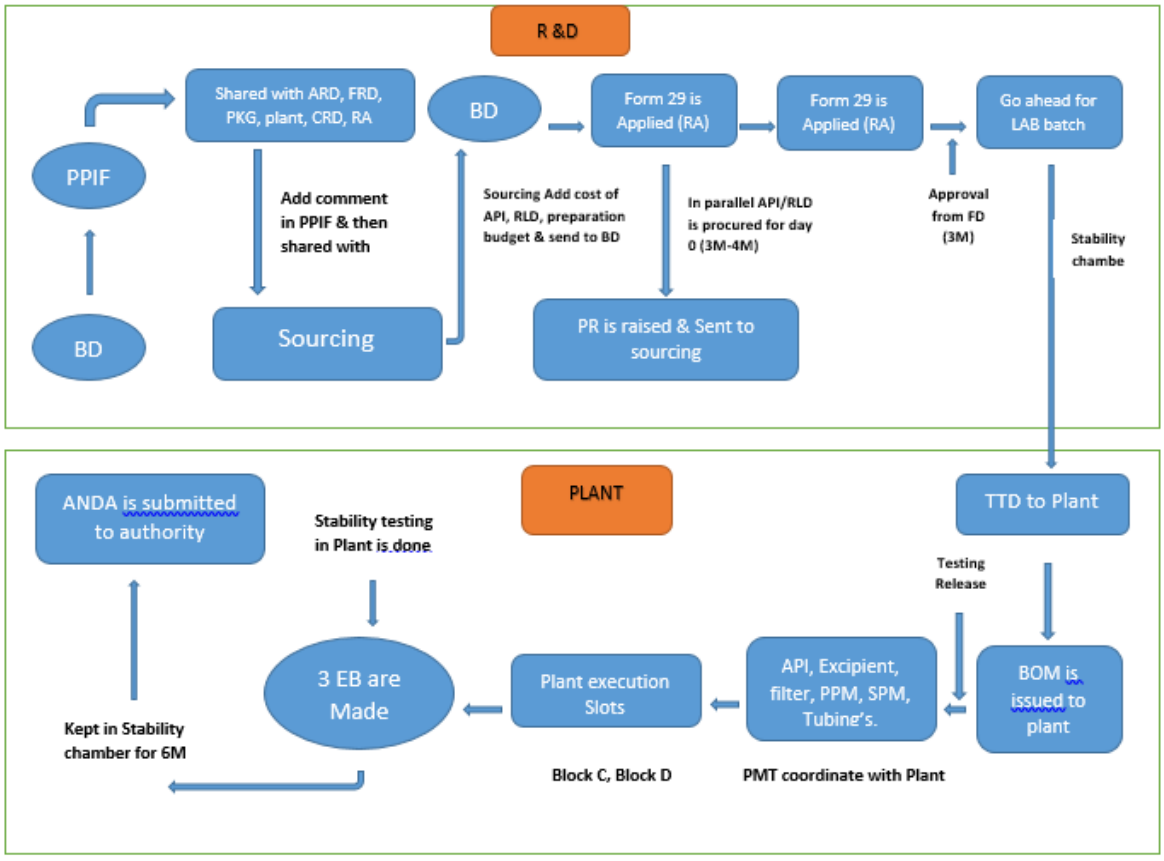

Figure-3.2: OSD Generic drug product development (Initiation to filing 1-3 Year)

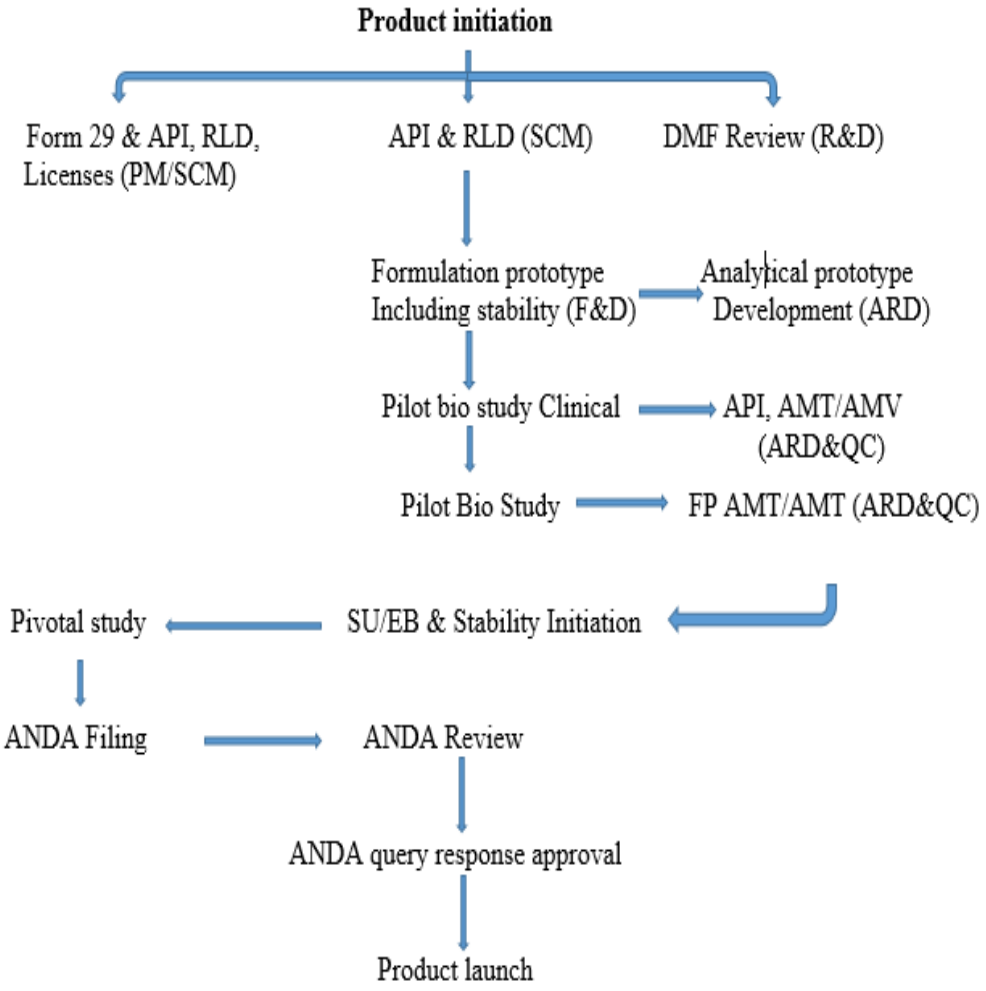

Figure-3.3: Product development cycle

A. Key Activities and Responsibilities:

Activity	Department	Description
NPD receive	BD Department	Receipt of new product development proposal
NOC/Form29	RA/ licensing Team	Regulatory approval process
RLD & API, RM, PM, analytical requirements	GSD	Reference Listed Drug and formulation development
COGS	GSD	Cost of Goods Sold
API procurement	FRD	Procurement of Active Pharmaceutical Ingredients
Formulation development	FRD	Formulation development
Analytical development	ARD	Analytical development
3-month stability data	ARD	Collection of stability data
AMV/AMT completions	ARD	Analytical Method Validation/Analytical Method Transfer
Pilot study	CRB	Conducting pilot bioequivalence study
Technology Transfer	TT team	Preparation of the manufacturing site
Procurement of RM/PM for EB	GSD	Raw material and packaging material procurement
EB execution	Production/TT/QA	Execution of Exhibit Batches
Stability testing	QC	Conducting stability testing for regulatory submission
Filing	RA	Submission of ANDA to regulatory authority
New drug approval	Regulatory Authorities	Final approval of the new generic drug
Commercialization	Marketing & Sales	Launching the product in the market

Table-3.1: Key Activities and Responsibilities:

PPIF Include:

- **Basic Information:** Brand / Company, Molecule, Dosage Form, RLD, Strength, Fill Volume, Approval Date, Territory, Earliest Launch Date, Expected Filing Date, RLD Formulation, RLD Trade Dress and Packs
- **Market Situation**: Approvals, IMS (MAT Jun-20), Growth (Val / Vol), MAT Jun-20/Jun-19, IMS (MAT Jun-20) Vol, Market API (Kgs MAT Jun-20), Known Generic filers/approvals, other potential Generic, DMF filers (2Q 2020)
- **IP Situation:** NCE-1 (US), Other Exclusivities (US), OB Patents, PTE, Non-OB patents
- **Mankind Target Product RLD:** API, Trade dress and Packs, BE / Clinical
- **Regulatory Strategy:** Regulatory Strategy

Objective: Preliminary assessment of market potential and regulatory feasibility.

Activities: Market research, initial risk assessment, regulatory pathway analysis.

Regulatory Considerations: Identification of reference listed drug (RLD) and patent landscape.

Risks: Incompatibility of API with excipients, stability issues.

Mitigation: Thorough preformulation studies, use of compatible excipients.

Tools & Techniques: Use X-ray diffraction (XRD), thermogravimetric analysis (TGA), and infrared spectroscopy (IR) for comprehensive characterization. and differential scanning calorimetry (DSC).

3.7.1.2. Budget and Timeline Preparation:

Consolidation of input from various departments. Preparation of a detailed budget considering costs related to Active Pharmaceutical Ingredients (API), Reference Listed Drug (RLD), excipients, analytical testing, packaging, technology transfer, and regulatory filing.

Timeline calculation based on activities such as literature review, RLD and API availability, formulation development, stability studies, and regulatory submission. Compilation of all costs and preparation of the final budget. Timeline finalization based on departmental inputs.

A. Cost Estimation:

I. Cost Components:

- API cost for development and SU/EB
- RLD cost
- Excipient cost
- Analytical cost
- Packaging and tubing cost
- Capital expenditure
- Technology transfer cost
- Litigation cost
- Long-term stability study cost
- Pilot and pivotal study cost
- Regulatory filing cost
- Miscellaneous costs

II. Cost Estimation Process:

- Collection of data from respective departments.
- Consolidation and finalization of the project budget.

III. Detailed Cost Estimation (Tentative cost for product XYZ)

Budget segment	INR	USD
RLD Cost	31011200	387640
API Price & Vendor, API Cost for Dev	436880000	546000
Excipient Cost	11904000	148800
API Cost for SU/EB	29760000	372000
Analytical Cost	60001920	75024
Packaging Material Cost	50000	625
Capital Expenses	NA	NA
Tech Transfer (if CMO)	NA	NA
Litigation Cost	NA	NA
L/E Studies	NA	NA
Pilot Bio Studies	7500000	31250
Pivotal Bio Studies (Common)	7500000	93750
Pivotal Bio Studies (Local)	NA	NA
Regulatory Filing Costs	42118880	526486
Misc. Costs / Other Costs (if any)	2500000	31250
TOTAL Costs	177026000	2212825

Table-3.2: Tentative cost estimation for product XYZ

B. Timeline Calculation:

i. Key Milestones:

- Project initiation and target completion dates, Literature review, API and RLD availability.
- Formulation prototype and pilot study completion, Stability data collection and readiness for ANDA filing.

ii. Timeline Overview:

Activity	Duration (Months)	Remarks
Project Initiation	-	NPD Received
Literature Review	NPD+1M	Background research
RLD available	NPD+2M	Procurement of necessary materials
Dev API available	NPD+2M	Procurement of necessary materials
Formulation Prototype	Kick-off+NPD+3M	Development and initial testing
Pilot Submission	Kick-off+9M	Bioequivalence study
Pilot Bio completion	Kick-off+12M	Bioequivalence study outcome
AMV/AMT	Kick-off+14M	ensuring accuracy
Scale up -if any	Kick-off+15M	Increase production capacity, if needed.
Exhibit Batch To	Kick-off+17M	Provide specific batches for examination
Pivotal Bio Initiation	Kick-off+18M	Start crucial biological phase in trials
Pivotal Bio completion	Kick-off+22M	Finish key biological endpoint assessments.
6M Stability Data	Kick-off+24M	Stability data collection
Readiness for ANDA Filing	Kick-off+25M	Preparation for regulatory submission

Table-3.3: Timeline Overview

3.7.2. NPD received from BD & Business Viability and Regulatory Approval:

Objective: Conceptualization and planning of the generic product.

Activities: Initial formulation development, feasibility studies, selection of excipients and manufacturing processes.

Risks: Suboptimal formulation, scalability issues.

Mitigation: Iterative formulation development, pilot studies.

Tools: Design of experiments (DoE) for optimizing formulation variables; application of quality by design (QbD) concepts.

If the endeavor is successful, BD team passed the NPD with the approval of management & the RA department applies for Form 29. Also, Procurement of API and RLD.

Requirement:

a) PIF or NPD from BD Team

b) Filing strategy & control correspondence by FRD & RA

c) Sourcing of API, RM, PPM & DMF Review comment from FRD, ARD, RA, Sourcing & PKG

d) RLD selection & availability from PMO & ARD

e) Form 29 document by FRD & ARD

f) Form 29 availability for research center, manufacturing licenses for plant & Import license by PMO

g) Budget allocation & COBS creation by PMO, Account & Finance

h) PDF value generation for MACCO value from PMO & FRD

3.7.3. Formulation & Analytical Development

3.7.3.1 Selection of Active Pharmaceutical Ingredient (API) and Excipients

API Selection: The selection of the API is based on its therapeutic equivalence to the reference listed drug (RLD). Factors such as solubility, stability, and bioavailability are considered.

Excipients Selection: Suitable excipients are chosen based on their compatibility with the API, functionality (e.g., fillers, binders, disintegrants), and regulatory acceptance. Common excipients include microcrystalline cellulose, lactose, starch, and magnesium stearate

3.7.3.2 Formulation Development

Pre-formulation Studies: Conduct studies to understand the physicochemical characteristics of the API, including its polymorphism, hygroscopicity, and dissolution.

Formulation Design: Develop various formulations using different ratios of API and excipients. Consider factors like as stability, manufacturability, and dissolving rate while evaluating these formulations.

Optimization: To optimize the formulation, apply Design of Experiments (DoE) and Quality by Design (QbD) techniques. To find the best formulation, this entails testing many variables systematically.

3.7.3.3 Analytical Method Development

Method Development: Create analytical techniques to measure the API and find contaminants. Methods including UV spectroscopy, mass spectrometry (MS), and high-performance liquid chromatography (HPLC) are frequently employed.

Method Validation: Examine criteria such as accuracy, precision, specificity, linearity, range, and robustness when validating the analytical methods in accordance with ICH principles.

Objective: Creating reliable and repeatable formulations and analytical techniques.

Activity: Completing the formulation and creating reliable analytical techniques for quality assurance.

Regulatory Considerations: Compliance with ICH Q8 and Q2(R1) guidelines.

Risks: Poor formulation stability, inadequate analytical methods.

Mitigation: Robust formulation development, validation of analytical methods.

Tools & Techniques: Gas chromatography (GC), dissolution testing, High-performance liquid chromatography, or HPLC, and additional standard operating procedures for the development and validation of analytical methods.

Requirement:

a) IPR clearance- PPAR report & RLD reverse engineering by ARD
b) API quantity calculation (development to EB) from FRD
c) Proposal for Q1/Q2 approval from FRD& RA
d) Prototype formulation optimization & Filter validation by FRD
e) Cleaning method development by ARD, FRD & plant
f) Identification of outsource lab by ARD, PMO & sourcing
g) Requirement for MACCO value for cleaning method development by FRD & ARD
h) Pilot bio & Pivotal BE for OSD product by FRD & CRB
i) Bio study result availability from FRD & CRB

3.7.4. Pilot Bio study

Feasibility Studies: Conduct small-scale studies to evaluate the feasibility of the developed formulation. Parameters such as blend uniformity, compression characteristics, and dissolution profiles are assessed.

Process Optimization: Optimize the manufacturing process based on pilot study results. This includes refining the blending, granulation, and compression steps.

Objective: Evaluate the feasibility of the proposed formulation on a small scale.

Activities: Small-scale production, initial stability studies, evaluation of manufacturing process feasibility.

Risks: Scale-up challenges, stability failures.

Mitigation: Application of Failure Mode and Effects Analysis (FMEA) and other risk management technologies. expedited stability testing and pilot-scale batch production.

Tools & Techniques: Miniaturized manufacturing equipment, accelerated stability chambers, statistical analysis of pilot data

3.7.5. AMV/AMT

To guarantee the quality and safety of products, analytical method validation is a crucial procedure in the food, biotechnology, and pharmaceutical industries. The purpose of an analytical method's validation is to confirm that it is appropriate for the intended usage. The formal procedure that authorizes a laboratory (the receiving unit) to employ an analytical test procedure is known as analytical method transfer.

Objective: Validation of analytical methods and transfer to production facilities.

Activities: Validation protocols, inter-laboratory transfer studies.

Risks: Method transfer issues, validation failures.

Mitigation: Detailed validation protocols, training of QC personnel

Tools: Statistical analysis software, Laboratory Information Management Systems (LIMS). Inter-laboratory studies, use of ICH Q2(R1) guidelines for method validation.

3.7.6. SU Batch execution

Scale-Up Batch Production: Transition from laboratory-scale to pilot-scale production. Ensure that the process is scalable and that the product quality remains consistent.

Equipment Selection: Select appropriate equipment that can handle larger batch sizes while maintaining process parameters.

Process Validation: Conduct process validation to ensure that the scaled-up process produces a product that meets all quality specifications. This involves multiple production runs to confirm consistency.

Objective: Scale-up of the formulation to commercial manufacturing scale.

Activities: Optimization of process parameters, scale-up validation batches.

Risk Mitigation: Process Analytical Technology (PAT) tools to monitor critical process parameters.

Tools & Techniques: Use of process analytical technology (PAT), real-time monitoring, statistical process control (SPC).

Requirement:

a) Availability of related documents to SU batch from FRD & ARD
b) Specification, Analytical method, cleaning method, AMV/AMT from ARD
c) RS & Working standard from ARD, QC & PMO

d) Availability of equipment for SU batch from plant, FRD & PMO
e) API, excipient & PPM Availability & release in SAP by QC, QA & PMO
f) Specification & STP availability from ARD, QC & PMO
g) Batch execution schedule & Slot block in plant by PMO
h) Pre- intimation to all concerned person regarding slot block & availability of all necessary item for batch execution by PMO
i) SU report from Plant TT team
j) Update risk assessment & control strategy by plant TT team

3.7.7. EB Batch execution

Full-Scale Production: Manufacture exhibit batches under full-scale production conditions. These batches provide as evidence that the procedure can reliably yield a product of a respectable caliber.

Documentation: Document all manufacturing steps, in-process controls, and quality checks to support regulatory submissions.

Objective: Production of batches for regulatory submission and clinical studies.

Activities: Manufacturing exhibit batches under GMP conditions, comprehensive testing.

Regulatory Considerations: Compliance with FDA/EMA guidelines for batch records and stability data.

Risks: Non-compliance with regulatory standards.

Mitigation: Adherence to regulatory guidelines, thorough documentation.

Tools & Techniques: Documentation management systems, compliance checklists.

Requirement:

a) Availability of related documents to EB batch from FRD & ARD
b) Specification, Analytical method, cleaning method, AMV/AMT from ARD
c) RS & Working standard from ARD, QC & PMO
d) Availability of equipment for EB batch from plant, FRD & PMO
e) API, excipient & PPM Availability & release in SAP from QC, QA & PMO
f) Specification & STP availability from ARD, QC & PMO
g) Batch execution schedule & Slot block in plant by PMO
h) Pre- intimation to all concerned person regarding slot block & availability of all necessary item for batch execution from PMO
i) EB Summary report from Plant TT team
j) EB stability loading & Analysis by QA, QC & PMO
k) Any deviation in exhibit batch by QA, QC & FRD

3.7.8. Pivotal Bio study

Bioequivalence Studies: Conduct pivotal bioequivalence studies to compare the generic product's pharmacokinetic profile with that of the RLD. This entails giving the medication to volunteers in good health and calculating metrics like AUC and Cmax

Safety and Efficacy: Obtain more information on the generic product's effectiveness and safety, if necessary, by regulatory bodies.

Objective: To prove therapeutic equivalency, carry out crucial bioequivalence investigations.

Activities: Clinical trial design, subject recruitment, data analysis.

Risks: Bioequivalence failure, adverse effects.

Mitigation: Rigorous study design, monitoring.

Tools: Clinical trial management systems (CTMS), electronic data capture (EDC) systems.), bioanalytical methods, pharmacokinetic (PK) and pharmacodynamic (PD) modeling.

Requirement:

a) Complete COA generation for pivotal batch from QC, PMO & FRD
b) Pivotal bio study batch dispatch from PMO

3.7.9 Stability Studies

3.7.9.1 Stability Testing

Study Design: Design stability studies as per ICH guidelines to evaluate The stability of the product in various environments (e.g., temperature, humidity).

Accelerated and Long-Term Studies: Conduct both accelerated (e.g., 40°C/75% RH for 6 months) and long-term (e.g., 25°C/60% RH for 12-24 months) stability studies.

Data Collection: Collect data at specified intervals to assess the product's physical, chemical, and microbiological stability

3.7.9.2 Stability Data Analysis

Data Interpretation: Determine the product's shelf life and suggested storage settings by analyzing stability data.

Regulatory Submission: Include stability data in the regulatory submission to support the proposed shelf life and storage conditions.

Objective: Generate stability data to support product shelf life.

Activities: Long-term and accelerated stability studies, data analysis.

Regulatory Aspects: Compliance with ICH Q1A(R2) guidelines.

Risks: Stability delays

Mitigation: Thorough stability testing and on-time data analysis.

Tools & Techniques: The instruments, hereby, in it, may, therefore, be stability chambers, automated data collection systems, ICH Q1A(R2) guidelines, etc.

3.7.10 ANDA Filing & Submission

I. Preparation of ANDA (US)

Cover letter should enclose the documents: The documents that have to be provided in support of the ANDA—the abbreviated new drug application—has to contain full information regarding the formulation, the process of manufacture, the analytical methods, stability data, and the Bioequivalency study's findings.

a) Electronic Submission: All ANDAs shall be submitted to the FDA in the electronic Common Technical Document format (eCTD).

b) Compliance: The development should completely align with the requirements set forth by the FDA, specifically the latest versions of the Good Manufacturing Practices and Good Laboratory Practices. (GLP).

II. Preparation of MAA (EU)

a) Submission dossier: Arrange submission of the MAA dossier with the EMA. The ANDA-like data in the dossier has been truncated in accordance with the requirements as given by the EMA.

b) Centralised Procedure: The application for the MAA under the centralized procedure will eventually result in the authorization for the selling of the product within all the EU member states.

c) Regulatory Interactions: Keep in touch with regulatory agencies during the entire assessment process in order to address queries/worries.

This may involve the provision of more details or arguments.

The objective is to submit a comprehensive application for approval from regulators.

Activities: gathering all information and creating the modules for the Common Technical Document (CTD).

Regulatory Considerations: Responding to regulatory inquiries and following FDA and EMA submission guidelines.

Risks: Incomplete or incorrect submissions, delays in approval.

Mitigation: Detailed review of submission requirements, use of regulatory experts.

Tools & Techniques: Electronic Common Technical Document (eCTD) software, regulatory intelligence tools.

Requirement:

a) List of documents that RA and PMO need to share with the plant
b) List of FRD-required papers that RA from FRD & PMO must share
c) A list of the documents that RA from ARD and PMO must exchange with ARD
d) Document from vendor like LOA from Sourcing, RA & PMO
e) Administration document from plant from Plant

3.7.11. Query response after ANDA Submission

Following the filing of the ANDA, or abbreviated new drug application, the USFDA may raise queries (Screening Deficiency/IRs/DRLs/CRL) to the ANDA holder for additional information/clarification on the content that has been included in the ANDA.

Requirement:

a) Received query to be circulated to concerned stakeholder from RA & PMO
b) Discussion for response against query- meeting arrangement from PMO
c) Follow up for response compilation from all concerned stakeholder- PMO
d) Complete response (CR) from RA
e) Tentative product approval & site audit from Plant, QA & RA
f) Site audit response from QA

3.8 FILING IN US & EU

3.8.1 Abbreviated New Drug Application-(ANDA):

An FDA request for approval and marketing authorization of a generic drug is known as an abbreviated new drug application. If the novel product has shown a human trial, generic drug manufacturers can show the safety and effectiveness of their goods without producing clinical or animal investigations.Instead, they can offer bioequivalence research that compares their product to the innovative treatment. This created opportunities for generics to develop and market generic drugs within 180 days, although final ANDA approval by the FDA took at least 18 months. [13] An application has been submitted to approve generic medications. The clinical trials conducted for the original, name-brand product do not have to be replicated by the sponsor.

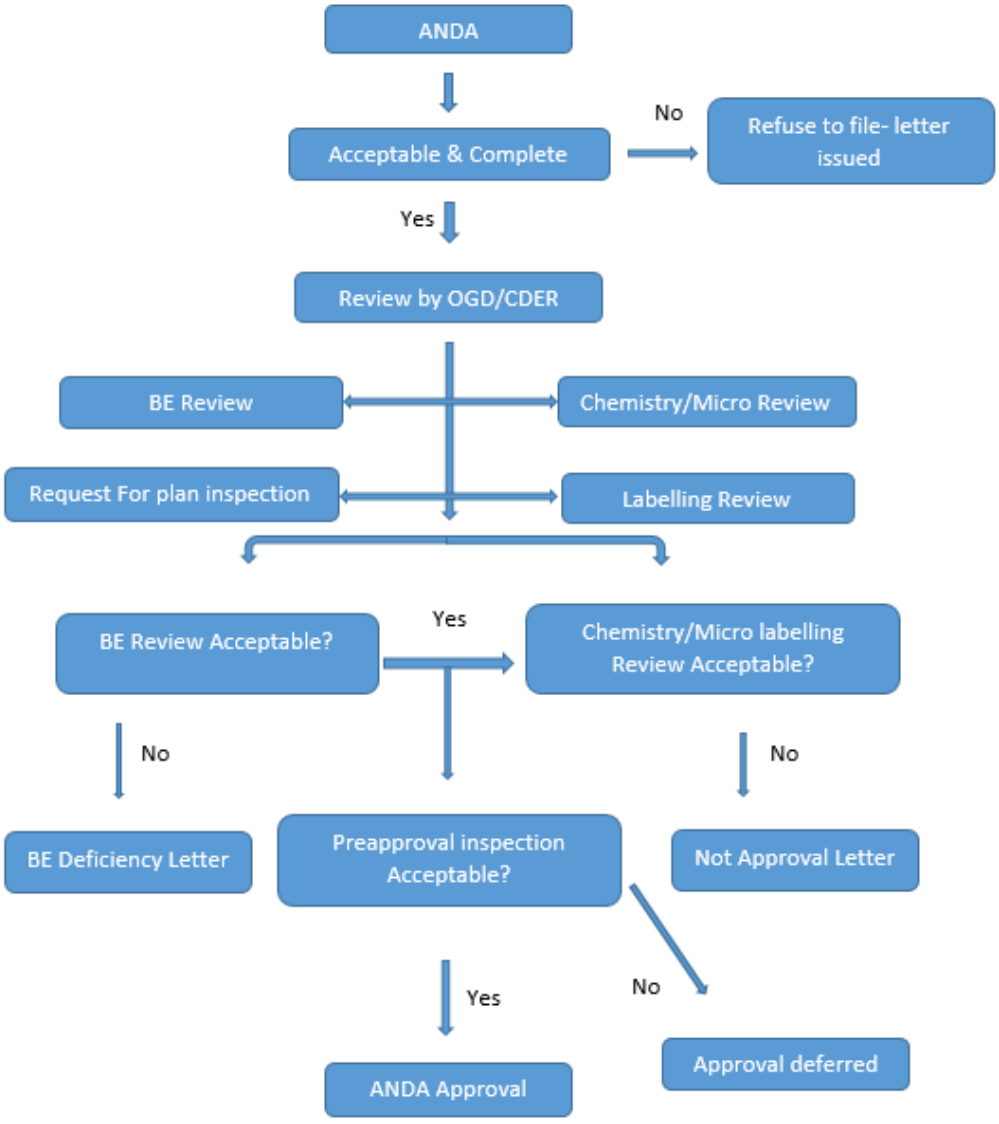

Figure-3.4: ANDA (Generic Drugs) [18]

3.8.2 Investigational New Drug Application-(IND):

The FDA has received this application, which requests permission to use the data from preclinical trials to start human clinical trials.

3.8.3 New Drug Application (NDA):

In the event that clinical trials demonstrate the new drug is safe, effective, and won't put patients at risk, the manufacturer files a NDA in the US.

3.8.4 Registration process (EU)

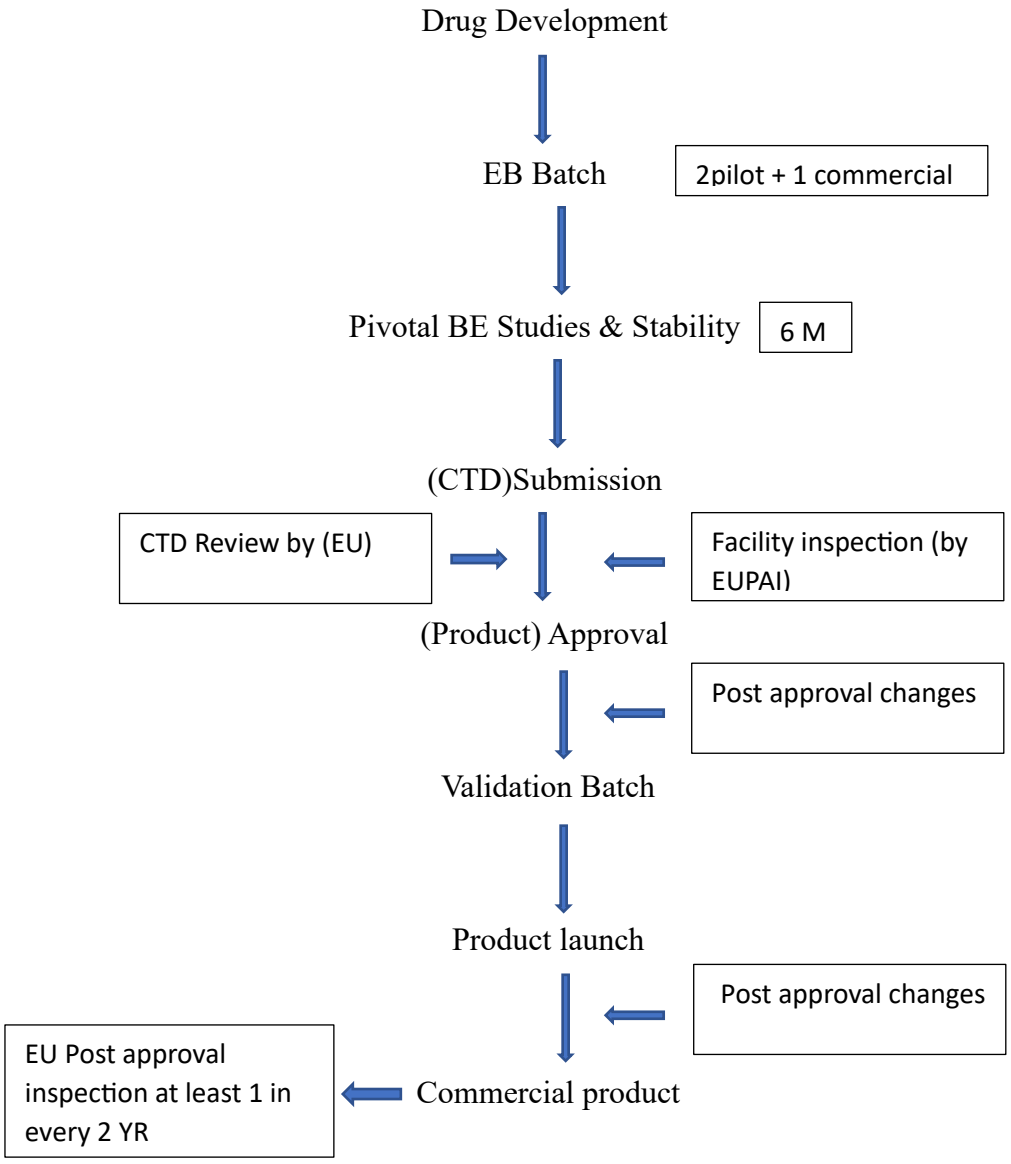

Figure 3.5 Generic drugs registration process in EU (national procedure)

3.8.5 Registration process (US)

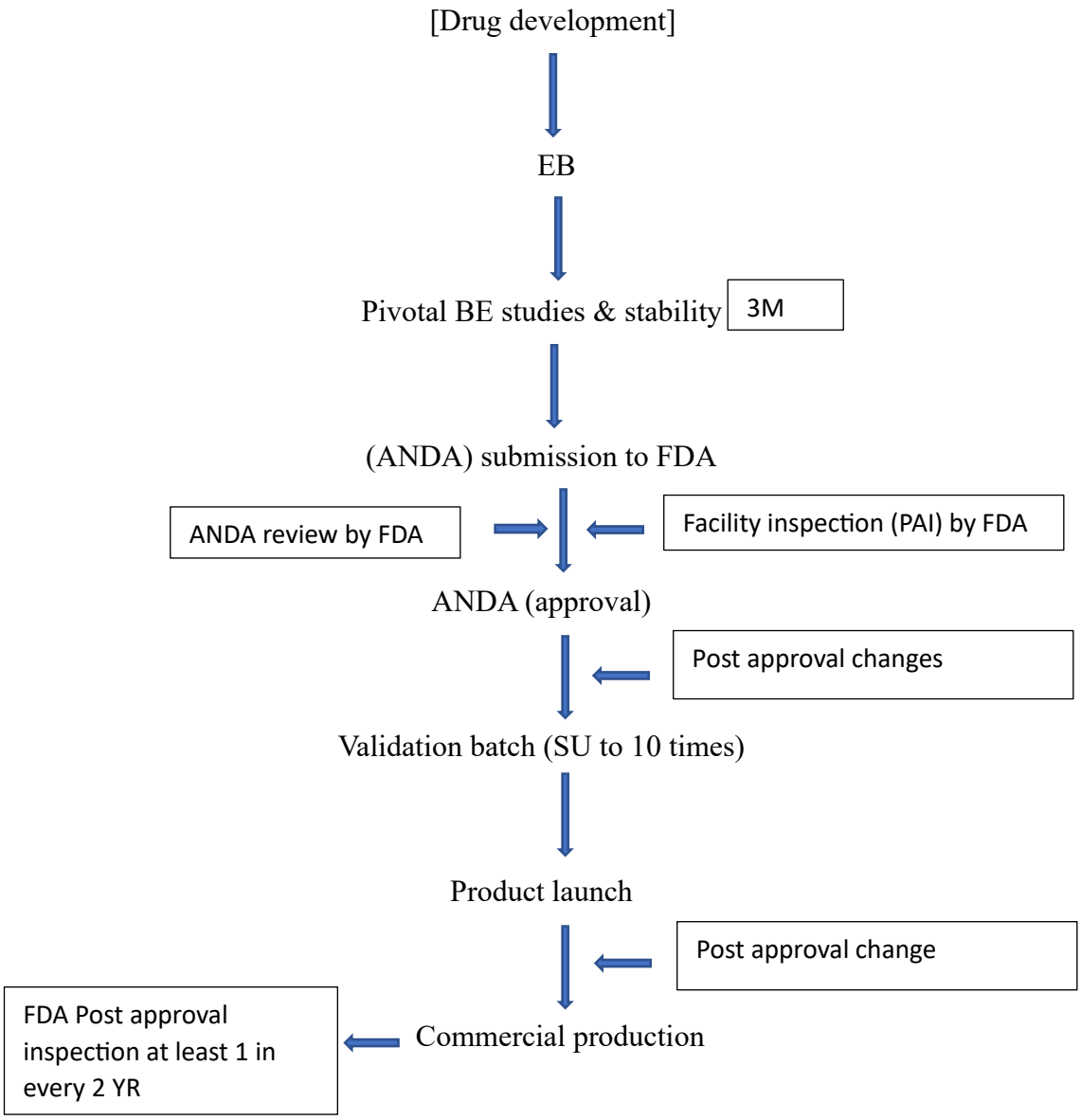

Figure-3.6: Generic drugs registration process in USA

3.8.6 Regulatory Aspects for the Development of OSD Generic Product:

Because different nations have different regulatory standards, it is difficult to design a single medicine that can be submitted for approval in all of them at once. Regulatory bodies guarantee that all generic products are of the best caliber, safe to use, and delivered in compliance with accepted practices. The regulatory body's main objective is to ensure that pharmaceutical products are manufactured in accordance with national laws and that generic producers try to meet these requirements. [15]

3.8.6.1 Regulatory Requirement (EU)

With 27 member states, the European Union has one of the most reputable and effectively run regulatory frameworks in the world. Norway, Iceland, and Liechtenstein are also participants in the European Free Trade Association. The scientific assessment of generic drugs intended for consumption by humans that are manufactured by pharmaceutical companies is under the purview of EMA. The European Medicines Evaluation Agency was the previous name of the company, which changed to EMA in 2004.[15]

3.8.6.2 Regulatory Requirement for USA

The United States, one of the world's tightest regulatory bodies, requires the submission of a shorter New Medicine Application in order to register a generic drug. Like the EU, the US FDA makes sure that testing, manufacturing, and medication development follow the law and that everything is properly documented as needed. The paper covers generic registration requirements as a file for gaining marketing authorization in the United States. The ICH has established a standardized framework for filing generic registration applications. [13]

Countries	Stability Condition	Stability Commitment while Filling	Number of Submission Batches	Bio equivalence Requirement	Dissolution Requirement
(EU)	Long term	On Three commercial batches	Two batches: 1 lacks unit	Fasting, feeding if required	Minimum in three media
(United State)	Accelerated Intermediate	-	One batch: 1 lacks unit	Fasting and feeding both	Only official media

Table 3.4. Comparative regulatory requirement for EU & US.

3.8.7 Types of Certifications

For every patent, producers of generic medications are required to prepare one of four certifications:

Point (I): The manufacturer of generic medications attests to the FDA that no patent applications have been filed for the name-brand medication in question.

Point (II): The generic company presents evidence of the patent's prior expiration.

Point (III): The generic manufacturer demonstrates that the patent is still valid but will run out soon before the release of their generic product.

Point (IV): The general corporation presents evidence demonstrating the accuracy of the patent data.

As soon as a generic medication receives Title I or Title II certification, the FDA accepts the manufacturer's ANDA; Title III certification is approved at any point after the patent expires. However, obtaining a Point IV certificate is not that easy. [13]

3.8.8 Common Technical Document (CTD)

A set of guidelines for application dossiers for the registration of medications is known as the Common Technical Documents (CTD). Their intended application in Europe, Japan, and the US was considered throughout development. It is a globally recognized procedure for creating new drug applications that are meant to be submitted to national regulatory bodies of member countries. The upkeep of CTD is the responsibility of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH).

3.8.9 (ANDA) Regulatory Review Process

Initially, the candidate submits an ANDA to the Center for Drug Evaluation and Research, often known as the "Generic Drug Office." The applicant is then provided with an ANDA number and a date-stamped an ANDA cover letter by registry staff who handle the ANDA. Following that, the consumer safety technician received the ANDA and was tasked with reviewing the first several sections of the checklist. Bioequivalency, microbiology, chemistry, and drug labeling are taken into account in addition to the ANDA application. Within sixty days, the evaluation will be completed. The ANDA is approved once the proposal and the associated documents have been examined and found to be satisfactory. [13]

3.8.10 Bio Equivalence Review Process

The novel medication and the generic version must share the same pharmacological characteristics, including as potency, dosage form, mode of administration, and capacity to function similarly in the same conditions. Bioequivalency is assessed using the area

under the curve (AUC) and the maximum medicine concentration (Cmax). It is believed that a generic medication is bioequivalent to an innovative product if the relative mean Cmax and mean AUC have 90 percent confidence intervals between 80 and 125 percent.[13]

3.8.11 Labeling Review Process

Consistency between innovator and generic medicine labels is ensured by the evaluation system. Upon resolution of any unresolved issues and resolution of any patents or exclusivities by the administrative review, individual disciplines, and the RLD, the application will receive a letter granting either full or provisional permission. [13]

3.9 Risk Identification and Mitigation:

3.9.1 Expected Risks:

a) Delays in regulatory approval
b) Procurement issues with API and RLD
c) Stability test failures
d) Cost overruns
e) Regulatory Changes: Constantly evolving regulatory landscapes can impact compliance.
f) Technical Failures: Difficulties with process formulation or scaling up.
g) Clinical Trial Delays: Unexpected clinical results or problems with recruitment **3.9.2 Mitigation Strategies:**

a) Creating backup plans in case procurement is delayed.
b) Consistent tracking of stability test results and prompt troubleshooting.
c) Keeping in close communication with regulatory bodies in order to expedite the approval process.
d) Strict administration and control of the budget.
e) Regulatory intelligence - Monitoring new regulations on a regular basis.
f) Sturdy Development Plans - Using QbD principles to ensure product stability.
g) Contingency Planning - Developing fallback plans for important occasions.

3.10 Tools and Techniques:

3.10.1 Project Management Tools:

- Gantt Charts: For tracking project timelines and milestones
- Risk Management Software: For identifying and managing project risks.
- Budget tracking and variance analysis tools.
- Collaboration platforms: for cross-departmental communication, For seamless communication among project teams
- LIMS: For managing laboratory data.
- PAT: For real-time monitoring of manufacturing processes.
- Statistical Software: For data analysis and validation studies

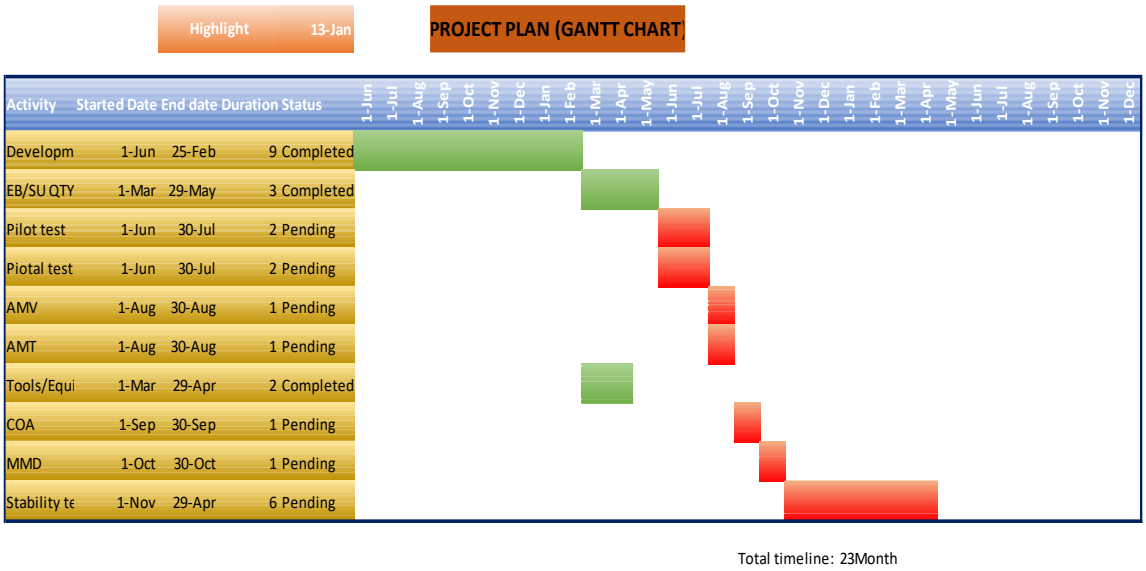

Figure 3.7: Project Timeline Gantt chart:

3.10.2 Techniques:

- Agile project management for flexibility and responsiveness.
- Lean methodologies to minimize waste and optimize resources.
- SWOT analysis for strategic planning

CHAPTER 4

RESULT AND DISCUSSION

4.1. Formulation Development

Results:

API and Excipients Selection: The stability, compatibility, and ability to produce a powerful formulation were taken into consideration when choosing the API and excipients. As excipients, binders, disintegrants, lubricants, and fillers were utilized to optimize the drug's stability and bioavailability.

Best Composition: A stable, effective oral solid dosage form was developed as a result of the identification of the ideal formulation following a number of trials. Stability, homogeneity, and disintegration rate were among the significant requirements that were met.

Validation of Analytical Methods: Two examples of authorized analytical techniques are mass spectrometry (MS) and high-performance liquid chromatography (HPLC). The processes proved to be accurate, precise, repeatable, and specific. Validation criteria like accuracy (98-102%), precise (RSD < 2%), and linearity ($r^2 > 0.999$) were found to have acceptable ranges.

Discussion:

Careful selection of the API and excipients was necessary to achieve the necessary formulation properties. Compatibility studies ensured that the selected excipients did not adversely affect the API.

The established analytical methods yielded dependable data, ensuring the product's consistency and quality. The high precision and accuracy of these procedures are crucial for regulatory compliance as well as quality assurance.

4.2. Pilot Studies and Scale-Up

Results:

Pilot studies: Pilot research was done to assess the composition's feasibility. The effectiveness of the composition, the method of planning, and the recommended concentration of the excipient were all confirmed by these studies.

A step-up Method: The consistent product quality that was demonstrated during the transition from laboratory to commercial production is proof that the scaling up procedure was carried out successfully. Parameters including compression, granulation, and mixing time were optimized.

Discussion:

Variability in dissolution rates and granulation consistency were identified in pilot experiments as possible problems that may be resolved by modifying formulation and process parameters.

Equipment variations and process variability were among the difficulties the scale-up process faced, but these were lessened by rigorous optimization and validation. To make sure that the commercial product fulfills the same requirements as the initial product, consistency in product quality during scale-up is crucial.

4.3. Exhibit Batches and Pivotal Studies

Results:

Exhibit Batches: Under full-scale production conditions, exhibit batches were created. The batches showed consistent quality and satisfied all predetermined requirements, such as stability, dissolution, and homogeneity of content.

Pivotal Studies: The reference listed drug (RLD) and the generic product were compared in the pivotal bioequivalence study. With the 90% confidence intervals for the pharmacokinetic parameters (Cmax, AUC) lying within the allowable range of 80–125%, the study satisfied all bioequivalence criteria.

Discussion:

The resilience of the manufacturing process was validated by the successful manufacture of exhibit batches. Regulatory approval depends on demonstration batches being consistently high-quality.

According to the significant bioequivalence investigation, the generic medication and the RLD have similar therapeutic effects.

Since the key prerequisite for ANDA and MAA approval is bioequivalence, this is a crucial milestone for regulatory submissions.

4.4. Regulatory Filing

Results:

Submission of the ANDA: The FDA received the ANDA, which contained extensive information on the creation of formulations, analytical techniques, exhibit batches, pilot

trials, and pivotal bioequivalence studies. After the submission was examined, approval was given a year later.

MAA Submission: A comparable dossier emphasizing the generic product's effectiveness, safety, and quality was created for the EMA. The unified procedure allowed multiple EU countries to approve petitions simultaneously. The approval process took around eighteen months to complete.

Discussion:

The timely and successful submission of MAA and ANDA applications highlights the need of careful planning and following rules and regulations. Effective management of the regulatory requirements that differ between the US and the EU was achieved by customizing the submission dossiers to satisfy particular regional requirements.

The deadlines for approval demonstrate how quickly and effectively regulatory agencies evaluate and accept applications that are properly prepared. The EU's lengthier approval process, however, indicates that applicants should factor in extra time for project delays.

Case Study 1: Successful Scale-Up and Manufacturing of Generic OSD

Context: A pharmaceutical company wanted to produce a generic OSD at a larger scale for the US market.

Variability in the process and preserving product quality are challenges.

Approach: Iterative process optimization employing DoE, PAT and SPC implementation.

Results include fewer batch failures, a smooth scale-up with consistent quality, and on-time ANDA submission.

Discussion: By employing cutting-edge monitoring and control methods, scale-up risks were considerably reduced, guaranteeing a seamless transfer from pilot to commercial production.

Case Study 2: Bioequivalence Study for Generic OSD

Context: Bioequivalence studies were carried out by a generic medication manufacturer for a new generic OSD aimed at the US and EU markets.

Managing unfavorable circumstances and proving bioequivalency are challenges.

Methods: PK/PD modeling, real-time monitoring, and rigorous clinical trial design.

Results: effective EMA file, no notable adverse events, and effective demonstration of bioequivalence.

Talk about how good risk management techniques, together with a strong research design and real-time monitoring, are crucial to the success of bioequivalence studies.

Case Study 3: Successful OSD Generic Drug Development

An extensive case study of a fictitious generic OSD medication development project illustrates how the described technique is put to use.

Few important conclusions include the following ones:

Efficiency gains: Significant reduction of time and cost savings were realized after the QbD and DoE practices were implemented.

Risk management: Proactive strategies reduced delays and technological breakdowns.

Regulatory Enforcement: Compliance to ICH & regulatory requirements ensured approval without any hurdles.

Comparative Analysis: US vs. EU Regulatory Landscapes

This comparative analysis has illustrated important differences between the regulatory regimes of the United States and the European Union and therefore underpins the case for developing market-specific solutions. For example, the EMA assigned a high priority to stability data and batch records, but the FDA did on extensive bioequivalency research.

CHAPTER 5

CONCLUSION

The study conclusion reiterates that the production of generic oral solid dose drugs is a process that needs to be systematic and organized. The careful selection of excipients and APIs, strong formulation development, comprehensive pilot studies, efficient processes

for scaling up, and tight validation of analytical methods are what it takes to be successful. This has resulted in the completion of requisite bioequivalency studies and successful demonstrating batch production that yielded data needed for regulatory filings.

Organization and compliance with the law also consider the MAA and ANDA approvals. The US and the EU are characterized by different approval timelines; this calls for strategic planning in regulatory applications.

It concluded that the development of generic oral solid dose might be successful if it is accompanied by proper planning, good procedures, risk reduction, suitable tools and techniques, and adherence to regulatory criteria. This would ensure final patients' access to inexpensive, quality pharmaceuticals. Emphasis for future research would have to be based on composition techniques and innovative technology. This shall probably hasten the development of generic medications which are under-dosed.

CHAPTER 6

REFERENCE

[1] Hasan, MdI.; Shimu, SA.; Akther, A.; Jahan, I.; Hamiduzzaman, Md.; Hasan, AHMN. Development of generic drug products by pharmaceutical Industries considering Regulatory aspects: a review. *Journal of Biosciences and Medicines*. **2021**;09(10):23-39. doi:10.4236/jbm.2021.910003

[2] Shakeel S.M., Shaik S.B., Nagabhushanam M.V., Reddy D.N., Bonthagarala B. COMPARISION OF REGULATORY REQUIREMENTS FOR GENERIC DRUGS DOSSIER SUBMISSION IN UNITED STATES AND CANADA. *Int J of Pharmaceutical Science and Health Care* 2016; Issue 6, Vol. 6

[3]https://www.researchgate.net/publication/367520913_COMPARATIVE_STUDIES_FOR_FILING_AND_MARKETING_AUTHORIZATION_OF_GENERICS_IN_EUROPE_UNITED_STATES_INDIA

[4] Wouters OJ, Kanavos PG, McKEE M. Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. *Milbank Q*. **2017**;95(3):554-601. doi:10.1111/1468-0009.12279

[5] https://www.marketdataforecast.com/market-reports/global-generic-drugs-market

[6] Handoo S, Arora V, Khera D, Nandi PK, Sahu SK. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. *Int J Pharm Investig*. 2012;2(3):99-105. doi:10.4103/2230-973X.104392

[7] Nikam NR, Vakhariya RR, Magdum CS. Generic vs. Brand Medicines: An Overview. *Asian Journal of Pharmaceutical Research*. 2019;9(2):109. doi:10.5958/2231-5691.2019.00018.2

[8] Barei F, Pen C.L., Simoens S. The generic pharmaceutical industry: moving beyond incremental innovation towards re-innovation. *GaBI Journal*. 2013;2(1):13-19. doi:10.5639/gabij.2013.0201.011

[9] Handoo, S., Arora, V., Khera, D., Nandi, P.K. and Sahu, S.K. (2012) A Comprehensive Study on Regulatory Requirements for Development and Filing of Generic Drugs Globally. International Journal of Pharmaceutical Investigation, 2, 99-105. https://doi.org/10.4103/2230-973x.104392

[10] Pramod K, Tahir MA, Charoo NA, Ansari SH, Ali J. Pharmaceutical product development: A quality by design approach. *Int J Pharm Investig*. 2016;6(3):129-138. doi:10.4103/2230-973X.187350

[11] Terblanche NS. New pharmaceutical product development: Barriers to overcome and opportunities to exploit. *Journal of Commercial Biotechnology*. 2008;14(3). doi:10.5912/jcb243

[12] Chawla K, Tofighi T, Agarwal A, Thomas J, Mondal T. A global comparison between Brand-Name and Generic Drugs. *Indian Journal of Pharmacy Practice*. 2014;7(3):23-28. doi:10.5530/ijopp.7.3.6

[13] Rafi N, Ds S, Narayanan A V. Regulatory requirements and registration procedure for generic drugs in USA. *Indian Journal of Pharmaceutical Education*. 2018;52(4):544-549. doi:10.5530/ijper.52.4.63

[14] Chawla K, Tofighi T, Agarwal A, Thomas J, Mondal T. A global comparison between Brand-Name and Generic Drugs. *Indian Journal of Pharmacy Practice*. 2014;7(3):23-28. doi:10.5530/ijopp.7.3.6

[15] Sravika, S., Bhavana, R., Sharmila, V., Anusha, S., Mounica, N.V.N. and Nagabhushanam, M.V. A Comprehensive Study on Regulatory Requirements for Development and Filing of Generic Drugs Globally. *Journal of Pharmaceutical Innovation*.2017; 6, 153-158

[16] Chow SC. Bioavailability and Bioequivalence in Drug Development. *Wiley Interdiscip Rev Comput Stat*. 2014;6(4):304-312. doi:10.1002/wics.1310

[17] Rahi S, Rana A. Role of ICH guidelines in registration of Pharmaceutical Products. *International Journal of Drug Regulatory Affairs*. 2019;7(4):14-27. doi:10.22270/ijdra.v7i4.365

[18] Kashyap U, Gupta NV, Raghunandan H. Comparison of drug approval process in United States & Europe. *ResearchGate*. June 2013. https://www.researchgate.net/publication/263657519.

[19] Smith, J. Project management for pharmaceutical development. *Journal of Pharmaceutical Sciences. 2022; 111(2),* 345-356.

[20] Jones, L., Risk Management in Generic Drug Development. *International Journal of Pharmaceutical Research.* 2021;10(4), 567-579.

[21] Brown, A., Cost Estimation Techniques in Pharmaceutical Projects. *Pharma Economics.* 2020; 15(3), 223-234.

[22] https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/hatch-waxman-letters

[23] http://www.fda.gov/newsevents/testimony/ucm115033.htm.

[24] Paragraph filings guidance compliance regulatory process

[25]. https://www.fda.gov/drugs/development-approval-process-drugs

Literature review

[26] Müller R, Zhai L, Wang A. Governance and governmentality in projects: Profiles and relationships with success. *International Journal of Project Management*. 2017;35(3):378-392. doi:10.1016/j.ijproman.2017.01.007

[27] Douroumis D. Orally disintegrating dosage forms and taste-masking technologies; 2010. *Expert Opinion on Drug Delivery*. 2011;8(5):665-675. doi:10.1517/17425247.2011.566553

[28] Lenić I, Blake K, Garcia-Arieta A, Potthast H, Welink J. Overview of the European Medicines Agency's Experience With Biowaivers in Centralized Applications. *Clin Transl Sci*. 2019;12(5):490-496. doi:10.1111/cts.12642

[29] EMA (European Medicines Agency). (2012). *Guideline on pharmaceutical development of medicines for paediatric use.* Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf

[30] FDA (Food and Drug Administration). (2003). *Guidance for industry: Q1A(R2) stability testing of new drug substances and products.* Retrieved from https://www.fda.gov/media/71750/download

[31] FDA (Food and Drug Administration). (2009). *Guidance for industry: Process validation: General principles and practices.* Retrieved from https://www.fda.gov/media/71021/download

[32] Ghaderi, S. F., & Hekmat, N. (2011). Scale-up challenges of high-shear wet granulation processes: Review of the literature. *Journal of Pharmaceutical Sciences, 100*(11), 4494-4509. https://doi.org/10.1002/jps.22602

[33] ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). (2003). *ICH guideline Q1A(R2): Stability testing of new drug substances and products.* Retrieved from https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf

[34] ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use). (2005). *ICH guideline Q2(R1): Validation of analytical procedures: Text and methodology.* Retrieved from https://database.ich.org/sites/default/files/Q2%28R1%29%20Guideline.pdf

Methodology References:

[35] Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;3(2):77-101. doi:10.1191/1478088706qp063oa

[36] Creswell, J. W. (2014). Research design: Qualitative, quantitative, and mixed methods approach (4th ed.). Thousand Oaks, CA: Sage Publications.

[37] Greenhalgh, T. (2018). How to read a paper: The basics of evidence-based medicine (6th ed.). Chichester, West Sussex, UK: Wiley-Blackwell.

[38] Guba, E. G., & Lincoln, Y. S. (1989). Fourth generation evaluation. Newbury Park, CA: Sage Publications.

[39] Tranfield D, Denyer D, Smart P. Towards a methodology for developing Evidence-Informed management knowledge by means of systematic review. *British Journal of Management*. 2003;14(3):207-222. doi:10.1111/1467-8551.00375

[40] Yin, R. K. (2014). Case study research: Design and methods (5th ed.). Thousand Oaks, CA: Sage Publications.

Case 1 & case 2 in result and discussion

[41] U.S. Food and Drug Administration. (2020). ANDA Submissions - Content and Format. Retrieved from FDA website.

[42] European Medicines Agency. (2020). Guidelines on the Quality of Oral Solid Dosage Forms. Retrieved from EMA website.

[43] Aulton, M. E., & Taylor, K. M. G. (2017). Aulton's Pharmaceutics: The Design and Manufacture of Medicines.

[44] FDA. (2018). Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. Retrieved from FDA website.

[45] ICH Harmonised Guideline. (2018). Stability Testing of New Drug Substances and Products Q1A(R2). Retrieved from ICH website.

Reference for development process PPIF to filing

[46] U.S. Food and Drug Administration. (2023). Guidance for Industry: ANDA Submissions – Content and Format.

[47] European Medicines Agency. (2023). Guideline on the Investigation of Bioequivalence.

[48] DiMasi, J.A., Hansen, R.W., Grabowski, H.G. The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*.2003; 22(2), 151-185.

[49] Qiu, Y., Chen, Y., Zhang, G.G.Z., Yu, L., Mantri, R.V. (2009). Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice. Academic Press.

[50] Lachman, L., Lieberman, H.A., Kanig, J.L. (1986). The Theory and Practice of Industrial Pharmacy. Lea & Febiger.

[51] Allen, L.V., Popovich, N.G., Ansel, H.C. (2011). Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams & Wilkins.