Defense of thesis (IIHMR-U/02/2022-24/0367

"Strategic management framework for OSD generic drug development in US and EU markets: A comprehensive analysis and implementation strategy”

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Overview

Overview
Mankind Pharmaceutical Ltd

Incorporated in 1995, we are India's fourth largest pharmaceutical company in terms of domestic sales and are engaged in developing, manufacturing and marketing a diverse range of pharmaceutical formulations across various acute and chronic therapeutic areas, as well as several consumer healthcare products.

We operate at the intersection of the Indian pharmaceutical formulations and consumer healthcare sectors with the aim of providing

quality products at affordable prices, and have an established track record of building and scaling brands in-house

Strong presence in India

FY 24 Revenue (INR): 10335Cr
Employees : 23K+
Domestic Revenue: 92%

INTRODUCTION

Background

Role of Project Manager:

- Critical for coordinating departments.
- Ensures project success within budget and timeline.

Definition of Generic Drugs:

- Comparable to branded drugs in use, quality, performance, dosage form, and administration route.
- Offered under chemical name without advertising.
- Same active ingredient as name-brand products.
- Identical pharmacokinetic and pharmacodynamic properties as branded medications (US FDA).

Market Impact:

- Introduction of generics reduces costs for both original and generic products.
- Patent protection: Generally 20 years, with potential 5-year extensions in the US and EU.
- Enormous and profitable market.

Key Factors for Lower Costs:

- No cost for identifying new chemical entities.
- Minimal R&D costs.
- Minimal marketing expenditure as safety and efficacy are already proven.

Regulatory and Market Insights:

- Generic markets in the US and Europe offer cost-saving potential.
- Regulators should facilitate market entry.
- Increased use and competition among generic manufacturers is encouraged.

Market Value and Growth:

- 2023: Global market valued at USD 320,307.22 million.
- Projected to grow at a CAGR of 7.13%, reaching USD 484,209 million by 2029.

Objective

- **Analyze Timeline Budgeting:** Explore its impact on project scheduling and resource allocation in OSD development.
- **Evaluate Risk Mitigation:** Assess risk measures in OSD drug development and identify effective strategies.
- **Verify Regulatory Compliance:** Ensure legal and regulatory adherence in both markets.
- **Analyze Case Studies:** Review industry case studies for insights into successful practices.
- **Enhancement Recommendations:** Suggest improvements for risk mitigation and timeline budgeting in OSD development

Scope

1.OSD Generic Drug Development
Phases: Formulation, procedure streamlining, validation, bioequivalency, regulatory filing, post-approval.

2.Timeline Budgeting
Focus: Improving project outcomes and resource allocation.
Risk Mitigation

3.Techniques: Risk identification, assessment, response plans, monitoring.

4.Regulatory Submission: Instructions for EU (EMA) and US (FDA).

5.Practical Recommendations: Tips for enhancing project management and productivity

LITERATURE REVIEW

1.Overview of OSD Generic Drug Development

- OSD generics provide affordable healthcare solutions post-patent expiry. Regulatory approval in EU (EMA) and US (FDA) requires bioequivalence, stability, and consistency (EMA, 2008; FDA, 2019).

2.Timeline Budgeting in Pharmaceutical Development

- Integrates project management with budget constraints for optimized resource allocation (Archer & Ghasemzadeh, 2017; Berman, 2012). Challenges include forecasting costs amidst regulatory uncertainties (Kwak & Ibbs, 2000).

3. Pre-Formulation Investigation (PPIF) and New Product Development (

- PPIF studies drug substance properties; NPD optimizes formulations (Martinez & Amidon, 2002; FDA, 2015).

4. Formulation Strategies: AMD, AMV, AMT

- AMD enhances solubility (Douroumis, 2012). AMV validates analytical methods (ICH, 2005). AMT predicts shelf life (FDA, 2003).

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

- Pilot studies ensure scalability (Ghaderi & Hekmat, 2011). SU maintains batch uniformity (FDA, 2009). EB ensures process consistency (Ghaderi & Hekmat, 2011).

LITERATURE REVIEW

6.Pivotal Studies and Stability Data Generation

- Demonstrate bioequivalence (EMA, 2014). Stability data follow ICH guidelines (ICH, 2003; FDA, 2017).

7. Regulatory Filings and Risk Mitigation Strategies

- Filings require comprehensive data (EMA, 2019). Risk mitigation includes compliance and contingency planning (Mishra & Deshmukh, 2016; FDA, 2014).

8. Comparative Analysis: EU vs. US Requirements

- Differing regulatory requirements affect documentation and approval timelines (EMA, 2018; FDA, 2020).

Methodology

Research Design

Using a mixed-methods approach, this study investigates timeline budgeting integration in OSD generic drug development processes (Creswell, 2014).

Data Collection Methods

- Literature Review: Comprehensive examination of peer-reviewed journals, regulatory guidelines (EMA, FDA), and industry reports (Greenhalgh, 2018; Tranfield et al., 2003).
- Case Studies: Selected based on relevance to OSD generic drug development stages. Data gathered through interviews and document analysis (Yin, 2014).

Analytical Techniques

- Data Analysis: Qualitative data analyzed using thematic analysis; quantitative data analyzed using descriptive statistics (Braun & Clarke, 2006).

Ethical Considerations

- Ethical Approval: Obtained from XYZ Ethics Committee prior to conducting interviews.

Validity and Reliability

- Validity: Triangulation of data sources and member checking during interviews (Guba & Lincoln, 1989).
- Reliability: Consistency ensured through standardized methods in data collection

Development strategy

1. Development Strategy

- Understand regulatory requirements for each target market.
- Ensure bioequivalence to branded drugs.
- Plan launch date strategically.

2. Patent Restriction Consideration

- Consider NDA listings and patent exclusivity.
- Assess market share impact.

3. Selection and Characterization of Reference Product

- Ensure bioequivalence with Reference Listed Drugs (RLD).
- Utilize FDA database (US) or public reports (EU).

4. Target Market Selection

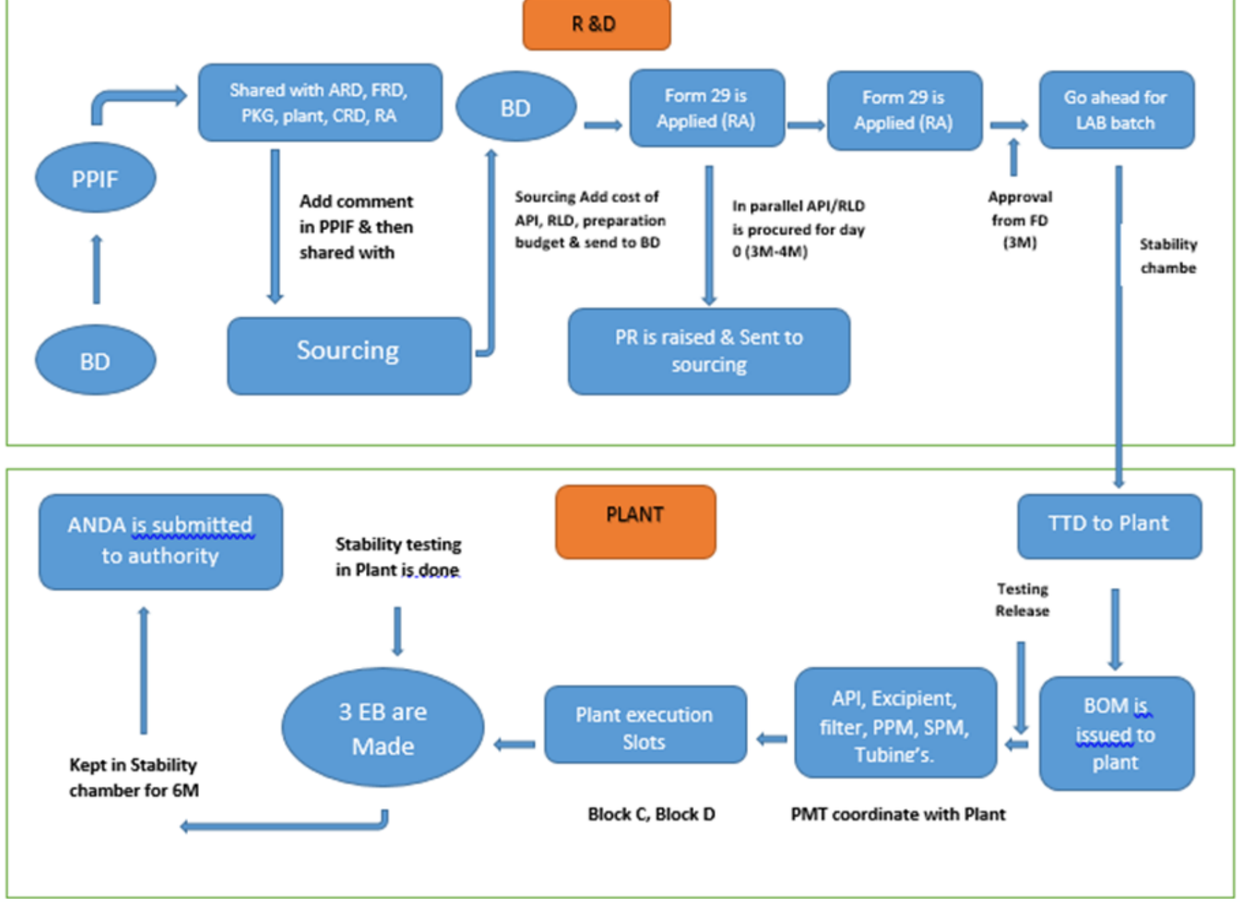
- Adhere to USP quality standards.
- Conduct stability tests.
- Consider dissolution profiles for market-specific approvals.

5. Feasibility of Production

- Assess profitability and feasibility.
- Obtain MHRA or GMP approval for manufacturing

Project Initiation:

1.Initial step



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

Project Proposal Information Form (PPIF) Process:

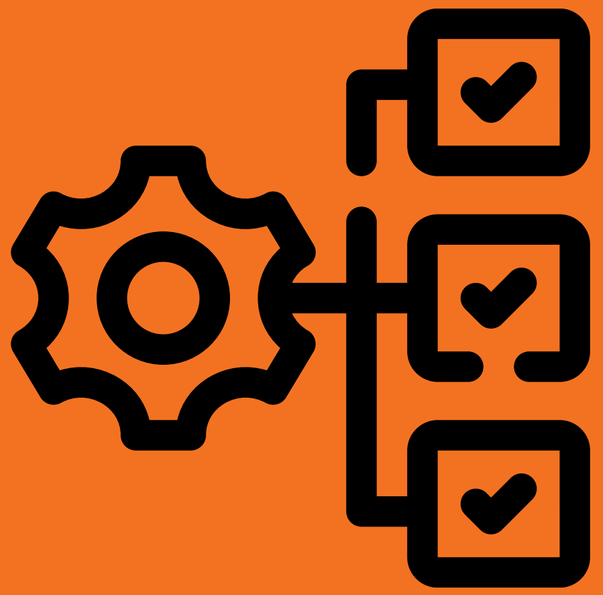
1.Received from BD Department
- Coordination with all departments for inputs.

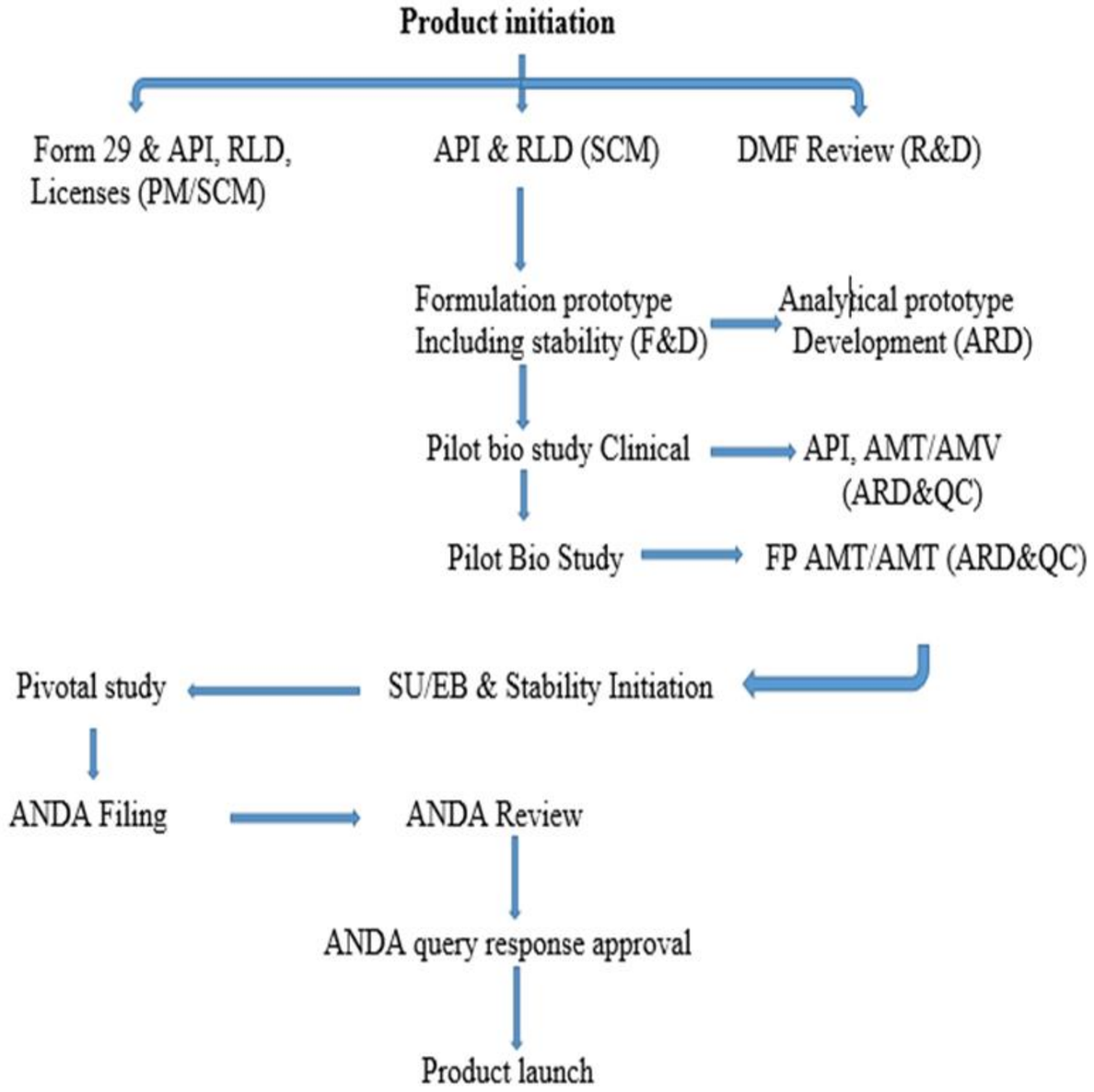
2.Sourcing Team
- Obtaining API and RLD cost estimates.

3.Distribution to Departments
- ARD, FRD, Packaging, Plant, CRD, and RA for feedback

Project Initiation:

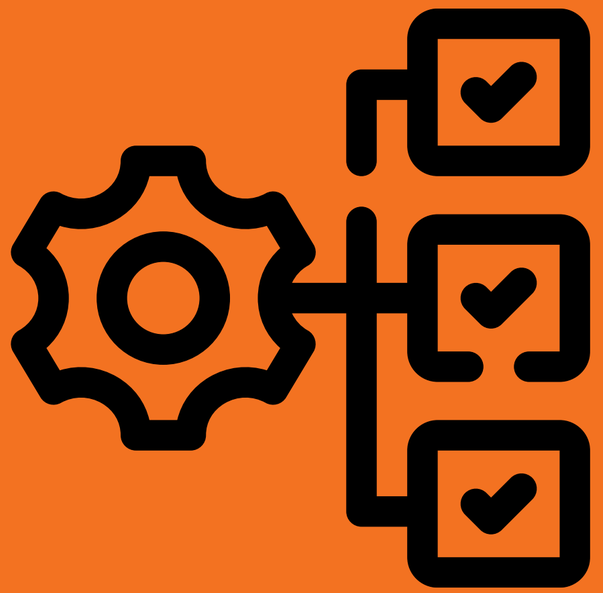
1.Initial step





Product development cycle

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

Budget and Timeline Preparation:

"Consolidate input from departments for detailed budget on API, RLD, excipients, testing, packaging, tech transfer, and regulatory filing. Calculate timeline for literature review, RLD/API availability, formulation, stability studies, and regulatory submission. Compile costs for final budget, finalize timeline based on departmental inputs."

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

Budget and Timeline Preparation:

Timeline Calculation:

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

2. New Product Development (NPD) Overview

Objective: Conceptualize and plan 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)
- Quality by Design (QbD) principles

3. Regulatory Approval Process

Objective: Secure regulatory approval for NPD.

Activities:

- Form 29 application (RA)
- API procurement
- Reference Listed Drug (RLD) selection

Tools:

- Regulatory submissions
- Compliance with ICH guidelines

4. Formulation & Analytical Development

Objective: Develop reliable formulations and analytical methods.
Activities:

- API and excipient selection
- Formulation optimization
- Analytical method development and validation

Tools & Techniques:

- DoE and QbD
- Method validation (ICH Q2)

5. Pilot Bio Study & Process Optimization

Objective: Evaluate feasibility and optimize manufacturing.
Activities:

- Feasibility studies
- Process optimization
- Small-scale production

Tools & Techniques:

- Miniaturized equipment
- Statistical analysis

6. Scale-Up Batch Production (SU Batch)

Objective: Transition to commercial scale production.

Activities:

- Equipment selection
- Process validation
- SU batch execution

Tools & Techniques:

- Process Analytical Technology (PAT)
- Real-time monitoring

7. Exhibit Batch Production (EB Batch)

Objective: Produce batches for regulatory submission.

Activities:

- Full-scale production
- EB batch execution
- Stability testing

Tools & Techniques:

- Compliance with GMP
- Documentation management

8. Bioequivalence Studies & Stability

Objective: Validate bioequivalence and ensure stability.

Activities:

- Pivotal bio studies
- Stability testing (ICH guidelines)

Tools & Techniques:

- Clinical trial management
- Stability chambers

9. **ANDA Filing & Submission**

Objective: Prepare and submit regulatory applications.

Activities:

- ANDA preparation (US)
- MAA preparation (EU)
- Regulatory interactions

Tools & Techniques:

- Electronic Common Technical Document (eCTD)
- Compliance with FDA/EMA guidelines

10. Query Response After Submission

Objective: Address regulatory queries post-submission.

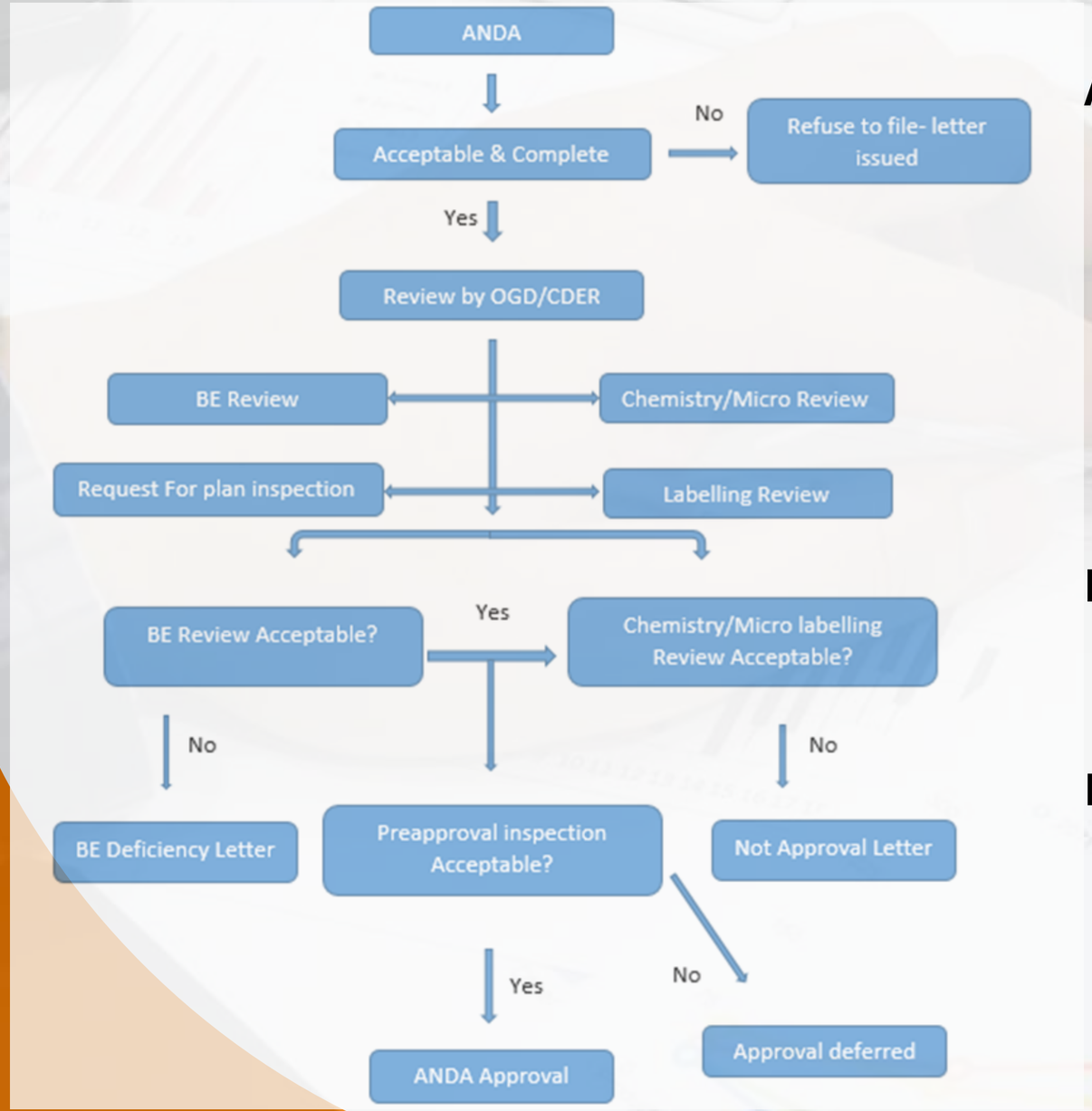
Activities:

- Query handling
- Response compilation
- Site audit preparation

Tools & Techniques:

- Regulatory intelligence
- Stakeholder coordination

FILING IN US & EU



Abbreviated New Drug Application (ANDA):

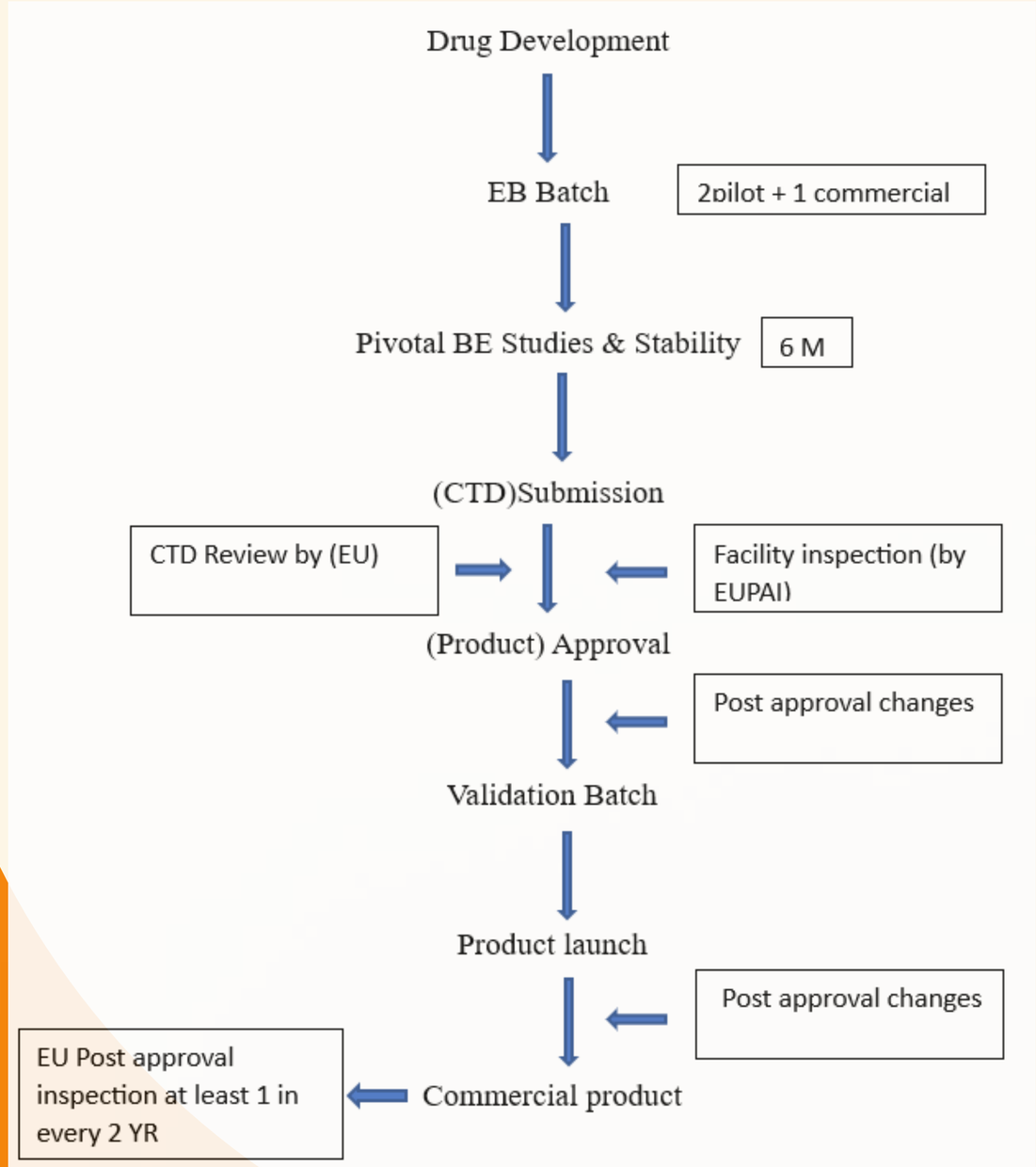
- An ANDA is a request to the FDA for approval to market a generic drug. Instead of conducting new clinical trials, manufacturers provide bioequivalence studies comparing their product to the original drug. This allows generics to be developed and marketed quickly, usually within 180 days, although final approval can take at least 18 months.

Investigational New Drug Application (IND):

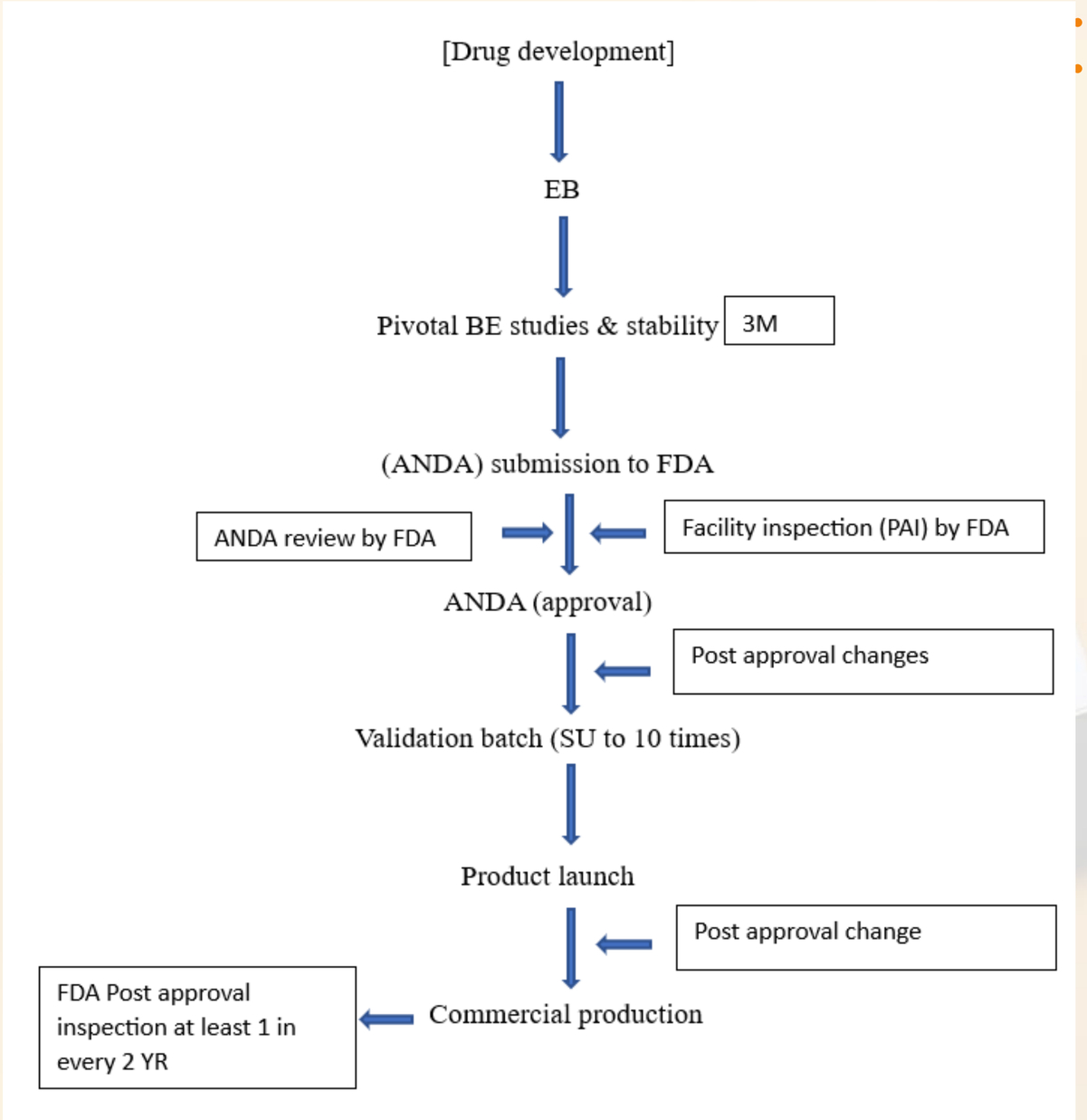
- An application to the FDA to begin human clinical trials based on preclinical data.

New Drug Application (NDA):

- Filed when clinical trials show a drug is safe and effective, seeking FDA approval for marketing.



Generic drugs registration process in EU



Generic drugs registration process in USA

Regulatory Aspects for the Development of Generic Product:

Regulatory Requirement for EU

The EU, with 27 member nations, has a highly respected regulatory system. The EMA (formerly the European Medicines Evaluation Agency, renamed in 2004) oversees the scientific evaluation of generic drugs for human use. Liechtenstein, Iceland, and Norway are part of the European Free Trade Association

Regulatory Requirement for USA

In the USA, the FDA requires a streamlined New Medicine Application for generic drug registration, ensuring compliance with stringent laws on testing, manufacturing, and documentation. Similar to the EU, this process is standardized by the ICH for consistent filing across regions.

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

Comparative regulatory requirement for EU & US

ANDA Regulatory Review Process

1. Applicant files ANDA with the Generic Drug Office (Center for Drug Evaluation and Research).
2. ANDA number and date-stamped cover letter are issued.
3. Consumer safety technician reviews initial sections of the checklist, including bioequivalency, microbiology, chemistry, and drug labeling.
4. Evaluation completed within 60 days.
5. ANDA is approved if all documents are satisfactory

Bio Equivalence Review Process

1. Same pharmacological properties: Potency, dosage form, route of administration, and similar function.
2. Bioequivalency evaluation: Area under the curve (AUC) and maximum concentration (Cmax).
3. Criteria for bioequivalence: 90% confidence intervals for mean AUC and mean Cmax must be between 80% and 125%.

Labeling Review Process

1. Ensures consistency between innovator and generic drug labels.
2. Resolves issues, patents, and exclusivities.
3. Application receives provisional or full approval

Risk Identification and Mitigation

Expected Risks:

- Regulatory approval delays
- Procurement issues (API & RLD)
- Stability test failures
- Cost overruns
- Regulatory changes
- Technical failures (process formulation, scaling up)
- Clinical trial delays

Mitigation Strategies:

- Backup procurement plans
- Consistent stability tracking
- Close regulatory communication
- Strict budget control
- Regular regulatory monitoring
- QbD principles for product stability
- Contingency planning

Tools and Techniques:

Project Management Tools:

- Gantt Charts: Track project timelines and milestones.
- Risk Management Software: Identify and manage project risks.
- Budget Tracking Tools: Monitor budget and analyze variances.
- Collaboration Platforms: Facilitate team communication.

Techniques:

- Agile Project Management: Enhance flexibility and responsiveness.
- Lean Methodologies: Minimize waste and optimize resources.
- SWOT Analysis: Strategic planning and decision-making tool.

RESULT AND DISCUSSION

1.Formulation Development

Results:

- API and Excipients Selection: Chosen based on stability, compatibility, and formulation efficacy. Utilized binders, disintegrants, lubricants, and fillers for stability and bioavailability optimization.
- Best Composition: Developed a stable, effective oral solid dosage form meeting stability, homogeneity, and disintegration criteria.
- Validation of Analytical Methods: Validated using mass spectrometry (MS) and high-performance liquid chromatography (HPLC). Methods proved accurate, precise (RSD < 2%), and specific ($r^2 > 0.999$).

Discussion:

- Careful API and excipient selection ensured desired formulation properties without adverse effects.
- Analytical methods provided reliable data, crucial for regulatory compliance and quality assurance.

2. Pilot Studies and Scale-Up

Results:

- Pilot Studies: Confirmed composition viability, effectiveness, and recommended excipient concentration.
- Scale-Up Method: Successfully maintained product quality from lab to commercial production through optimized parameters (compression, granulation, mixing time).

Discussion:

- Identified challenges like dissolution rate variability and granulation consistency, resolved through formulation and process adjustments.
- Equipment and Process Optimization: Addressed variability with rigorous optimization and validation to ensure consistent product quality during scale-up.

3. Exhibit Batches and Pivotal Studies

Results:

- Exhibit Batches: Produced under full-scale conditions, demonstrating consistent quality and meeting stability, dissolution, and homogeneity criteria.
- Pivotal Studies: Showed bioequivalence with the reference drug (RLD), with pharmacokinetic parameters (Cmax, AUC) falling within the acceptable range of 80-125% confidence intervals.

Discussion:

- Successful exhibit batches validate manufacturing process resilience. Bioequivalence study confirms similar therapeutic effects between generic and RLD, crucial for regulatory approval (ANDA/MAA).

4.Regulatory Filing

Results:

- ANDA Submission (FDA): Extensive information on formulations, analytical techniques, and studies led to approval one year post-submission.
- MAA Submission (EMA): Similar dossier emphasized product safety, efficacy, and quality; approval across multiple EU countries took eighteen months.

Discussion:

- Effective regulatory management tailored to US and EU requirements ensured timely approvals. US processes were quicker, while EU approvals required additional time, highlighting the importance of strategic planning and adherence to regulatory guidelines.

CONCLUSION

This study underscores the importance of a structured approach in developing generic OSD medications. Key factors include selecting appropriate API and excipients, robust formulation, pilot studies, scale-up procedures, and stringent analytical validation. Successful bioequivalence studies and exhibit batch production are crucial for regulatory applications.

MAA and ANDA approvals highlight the need for compliance and strategic planning due to different US and EU timelines.

Careful planning, sound procedures, risk mitigation, and regulatory adherence ensure the successful development of high-quality, affordable generic OSD products. Future research should focus on innovative methods and technologies to accelerate this process

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THANK YOU