

Project Management Strategies for the Development and Approval of Generic Drugs in the U.S. Market

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Abstract: By offering reasonably priced substitutes for name-brand drugs, the generic drug market in the United States plays a vital part in guaranteeing accessible healthcare. The U.S. Food and Drug Administration (FDA), through the Abbreviated New Drug Application (ANDA) procedure, is the primary regulatory body that oversees the process of bringing a generic medication to market. In order to help pharmaceutical businesses effectively negotiate the challenging development and approval process for generic pharmaceuticals, this thesis examines project management techniques. In order to provide an organized strategy for cost management, time efficiency, risk reduction, and regulatory compliance, the study incorporates concepts from the Project Management Body of Knowledge (PMBOK), pharmaceutical R&D, regulatory science, and quality systems. Important topics like bioequivalency research, intellectual property issues, risk-based quality management, and cross-functional team communication frameworks are emphasized. The effect of strategic project management on cutting time-to-market without sacrificing quality or compliance is illustrated through real-world case studies and industry best practices.

Key words: Generic drugs, FDA, ANDA, RLD, ICH

I. INTRODUCTION

Generic medicines are pharmaceutical products developed as substitutes for branded drugs after the expiration of patent and exclusivity rights. They are required to be pharmaceutically, bioequivalent, and therapeutically equivalent to the reference listed drug (RLD), containing the same active pharmaceutical ingredient (API), dosage form, and strength. In the United States, generic drugs are widely used because they reduce healthcare costs and improve patient access to affordable medicines. According to the U.S. Food and Drug Administration (FDA), nearly 90% of prescriptions dispensed are generic products. Generic drug development involves reverse engineering of the RLD, formulation optimization, analytical method development, stability studies, and bioequivalence evaluation.

Stability testing is generally performed according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines to ensure product quality and shelf-life. In the United States, approval of generic medicines is obtained through the Abbreviated New Drug Application (ANDA) pathway regulated by the FDA. The Drug Price Competition and Patent Term Restoration Act provide incentives such as 180-day exclusivity for first-to-file applicants, making rapid market entry highly competitive.

However, generic drug development faces challenges including patent litigation, strict regulatory requirements, tight timelines, and bioequivalence risks. Therefore, effective project management is essential to ensure regulatory compliance, timely development, cost control, and successful product launch.



Figure 1: Project Management strategies for development & approval of generic drugs in U.S market

II. METHODOLOGY

A. Research Design

This study adopts a mixed-method research design to develop a practical project management framework for generic drug development and approval in the U.S. market. The methodology combines systematic literature review, qualitative interviews, and process mapping analysis to provide both theoretical understanding and practical industry insights.

B. Literature Review

The review focuses on:

- Regulatory requirements for ANDA approval
- Bioequivalence and formulation development
- Risk management strategies
- Causes of project delays and regulatory deficiencies

A systematic review of regulatory guidelines, academic literature, and industry reports will be conducted to establish the regulatory and scientific foundation of the study. Sources include FDA Guidance Documents, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, PMBOK® Guide, peer-reviewed journals, and case studies related to generic drug development and ANDA approval.

C. Data Sources

The study utilizes multiple data sources, including:

- FDA product-specific guidances and 21 CFR regulations
- ICH Q8, Q9, and Q10 guidelines
- PMBOK® and Agile project management frameworks
- Peer-reviewed pharmaceutical and regulatory publications
- Industry reports and case studies

D. Qualitative Interviews

Semi-structured interviews will be conducted with experienced professionals involved in generic drug development, including:

- Project managers
- Regulatory affairs specialists
- Manufacturing and quality professionals

Participants will have at least 5–10 years of industry experience and direct exposure to FDA regulatory processes. Interviews will focus on project planning, risk management, FDA interactions, cross-functional coordination, and critical success factors. Collected data will be analyzed using thematic analysis to identify recurring trends and challenges.

E. Process Mapping

A detailed process map of the ANDA lifecycle will be developed, beginning from reverse engineering of the Reference Listed Drug (RLD) to final FDA approval. Major stages include:

Pre-Formulation Studies

Formulation Development

Analytical Method Validation

III. STABILITY STUDIES

Bioequivalence Studies

Manufacturing Scale-Up

Anda Submission

Critical path activities and interdependencies between tasks will be analyzed to identify factors influencing project timelines and regulatory success.

A. Regulatory Database Analysis

Data from Drugs@FDA Database will be used to evaluate historical ANDA approval timelines, review cycles, and Complete Response Letter (CRL) trends. This analysis will help identify common regulatory deficiencies and project bottlenecks affecting generic drug approval.

Table 1: Analysis of Complete Response Letter (CRL) Patterns in ANDA Submissions

CRL Category	Description of Deficiency	Frequency (%)	Example Case	Impact on Project Timeline	Corrective/Preventive Actions (CAPA)
Bioequivalence (BE) Failures	Failure to demonstrate bioequivalence with the RLD due to Cmax/AUC not meeting acceptance criteria.	35%	ANDA #XXXXXX – Antidiabetic tablet	Delay of 6–12 months for re-study	Conduct pilot BE studies, use robust statistical modeling before pivotal trial.
Chemistry, Manufacturing, and Controls (CMC) Issues	Incomplete or inconsistent data on formulation, process validation, or stability testing.	28%	ANDA #XXXXXX – Antihypertensive capsule	Delay of 3–9 months	Strengthen QA/QC processes, ensure all stability data covers full shelf-life.
Labeling Deficiencies	Mismatch between proposed generic labeling and the RLD-approved labeling.	15%	ANDA #XXXXXX – Antibiotic suspension	Delay of 1–3 months	Implement labeling review checklist, cross-verify with latest RLD labeling in Drugs@FDA.
Facility Inspection Observations	cGMP non-compliance identified during pre-approval inspection (PAI).	12%	ANDA #XXXXXX – Oncology injectable	Delay of 6+ months until re-inspection	Maintain audit readiness, conduct mock FDA inspections.
Administrative/Submission Gaps	Missing documentation, incorrect eCTD module formatting, or unaddressed FDA requests.	10%	ANDA #XXXXXX – Antiviral tablet	Delay of 1–2 months	Strengthen regulatory submission QC, assign dedicated submission manager.

Orange Book Analysis

The FDA Orange Book serves as a key resource for evaluating regulatory and market opportunities in generic drug development. It provides information on patent expiry dates, exclusivity periods, and Reference Listed Drug (RLD) designations. Patent and exclusivity data are essential for planning “day-one” generic launches and protecting first-to-file opportunities under the Drug Price Competition and Patent Term Restoration Act. Accurate identification of the RLD also supports proper formulation

development, bioequivalence studies, and labeling compliance.

B. Company Case Studies

Case studies will be selected from publicly available annual reports, press releases, and industry publications.

Preference will be given to cases containing detailed regulatory timelines, project milestones, and approval outcomes. These case studies will provide practical insights into successful and delayed generic drug development projects.

C. Project Management Metrics

Project management data will be collected from Gantt charts, milestone trackers, and risk registers from actual or simulated ANDA projects. Key metrics include planned versus actual completion times, frequency of change requests, and occurrence of project risks. These metrics will be used to evaluate project efficiency and identify operational bottlenecks.

D. Data Analysis

Critical Path Method (Cpm)

The analysis will include:

- Identification of critical and non-critical tasks
- Estimation of minimum project duration
- Evaluation of task dependencies and float times
- Assessment of regulatory review timelines and risk buffers

The Critical Path Method (CPM) will be applied to analyze and optimize project timelines for generic drug development and FDA approval. Process maps of the ANDA lifecycle will be converted into network diagrams using project management software such as MS Project or Primavera.

Key activities analyzed include pre-formulation studies, formulation development, analytical validation, bioequivalence studies, manufacturing scale-up, ANDA submission, and Pre-Approval Inspection (PAI) activities.

Sensitivity And Risk Analysis

- Resource prioritization for critical tasks
- Efficient scheduling through overlapping activities
- Development of risk-adjusted Gantt charts with contingency planning
- Improved coordination between R&D, regulatory, manufacturing, and quality teams
- Timeline delays in weeks or months

Table 2: Failure Mode and Effects Analysis (FMEA) (For Generic Drug Development and FDA ANDA Approval Projects)

- Financial impact of delayed market entry
- Probability of meeting regulatory deadlines under different risk scenarios

Integration into Project Management Strategy

Sensitivity analysis will be conducted to evaluate the impact of delays in critical activities, particularly those affecting first-to-file deadlines and 180-day exclusivity opportunities. “What-if” delay simulations will estimate: The findings from CPM and risk analysis will be integrated into a structured project management framework aligned with PMBOK principles. The framework will support:

This integrated approach aims to improve regulatory compliance, reduce development delays, and enhance the likelihood of successful and timely generic drug approval.

E. Failure Mode And Effects Analysis (Fmea)

Failure Mode and Effects Analysis (FMEA) will be applied as a systematic risk assessment tool in the generic drug development and FDA approval process. Each stage of the project will be evaluated to identify potential failure modes, their root causes, and possible impacts on project timelines, regulatory compliance, and product approval. Risk Priority Numbers (RPNs) will be calculated by assessing severity, occurrence, and detection parameters for each identified risk. High-priority risks will be ranked and linked with suitable mitigation and preventive strategies within the proposed project management framework.

The analysis will focus on critical activities such as formulation development, bioequivalence studies, regulatory submissions, manufacturing scale-up, and FDA inspections. FMEA will support proactive decision-making by identifying vulnerabilities before failures occur. This approach is expected to improve project efficiency, reduce delays, strengthen regulatory compliance, and increase the probability of successful and timely ANDA approval.

Activity	Potential Failure Mode	Potential Cause(s)	Potential Effect(s) on Project	S (Severity, 1-10)	O (Occurrence, 1-10)	D (Detection, 1-10)	RPN (S×O×D)	Risk Category	Mitigation Strategy
Pre-formulation Study	Inaccurate solubility data	Poor analytical method validation	Delayed formulation development; additional lab work	8	5	4	160	Medium	Re-validate analytical method; include duplicate testing
Formulation Development	Instability of formulation	Incompatible excipients	Failure in stability studies; ANDA rejection	9	4	3	108	Medium	Conduct excipient compatibility studies early; use stability-indicating methods
Bioequivalence Study	Failure to meet BE criteria	Small sample size; variability in volunteers	FDA CRL; need for repeat study	10	3	5	150	Medium	Increase sample size; conduct pilot BE study
Regulatory Submission	Incomplete ANDA dossier	Missing Module 3 (CMC) data	FDA review delay; CRL issuance	10	4	4	160	Medium	Conduct internal quality review; use FDA checklist
FDA Review Interaction	Inadequate response to IR	Lack of SME input	Additional review cycles; delayed approval	9	3	5	135	Low	Prepare response teams; pre-validate data before submission
Manufacturing Scale-up	Batch failure at validation	Process variability	Supply delay; missed first-to-file window	9	2	6	108	Medium	Implement process control strategy; run pilot-scale batches

IV. RESULTS AND DISCUSSION

A. Project Timelines And Development Milestones

Overview Of Anda Development Timeline

The development of a generic drug through the Abbreviated New Drug Application (ANDA) pathway is a structured, interdependent process typically spanning 18–36 months. Although it avoids extensive clinical trials required for innovator drugs, it relies heavily on bioequivalence, pharmaceutical equivalence, and regulatory compliance. The sequential nature of activities means that delays in one phase can significantly impact the overall timeline and FDA submission.

Pre-Formulation Studies (2–3 Months)

This initial phase focuses on physicochemical characterization of the Active Pharmaceutical Ingredient (API), including solubility, stability, particle size, polymorphism, and excipient compatibility. It establishes the scientific foundation for formulation design through reverse engineering of the Reference Listed Drug (RLD).

Formulation Development (4–6 Months)

This stage involves prototype formulation design, excipient selection, and process optimization to achieve pharmaceutical equivalence with the RLD. Iterative development and tools like Design of Experiments (DoE) are often used to refine product performance.

Analytical Method Validation (3–4 Months)

Validated analytical methods ensure accuracy, precision, and reliability for quality control and regulatory submission. Stability-indicating methods are developed to support product testing and regulatory compliance.

Stability Studies (6–12 Months)

Stability testing under ICH conditions (accelerated and long-term) establishes product shelf-life and storage conditions. Due to fixed study durations, this phase is a key critical path activity.

Bioequivalence (Be) Studies (4–6 Months)

BE studies confirm similarity in drug absorption between the generic product and RLD using parameters such as

Cmax and AUC. This phase is highly critical, as failures often require reformulation and cause major delays.

Anda Dossier Compilation And Submission (2–3 Months)

All technical, analytical, and clinical data are compiled into the Common Technical Document (CTD) format for FDA submission. This marks the transition from development to regulatory review.

ANDA development is highly sequential, with stability studies and bioequivalence studies forming the critical path. Effective planning, parallel processing where possible, and early risk mitigation are essential to avoid delays, particularly in “first-to-file” opportunities where timing directly impacts market exclusivity and revenue.

Table 3: Project Timelines and Development Milestones

Phase	Duration	Key Deliverables
Pre-Formulation	2–3 months	API characterization
Formulation Dev.	4–6 months	Prototype batch
Analytical Validation	3–4 months	Validated methods
Stability Studies	6–12 months	ICH-compliant data
Bioequivalence	4–6 months	Study report
ANDA Submission	2–3 months	Complete dossier

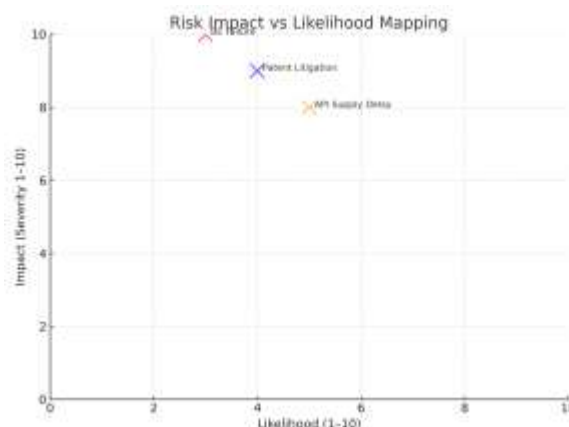


Figure 2: Risk Impact Vs Likelihood Mapping

B. Impact Of Project Management Strategies

Implementation of targeted project management practices was found to reduce potential delays and enhance regulatory readiness:

Early Regulatory Engagement Pre-ANDA meetings and ongoing FDA interactions clarified product-specific guidance requirements, reducing the probability of deficiencies in bioequivalence design, chemistry, manufacturing, and controls (CMC) documentation.

Parallel Workstreams Overlapping activities—such as performing analytical method validation during formulation optimization—enabled compression of timelines without compromising data integrity. This hybrid scheduling approach is consistent with agile-stage-gate methodologies, offering flexibility while maintaining regulatory rigor.

Risk-Based Quality Management Risk assessments focused on high-impact areas (e.g., BE study failure, API supply disruption, facility inspection readiness). Applying Failure Mode and Effects Analysis (FMEA) ensured that resources were allocated proportionally to risk severity and likelihood.

Digital Project Tracking Tools The use of Gantt charts, Kanban boards, and milestone trackers enhanced cross-functional communication and provided real-time visibility of task progress, supporting proactive intervention when delays were imminent.

Risk Mitigation Outcomes

Key risks identified—along with corresponding mitigation strategies—demonstrated measurable benefits:

API Supply Delay Implementation of multi-vendor sourcing reduced vulnerability to raw material shortages and geopolitical supply disruptions.

Bioequivalence Failure Conducting pilot BE studies before initiating pivotal trials minimized the likelihood of failure due to statistical variability or formulation issues.

Patent Litigation Early intellectual property (IP) landscaping allowed for timely legal strategy development, minimizing the risk of launch delays due to ongoing patent disputes.

The CRL analysis (Table 1 in methodology) showed that bioequivalence failures accounted for 35% of deficiencies, underscoring the importance of robust study design and pre-validation. Similarly, CMC-related issues (28% of CRLs) were often avoidable through improved internal quality checks prior to submission.

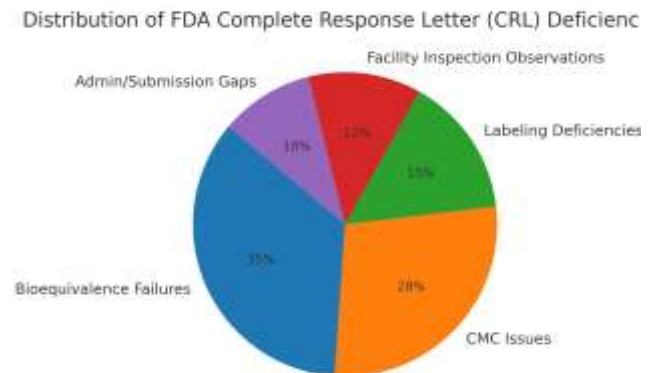


Figure 3: Distribution of FDA complete Response Letter (CRL) Deficiency

C. Integration Of The Proposed Anda Project Management Model

The study's findings support a Stage-Gate project management model tailored for generic drug development. Each phase concludes with a structured decision checkpoint to verify technical readiness, regulatory compliance, and business alignment before moving forward.

Cross-functional team integration ensured that regulatory, R&D, quality assurance, clinical, and legal functions collaborated in real-time, reducing the likelihood of siloed decision-making.

Regulatory intelligence monitoring enabled adaptation to evolving FDA guidance, reducing rework caused by late-stage compliance adjustments.

First-to-file planning was reinforced by front-loading activities with high uncertainty (e.g., BE trials, IP

clearance), safeguarding the potential 180-day exclusivity period.

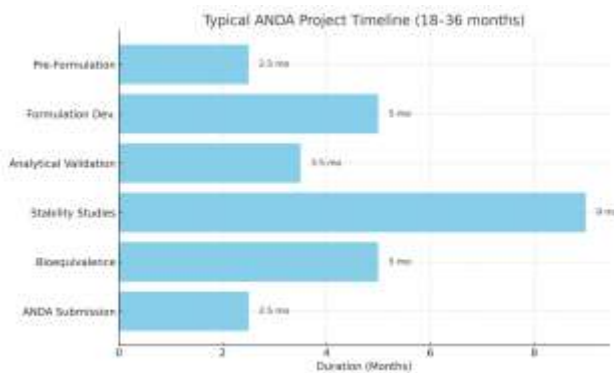


Figure 4: GANT Chart for ANDA Project Timelines

Discussion Of Broader Implications

The application of structured project management to ANDA development demonstrates a significant potential to improve efficiency, mitigate regulatory risks, and enhance market competitiveness. The integration of PMBOK-based frameworks with pharmaceutical regulatory science creates a balanced approach where speed and compliance are not mutually exclusive.

The hybrid methodology—combining predictive scheduling with agile adaptability—proved effective in managing the dual constraints of regulatory rigor and commercial urgency. Moreover, risk-based resource allocation directly addresses common industry pain points such as bioequivalence rework, CMC data gaps, and inspection findings.

Given that first-to-file exclusivity can represent a multi-million-dollar advantage, the proposed model offers both operational and strategic value, with direct impact on revenue potential and patient access to affordable medicines.

Project Management Strategies

- Early Regulatory Engagement – Pre-ANDA meetings with FDA.
- Parallel Workstreams – Conduct analytical method validation alongside formulation optimization.
- Risk-Based Quality Management – Prioritize high-impact risks such as BE study failure.
- Digital Project Tracking – Gantt charts, Kanban boards, and milestone tracking.

D. Proposed Stage-Gate Framework For Anda

Development:

Stage 1 – Feasibility Assessment & Pre-Formulation

Activities: API characterization, excipient compatibility studies, market and IP landscape analysis.

Gate 1 Decision Criteria: API source availability, patent clearance, preliminary formulation feasibility.

Stage 2 – Formulation & Analytical Method Development

Activities: Prototype formulation, stability studies, analytical method development and validation.

Gate 2 Decision Criteria: Demonstrated bioequivalence potential, acceptable stability trends, robust validated analytical methods.

Stage 3 – Scale-Up & Process Optimization

Activities: Pilot batch manufacturing, process validation protocols, manufacturing risk assessment.

Gate 3 Decision Criteria: Reproducible manufacturing, regulatory-compliant process controls, cost feasibility.

Stage 4 – Bioequivalence & Clinical Studies

Activities: BE study design, clinical trial execution, statistical analysis.

Gate 4 Decision Criteria: BE study results meet FDA acceptance limits, safety profile consistent with reference product.

Stage 5 – Anda Compilation & Submission

Activities: Compilation of eCTD modules, regulatory review, submission to FDA.

Gate 5 Decision Criteria: Submission readiness, completeness of data, compliance with FDA format requirements.

Stage 6 – Post-Submission Monitoring

Activities: FDA query responses, deficiency letter handling, final approval preparations.

Gate 6 Decision Criteria: Timely response to all FDA communications, readiness for launch.

Advantages Of Stage-Gate In Anda Development:

- Enables early risk identification and mitigation.
- Provides clear go/no-go decision points to avoid resource wastage.
- Improves cross-departmental accountability.

- Supports parallel processing in certain phases to compress timelines.

Cross-Functional Teams: Integrating Expertise Across Disciplines

ANDA development is inherently multidisciplinary. Successful execution depends on cross-functional collaboration among the following core teams:

Regulatory Affairs

Interpretation of FDA guidance, compilation of submission documents, communication with regulatory agencies. Ensures the ANDA aligns with 21 CFR Part 314 requirements.

Research & Development (R&D)

Formulation scientists and analytical chemists develop and optimize the product. Conducts method validation, dissolution profile matching, and scale-up trials.

Quality Assurance (Qa)

Implements cGMP compliance, audits, and quality system monitoring. Reviews batch manufacturing records and laboratory data before regulatory submission.

Clinical/Bioequivalence Team

Designs and executes BE studies per FDA Product-Specific Guidance (PSG). Ensures protocol adherence and GCP compliance during clinical trials.

Intellectual Property (Ip) Legal Team

Conducts Paragraph IV certifications and evaluates Orange Book patent listings. Monitors litigation risks and strategizes around patent challenges.

V. CONCLUSION

The present study analyzes the complexities of FDA approval for generic drugs under the ANDA pathway, emphasizing the integration of project management principles to improve efficiency and regulatory compliance. It reviews the U.S. regulatory framework under the Drug Price Competition and Patent Term Restoration Act and highlights the significance of “first-to-file” exclusivity in generic drug development. Although technical requirements such as formulation development, stability studies, and bioequivalence testing

are well defined, execution is challenged by tight timelines and multidisciplinary coordination. The literature review identified gaps in existing ANDA-specific project management models and emphasized the need for structured frameworks.

Methodologies including process mapping, Critical Path Method (CPM), and Failure Mode and Effects Analysis (FMEA) were applied to identify time-critical activities and major risk factors. Bioequivalence studies and stability testing were found to be the most critical path elements.

A Stage-Gate Project Management Model was developed incorporating decision checkpoints, cross-functional collaboration, and continuous regulatory intelligence. Risk mitigation strategies addressed key issues such as BE failures, CMC deficiencies, and regulatory delays. Findings indicate that early regulatory engagement, parallel workstreams, and risk-based resource allocation significantly reduce development delays. Digital tracking tools further enhance transparency and coordination across teams.

In conclusion, the proposed framework improves efficiency, ensures compliance, and supports timely market entry while maintaining quality standards. It balances speed and regulatory rigor, enabling better exploitation of “first-to-file” opportunities.

Future work should focus on real-world validation across multiple ANDA projects and integration of AI-driven predictive analytics for improved decision-making and timeline optimization.

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