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Original Article

NAVIGATING ANDA APPROVAL: A COMPREHENSIVE ANALYSIS OF SUBMISSION STRATEGIES AND POLICIES AND PROCEDURES FOR DEFICIENCY HANDLING

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ABSTRACT

Objective: This review provides a comprehensive understanding of regulatory expectations for generic drug approval in the United States. It highlights essential submission components, evaluation procedures, and common scientific and administrative issues that may lead to Refuse-to-Receive decisions. The review aims to guide applicants in improving submission quality and streamlining regulatory assessment.

Methods: Information was collected from official guidance documents, federal regulations, national generic drug program performance reports, and peer-reviewed literature related to regulatory science and generic drug development. Publications addressing filing requirements, laboratory and manufacturing standards, comparative clinical study principles, and deficiency management strategies were included, while outdated or irrelevant sources were excluded.

Results: This review summarizes the administrative, scientific, and technical requirements for complete generic drug submissions. It describes regulatory evaluation procedures, common deficiencies identified during review, and mechanisms for information requests. Although recent trends indicate improved submission quality and reduced approval timelines, gaps in scientific and technical documentation continue to limit first-cycle approvals.

Conclusion: Structured ANDA submissions supported by robust scientific evidence and early engagement with regulatory authorities can significantly reduce review delays and Refuse-to-Receive outcomes. Ensuring data completeness, adherence to regulatory guidelines, and systematic documentation from the early development stage improves the likelihood of timely approval for generic medicines.

Keywords: Abbreviated new drug application, Generic drug regulatory approval, Refuse-to-receive, Submission quality and completeness, Chemistry, Manufacturing, Controls, Bioequivalence studies, FDA regulatory guidance, Deficiency management strategies

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INTRODUCTION

The Abbreviated New Drug Application (ANDA) process is a pivotal gateway for generic drug manufacturers seeking approval from the Food and Drug Administration (FDA). Unlike traditional drug applications, ANDAs require an "abbreviated" set of data, focusing on the demonstration of bioequivalence rather than redundant preclinical and clinical studies. Bioequivalence ensures that generic drugs reach the systemic circulation at the same rate and extent as the innovator product. The Hatch–Waxman Amendments of 1984, formally known as the Drug Price Competition and Patent Term Restoration Act, significantly accelerated generic drug approvals, promoted market competition, reduced healthcare costs, and maintained stringent safety and efficacy standards [1]. Each ANDA submission is carefully evaluated to determine whether it is sufficiently complete for substantive review, ensuring that applications meeting regulatory standards progress efficiently toward approval and timely market entry.

Despite comprehensive guidance from the FDA, many applicants continue to face Refuse-to-Receive decisions and Complete Response Letters due to preventable deficiencies. These outcomes reflect persistent challenges in regulatory submission quality reported in generic drug approval studies [2]. Consolidated literature summarising practical strategies for preparing complete ANDA submissions and effectively addressing deficiencies remains limited [3–5].

While the FDA's ANDA framework is robust, global regulatory practices vary considerably, with notable differences across Europe, Australia, and India [6]. This review addresses this gap by providing a structured overview of submission best practices and regulatory expectations. It also outlines strategic approaches to facilitate efficient approval of generic medicines [4, 5].

MATERIALS AND METHODS

Literature for this review was identified through a targeted narrative search of regulatory and scientific sources, including USFDA guidance documents, the Code of Federal Regulations (21 CFR), Generic Drugs Program Activities Reports, and peer-reviewed literature indexed in PubMed and Google Scholar. The search strategy employed keywords such as Abbreviated New Drug Application, ANDA approval, Refuse-to-Receive, generic drug regulatory approval, ANDA filing review, and regulatory deficiencies. Publications published between 2014 and 2024 were prioritised to ensure regulatory relevance and currency. Inclusion criteria focused on articles, regulatory reports, and guidance documents addressing ANDA submission requirements, review processes, and deficiency management strategies. Exclusion criteria included non-relevant, outdated, duplicate publications, conference abstracts, and non-English literature. This review follows a narrative review approach and does not constitute a systematic or PRISMA-based systematic review.

Efficient and submissions

Timely approval of generic drugs depends on well-prepared and structured submissions. The FDA has established a framework to ensure that applications are transparent, consistent, and scientifically robust. Complete and precise submissions reduce the risk of RTR decisions and accelerate

review timelines [4, 5]. Applicants must accurately complete all required application forms in accordance with FDA procedural manuals. Key documents include Form FDA 356h for marketing authorisation of human drugs, Form FDA 3794 for payment of user fees under the Generic Drug User Fee Amendments (GDUFA), and Form FDA 3674 for certification of clinical trial registration and results submission to ClinicalTrials. gov [7]. Accurate documentation reduces administrative delays and demonstrates regulatory diligence. Drug Master Files (DMFs) play a critical role in ANDA submissions by providing confidential information related to active pharmaceutical ingredients (APIs), excipients, manufacturing processes, and quality control. These files allow applicants to reference proprietary supplier data without duplicating information. The FDA recognises four major categories of Drug Master Files covering manufacturing sites, drug substances, packaging materials, and excipients. Appropriate cross-referencing of Drug Master Files strengthens compliance with safety, quality, and consistency requirements [3, 7]. Obtaining a pre-assigned ANDA number facilitates accurate submission tracking and correspondence management within FDA electronic systems. Maintaining this number during conversion to the electronic Common Technical Document (eCTD) format ensures data continuity and reduces administrative errors during regulatory review. All ANDA submissions must comply with the electronic Common Technical Document technical requirements. Files up to 10 GB are transmitted through the FDA Electronic Submission Gateway (ESG), while larger datasets may be submitted using physical media in accordance with FDA guidance. Adherence to technical validation criteria and appropriate file structuring prevents rejection during submission validation [7].

Post-submission responsibilities include continued regulatory communication and pharmacovigilance reporting. Applicants are required to submit adverse event notifications using Form FDA 3500A, ensuring ongoing safety monitoring and regulatory transparency throughout the product lifecycle [4, 7]. A sufficiently complete ANDA includes all information required under Section 505 (j) (2) (A) of the Federal Food, Drug, and Cosmetic Act (FD and C Act) and must not contain deficiencies described under 21 CFR 314.101(d) and (e) [5]. Complete submissions typically include Chemistry, Manufacturing, and Controls (CMC) data, bioequivalence studies, labelling information, environmental assessments, and statements confirming compliance with Good Manufacturing Practice (GMP) requirements [3–5]. Well-prepared submissions facilitate substantive review and improve the likelihood of first-cycle approval [3, 5]. Efficient ANDA submission, therefore, requires regulatory precision, scientific rigour, and strict adherence to FDA procedural standards. Applicants who prioritise documentation accuracy, effective use of Drug Master Files, and compliance with electronic submission requirements can minimise deficiencies, reduce review timelines, and support timely access to safe and affordable generic medicines [4, 5].

ANDA submission and review process

The submission and evaluation of an ANDA follow a structured review process established by the FDA to ensure completeness, compliance, and scientific rigour [3–5]. This process determines whether an application is sufficiently complete to permit substantive review and timely approval. The overall workflow of the ANDA submission and review process is illustrated in fig. 1.

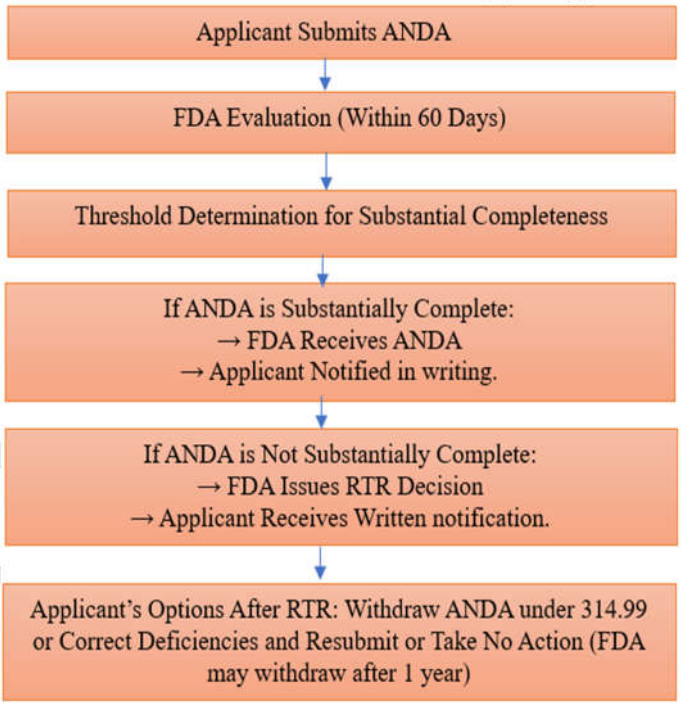

Fig. 1: Simplified workflow of the ANDA submission and review process. (Author's depiction based on the FDA ANDA review framework and Ref [6]
Note: This flowchart is a schematic representation provided for explanatory purposes and is not to scale

The applicant formally submits the ANDA to the FDA, including all required components such as forms, supporting data, and documentation. Within 60 calendar days of receipt, the FDA conducts a preliminary assessment to determine whether the application meets the threshold criteria for a "substantially complete" submission. This evaluation, referred to as the filing review, ensures that only applications meeting regulatory standards proceed to substantive review [3, 4]. If the ANDA is substantially complete, the FDA formally receives the application and notifies the applicant in writing, indicating that the submission is ready for full scientific evaluation. However, if significant deficiencies are identified under 21 Code of Federal Regulations (CFR) 314.101(d) or (e), the FDA issues an RTR decision. The applicant receives written notification specifying the reasons for refusal. Common deficiencies include incomplete CMC data, missing BE study results, or errors in forms and labelling [3, 5]. Upon receiving an RTR notification,

applicants may withdraw the ANDA in accordance with 21 CFR 314.99, correct deficiencies, and resubmit the application, or take no immediate action. If no response is provided within one year, the FDA may consider the ANDA withdrawn from active review [3–5].

FDA review of ANDA for deficiencies

During the review of an ANDA, the USFDA performs an initial screening to determine whether the application is substantially complete in accordance with 21 CFR 314.101(b)(1). This preliminary evaluation ensures that the submitted dossier contains all essential scientific, technical, and administrative components necessary for a comprehensive review. If critical omissions or inconsistencies are identified, the FDA issues an RTR notification specifying the deficiencies. Deficiencies under Paragraphs D and E of 21 CFR 314.101(d) and (e) are classified into two main categories: application content deficiencies and regulatory eligibility deficiencies, as summarised in table 1 [4, 5, 7].

Table 1: Common deficiencies leading to RTR decisions in ANDA submissions

Category	Specific deficiencies	Description/Implication
Paragraph D (Application content) Deficiencies	Incomplete application details	Omission of required data fields or incomplete information in the submitted dossier.
	Non-compliance with formatting standards (21 CFR 314.50 or 314.94)	Failure to structure data as per FDA-specified formats for ANDA documentation.
	Missing or incomplete required information	Absence of critical data necessary under FDA regulations, impeding technical review.
	Environmental impact assessment is missing	Lack of a comprehensive environmental evaluation as mandated by NEPA requirements.
	Inaccurate or missing translations	Non-English sections without verified English translations compromise data integrity.
	Non-clinical laboratory compliance omissions	Missing statements confirming adherence to Good Laboratory Practice (GLP) under 21 CFR part 58.
	Clinical compliance omissions	Failure to include statements confirming compliance with Institutional Review Board (IRB) and informed consent requirements under 21 CFR parts 56 and 50.
	Duplicate submissions	Application submitted for a product already approved under an existing NDA or ANDA.
	Incorrect submission type	A 505(b) (2) application was incorrectly submitted for a product eligible for 505(j) approval.
Paragraph E – Regulatory Eligibility Deficiencies	Product subject to FDA licensing	Submission involves a biological product requiring a Biologics License Application (BLA) under the Public Health Service Act.
	Non-permissible submission under the FD and C Act	Application does not comply with provisions under sections 505(c)(3)(E)(ii), 505(j)(5)(F)(ii), 505A(b)(1)(A)(i)(I), 505A(c)(1)(A)(i)(I), or 505E(a).
	Regulatory non-compliance	Failure to meet statutory exclusivity or eligibility requirements under the FD and C Act.

Footnote: Deficiencies are classified as per 21 CFR 314.101(d) (application content deficiencies) and 21 CFR 314.101(e) (regulatory eligibility deficiencies) [4, 5, 7].

Outcome of FDA review process

Following an ANDA submission, the FDA undertakes a comprehensive evaluation to assess completeness, regulatory compliance, and scientific adequacy. The standard review period typically extends up to 180 days, with possible extensions for complex applications or requests for additional information. The applicant submits the complete ANDA dossier, including supporting data and required forms, after which the FDA performs a scientific and administrative assessment to ensure that the application meets statutory and regulatory standards. Extensions may be granted under specific conditions [8, 9]. Upon completion of the review, the FDA issues either an approval or a disapproval, with approval indicating compliance with all requirements and disapproval reflecting unresolved deficiencies.

If a disapproval occurs, the applicant is notified via a CRL and may request a formal hearing, referred to as a Notice of Opportunity for Hearing (NOOH), to contest or clarify the decision [8]. The applicant may submit additional documentation or request a hearing, which the FDA evaluates within a prescribed timeframe before issuing a final decision [9]. Based on the FDA's final review, the ANDA is either approved or withdrawn. In cases where deficiencies are identified during preliminary screening, an RTR determination is issued, indicating that the application is not substantially complete and cannot proceed to full evaluation [8, 9]. The regulatory journey of an ANDA from initial submission to the final FDA decision is shown in fig. 2.

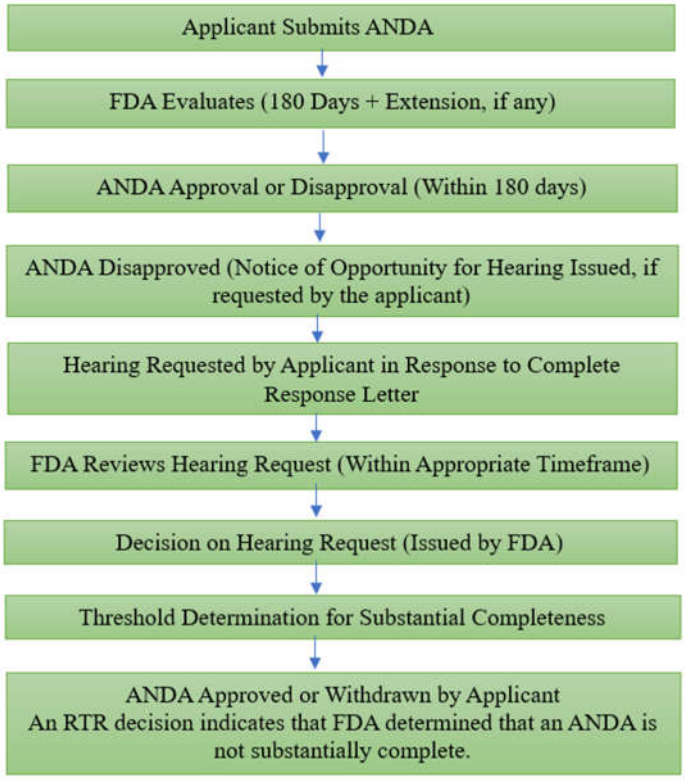

Fig. 2. ANDA regulatory journey from submission to FDA decision. Compiled from [8, 9]
Note: This flowchart is a schematic representation provided for explanatory purposes and is not to scale

Generic drugs program activities: performance overview and regulatory insights (FY2022 – FY2023)

The FDA publishes the Generic Drugs Program Activities Report annually to assess the performance of the Office of Generic Drugs (OGD) under the GDUFA. These reports provide quantitative insights into ANDA submission quality, review efficiency, regulatory outcomes, and evolving challenges in generic drug regulation. A comparative assessment of Fiscal Year (FY) 2022 and FY 2023 highlights the transition from GDUFA II to GDUFA III and its impact on regulatory performance [10, 11].

Performance overview under GDUFA II (FY 2022)

FY 2022 marked the final year of GDUFA II and focused on improving review timelines, communication practices, and structural completeness of ANDA submissions. During this period, the FDA issued a total of 49 Refuse-to-Receive (RTR) decisions for original ANDAs, with the highest monthly count observed in February, primarily due to deficiencies under 21 CFR 314.101(d). The Agency completed 38 standard and 11 priority GDUFA II actions, reflecting steady regulatory throughput. A total of 819 original ANDA acknowledgements were issued, indicating consistent submission activity. Additionally, 437 ANDAs were withdrawn, often to allow applicants to correct significant deficiencies prior to resubmission. By the end of FY 2022, 316 ANDAs were approved, while 121 remained unapproved, underscoring persistent scientific and regulatory challenges [10]. Monthly FDA regulatory actions on ANDAs under GDUFA II (FY 2022) are presented in fig. 3.

GDUFA YEAR/ Actions This Month	21-Oct	21-Nov	21-Dec	22-Jan	22-Feb	22-Mar	22-Apr	22-May	22-Jun	22-Jul	22-Aug	22-Sep	FY-2022
Refuse to Receive (RTR) - Originals	3	3	3	3	9	3	5	5	6	2	4	3	49
Standard - GDUFA II	3	2	1	1	8	3	3	5	5	2	2	3	38
Priority - GDUFA II	0	1	2	2	1	0	2	0	1	0	2	0	11
GDUFA I	0	0	0	0	0	0	0	0	0	0	0	0	0
Acknowledgement - Original	61	63	45	83	91	62	70	94	77	48	56	69	819
Refuse to Receive (RTR) - PAS	0	1	0	0	0	0	1	0	0	0	0	0	2
Withdrawals (all original ANDAs)	201	5	31	17	10	25	30	25	20	6	61	6	437
Approved ANDA	193	0	18	12	2	15	4	16	16	0	38	2	316
Unapproved ANDA	8	5	13	5	8	10	26	9	4	6	23	4	121

Fig. 3: Monthly FDA regulatory actions on ANDAs under GDUFA II (FY 2022). Data compiled from the FDA generic drugs program activities report FY 2022 [10]
Note: The fig. depicts the monthly distribution of RTR decisions; the total number of RTR decisions issued in FY 2022 was 49

Interpretation

FY 2022 represented a transitional phase, with higher RTR and withdrawal rates highlighting recurring weaknesses in Chemistry, Manufacturing, and Controls (CMC) and bioequivalence documentation. These findings informed process improvements later implemented under GDUFA III [10, 11].

Performance overview under GDUFA III (FY 2023)

FY 2023 was the first full year of GDUFA III (2023–2027), which emphasized enhanced communication, reviewer accountability, and support for complex generic products. During this period, the FDA approved 782 ANDAs, representing a 147% increase compared with FY 2022. Approval peaks were observed in March and August, reflecting increased review efficiency. A total of 89 first-time generics were approved, improving market competition and patient access. Additionally, 148 ANDAs achieved first-cycle approval, indicating improved initial submission quality. The FDA also granted 172 tentative approvals for products affected by patent or exclusivity constraints. Despite these improvements, 1,476 Complete Response Letters (CRLs) were issued, primarily due to deficiencies in CMC data, bioequivalence studies, and labelling. Only 33 RTR decisions were recorded, reflecting improved adherence to eCTD structure and filing requirements [11]. The performance of the FDA generic drug program under GDUFA III (FY 2023) is summarized in fig. 4.

ACTIONS BY MONTH	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	FY-2023
Approvals	58	60	52	56	46	96	64	63	76	69	98	44	782
First-Time Generics	1	3	7	4	5	4	5	6	8	18	22	6	89
First-Cycle Approvals	14	13	10	9	6	16	11	13	13	10	23	10	148
Imminent Actions	7	10	7	9	6	14	4	7	5	10	14	6	99
Tentative Approvals	13	13	7	20	21	21	10	18	12	15	12	10	172
First-Cycle Tentative Approvals	0	2	1	2	0	3	2	3	1	2	2	2	20
Imminent Actions	1	3	3	1	3	6	2	5	3	3	4	1	35
Complete Responses	148	120	124	140	141	161	92	105	120	104	118	103	1476
Original ANDA Refuse to Receive	1	2	5	5	3	4	3	2	4	1	2	1	33
Standard	1	2	4	3	2	3	1	1	4	1	1	1	24
Priority	0	0	1	2	1	1	2	1	0	0	1	0	9
Original Acknowledgements	26	97	40	83	76	50	47	93	51	45	53	60	721
Withdrawals	3	9	11	28	9	23	22	4	23	13	16	11	172
Approved ANDA	0	0	7	0	0	12	14	0	1	7	0	0	41
Unapproved ANDA	3	9	4	28	9	11	8	4	22	6	16	11	131

Fig. 4: FDA generic drug program performance under GDUFA III (FY 2023). Data compiled from the FDA generic drugs program activities report FY 2023 [11]

Interpretation

FY 2023 demonstrated substantial regulatory gains, with increased approvals and reduced RTRs reflecting better alignment between applicants and FDA expectations. However, the continued high volume of CRLs indicates ongoing challenges in scientific robustness and regulatory compliance [11].

Comparative regulatory insights: FY 2022 vs. FY 2023

A comparative evaluation of FY 2022 and FY 2023 highlights the positive impact of GDUFA III reforms on regulatory efficiency. Reductions in RTR decisions and increases in first-cycle approvals indicate improved submission discipline and clearer regulatory communication. However, persistent CRL issuance underscores the need for continued improvement in analytical method validation, process control strategies, and bioequivalence study design.

Table 2: Comparative evaluation of FY 2022 and FY 2023 Metrics

Performance metric	FY 2022	FY 2023	Regulatory trend/Observation
ANDA Approvals	316	782	147% increase; improved review efficiency under GDUFA III
First-Time Generics	NR	89	Enhanced market competition and accessibility
First-Cycle Approvals	NR	148	Improved dossier quality and communication
Tentative Approvals	NR	172	Increased readiness for future market entry
Complete Response Letters	NR	1,476	Persistent CMC and labelling deficiencies
RTR Decisions	49	33	33% reduction; better submission discipline
Acknowledgements	819	721	Stable influx of new ANDAs
Withdrawals	437	211	52% decrease; early deficiency resolutions are improving
Unapproved ANDAs	121	131	Slight rise; linked to complex formulations

Data source: FDA Generic Drugs Program Activities Reports for FY 2022 and FY 2023 [10, 11]. Note: Not reported (NR) separately in the FDA Generic Drug Program Activities Report for FY 2022. These performance metrics were not disaggregated in the FY 2022 report and were explicitly reported beginning in FY 2023.

Integrated evaluation and regulatory insights

Certain performance indicators, including first-time generics, first-cycle approvals, tentative approvals, and complete response letters, were not reported as separate metrics in the FDA FY 2022 generic drug program activities report and are therefore denoted as NR in table 2. The transition from GDUFA II to GDUFA III has strengthened the overall ANDA review framework. FY 2023 emerged as one of the most productive years for the Generic Drugs Program, supported by increased reviewer–applicant interaction, clearer communication channels, and improved application discipline. Reductions in RTR decisions and growth in first-cycle approvals demonstrate better alignment between applicants and FDA expectations.

However, the consistently high number of CRLs suggests that the industry continues to face challenges in scientific rigour, particularly in analytical robustness, process validation, and bioequivalence study design. Continued collaboration, improved data integrity, and adherence to structured communication pathways remain essential for maintaining regulatory efficiency and ensuring timely access to affordable generic medicines.

Recent peer-reviewed regulatory science literature published over the past decade has critically examined the factors contributing to delayed approvals and repeated review cycles in ANDA submissions. These studies consistently identify deficiencies in analytical method validation, inadequate control strategies within Chemistry, Manufacturing, and Controls documentation, and suboptimal bioequivalence study design as the most frequent causes of Complete Response Letters and failure to achieve first-cycle approval. Importantly, these academic analyses complement FDA performance reports by providing root-cause interpretations of regulatory deficiencies rather than descriptive metrics alone, reinforcing the need for early scientific rigor and regulatory alignment during generic product development [2, 4, 5, 12].

A comprehensive overview of policies and procedures for handling deficiencies in ANDA

A structured and transparent system for identifying and addressing deficiencies in ANDAs is essential for ensuring regulatory efficiency and maintaining compliance with FDA standards, consistent with published analyses on regulatory control and deficiency management in generic pharmaceutical submissions [12]. The Division of Filing Review (DFR) plays a central role in assessing the completeness of ANDA submissions, identifying major and minor deficiencies, and determining whether an application is suitable for formal review or warrants an RTR action [13]. The filing review process and Refuse-to-Receive determination for ANDA submissions are depicted in fig. 5.

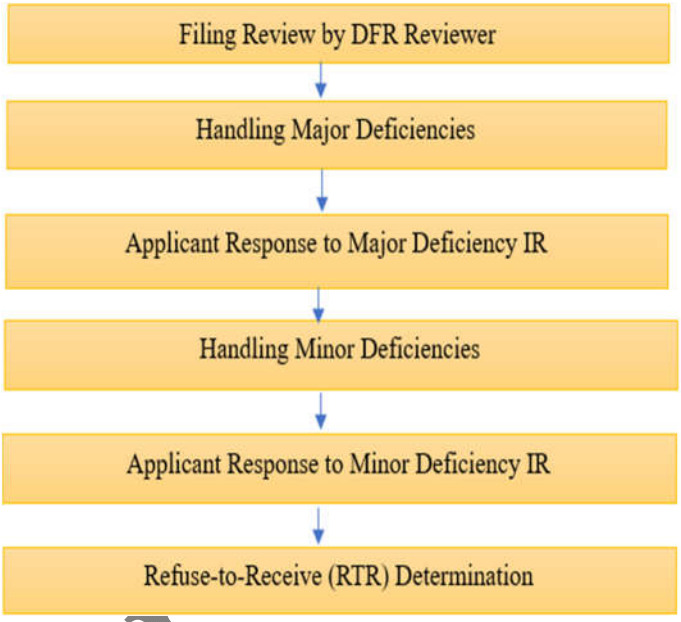

Fig. 5: Filing review process and RTR determination for ANDAs (Based on CDER manual of policies and procedures, MAPP 5220.3 [13])
Note: This flowchart is a schematic representation provided for explanatory purposes and is not to scale

The filing review process, as outlined in the CDER Manual of Policies and Procedures (MAPP 5220.3), involves a comprehensive evaluation to verify administrative, technical, and scientific completeness. During the initial filing review, the DFR identifies all major and minor deficiencies that may impact the acceptance of the application for further evaluation. If a major deficiency is detected but may be resolved by referencing information already included in the original ANDA, the DFR issues an Information Request (IR) specifying the major deficiency along with up to nine minor deficiencies, with a 7-calendar-day response deadline. The DFR Project Manager (PM) contacts the applicant's designated point of contact to notify them of the forthcoming IR, and if direct communication cannot be established, a voicemail is left with instructions. The IR is emailed to the contact address listed on Form FDA 356h or to the applicant's general email address if no individual contact is specified. Upon receiving the applicant's response, if the major deficiency is adequately addressed, the DFR continues its evaluation. If the response is inadequate, the DFR Reviewer prepares an RTR determination, which is then issued by the DFR PM [13].

When no major deficiencies are present, and nine or fewer minor deficiencies are identified, the DFR Reviewer prepares an IR outlining these minor deficiencies and assigns a 7-calendar-day response timeframe. The DFR PM contacts the applicant to provide notice, and the IR is sent to the email listed on Form FDA 356h or to the general mailbox if no individual contact is available. Upon receipt of the applicant's response, the DFR Reviewer evaluates the submission promptly. If deficiencies remain unresolved and the application is still not substantially complete, an RTR determination is prepared. An RTR determination is issued when the applicant fails to respond to an IR within 7 calendar days, a major deficiency cannot be resolved using information already included in the ANDA, or the application contains ten or more minor deficiencies. Before issuing the RTR letter, the DFR PM contacts the applicant's designated point of contact to notify them of the forthcoming action, and the RTR determination is emailed to the contact listed on Form FDA 356h or to the applicant's general mailbox if no individual contact is available [13].

Consequences of RTR in ANDA submissions

The ANDA pathway is essential for approving generic drug products. However, submissions may face challenges, including an RTR determination by the FDA, which can have significant regulatory, financial, and strategic consequences [3]. An RTR decision imposes a 25% penalty on the application fee and requires resubmission after correcting all deficiencies. This not only increases costs but also delays the overall review and approval timeline, affecting the product's timely market entry. For Paragraph IV applications, RTR determinations are especially critical, as they may compromise the applicant's ability to secure the 180-day exclusivity period, directly affecting market competitiveness and potential revenue [14].

Strategies to minimise RTR risk

To minimize the risk of an RTR determination, comprehensive preparation of the ANDA dossier is essential. Successful submissions require thorough documentation, precise formatting, and strict adherence to regulatory requirements. Consistency and completeness across all sections are critical to prevent avoidable deficiencies. Alignment with regulatory expectations should begin during early product development, including formulation strategy, compliance with the Inactive Ingredient Guide (IIG), matching physicochemical properties to the reference product, and accurate identification of the reference listed drug. Oversights during this stage can result in regulatory delays and increased costs. In addition, proactive regulatory engagement, such as controlled correspondence with the FDA prior to submission, can clarify uncertainties regarding formulation, excipient levels, or technical requirements. Early interaction with the Agency helps mitigate deficiencies that could trigger an RTR determination [4, 5, 14].

Future perspectives

The regulatory environment for generic drugs is shifting toward digitalisation, transparency, and international harmonisation [1, 7]. The FDA is expected to integrate artificial intelligence, machine learning, and advanced data analytics to enhance dossier assessment, anticipate deficiencies, and streamline decision-making [1]. Automation within the eCTD framework will reduce errors and improve communication between reviewers and applicants [7]. Proactive engagement through pre-ANDA meetings and controlled correspondence will continue to be critical for clarifying regulatory requirements and avoiding preventable delays [13]. Global regulatory collaboration may also lead to standardised submission protocols, facilitating faster approvals across multiple jurisdictions [1, 6, 7]. These developments will strengthen the agility and responsiveness of the ANDA process, supporting timely access to high-quality, cost-effective generic medicines.

CONCLUSION

The ANDA pathway underpins the availability of therapeutically equivalent and affordable generic medicines. Successful approval depends on meticulous dossier preparation, strict adherence to FDA procedural standards, and comprehensive scientific documentation. The DFR plays a central role in ensuring submission completeness through IR and RTR determinations, underscoring the importance of accuracy at the initial filing stage. From a regulatory practice perspective, applicants can significantly reduce the risk of deficiencies by maintaining well-organised data packages, aligning formulations with the IIG, accurately identifying the Reference Listed Drug (RLD), and complying fully with eCTD formatting and validation standards. Early and strategic regulatory consultation further mitigates review delays and facilitates efficient evaluation cycles. Effective management of ANDA submissions not only accelerates market entry but also preserves the integrity of the regulatory review process, ultimately ensuring safe, reliable, and accessible generic medicines for patients worldwide. From a practical regulatory perspective, ANDA applicants should prioritise early CMC readiness, implement robust bioequivalence study designs, and ensure strict adherence to eCTD validation standards to enhance first-cycle approval outcomes. Proactive regulatory engagement and controlled correspondence can further mitigate filing deficiencies and review delays, providing a strategic pathway to timely market access.

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AUTHORS CONTRIBUTIONS

R. S. Sailesh: Conceptualized the review topic and contributed to the critical evaluation of manuscript content. Pathipati Sunitha: Conducted the literature search, drafted the manuscript, and integrated scientific content. A. R. Aravind: Assisted with manuscript organization, content review, and scientific discussion. S. Nagalakshmi: Supervised the study, edited and formatted the manuscript according to journal requirements, and provided final approval for submission.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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