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ANDA DEFICIENCIES AND REGULATORY STRATEGIES

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ABSTRACT

The Abbreviated New Drug Application (ANDA) pathway plays a critical role in the timely approval and market entry of generic pharmaceuticals. However, a significant proportion of ANDA submissions face delays or are refused due to deficiencies identified during regulatory review. This study investigates the common causes of ANDA deficiencies, focusing on areas such as bioequivalence data, chemistry, manufacturing, and control (CMC), labeling inaccuracies, and procedural non-compliance. Data were collected through a review of FDA refusal-to-receive (RTR) letters, guidance documents, and case studies from recent submissions. The analysis reveals recurring technical and administrative shortcomings that hinder approval timelines and increase regulatory burden. Furthermore, this research explores effective regulatory strategies for minimizing ANDA deficiencies, including the use of pre-submission meetings, quality-by-design (QbD) approaches, third-party audits, and alignment with FDA guidance documents. By identifying trends and proposing actionable best practices, the study aims to support generic drug manufacturers in optimizing ANDA submissions, ultimately improving patient access to affordable medications.

INTRODUCTION

This study was undertaken to summarize various aspects of regulatory standards to support ANDA filing as per current expectations by FDA. Additionally, while meeting the current requirements, the study also summarizes the results of review findings and recommendations to minimize the deficiencies in the ANDA submission and the regulatory strategic recommendations to reduce the repetitive works, where possible. A thorough reading of the FDA guidances specifically related to refusal to receive(RTR) standards, drug product stability requirements, impurities in active ingredients (drug substance) and finished products (drug product), pdf document requirements, Electronic CTD requirements, bioequivalence data requirements, dissolution profiles data requirements and attending FDA's webinars will help understand the baseline requirements and areas to be covered requiring careful planning of the ANDA preparation activities. The summary covers the baseline regulatory strategic recommendations considering an example ANDA for Tablet Dosage-Form.

Discussion

ANDA Module 1 - Administrative Sections:

Deficiencies: Following deficiencies are regarded as major deficiencies pertaining to the administrative Sections: Missing Form-356h Incorrectly organized ANDA, Unpaid GDUFA fees, Not designating U.S. Agent by the firm, where required. Basing or Citing an un-approved Suitability or Citizen Petition under Basis for Submission sections.[1] Regulatory Strategic Recommendations for ANDA Module 1: (To prevent major and minor deficiencies or comments) It is required to submit fillable 356h form if the applicant submits scanned 356h form. US agent details in field 6 and countersignature in field 38 are required for foreign applicants.

All the documents, files to be inserted must meet submission requirements such as: TOC,

Bookmarks, Hyperlinks, Fast Web View etc. The contents of the ANDA file should be in English language. If there are any documents contain language except English, they should be translated into English. It is advisable to use "Times New Roman" font during initial document preparation across the sections in the write up sections and by the cross functional team as well so that the pdf files prepared from the word files will retain the embedded fonts. However, this expectation may not practical always or the case to have the "Times New Roman" font in all documents since some of them may be received outside of the applicant's activities such as statements, cofas etc. from the suppliers. Some statements must be signed by firm along the contract manufacturer (if utilized) such as "Environmental Assessment Statement". Bases for submission must utilize Innovator's NDA Drug (Reference Listed Drug) and approved ANDA suitability or citizen's petitions (if applicable). ANDA Module 2 - Summaries Sections: Deficiencies: The following deficiencies are regarded as major deficiencies pertaining to Summaries Sections: Not providing comparative dissolution profiles for whole tablets and split tablets (if scored) Not providing external hyperlinks to applicable sections in summary-biopharm. LTSS Time Period (Long Term Storage Stability) is less than samples storage time period. LTSS Temperature (Long Term Storage Stability) is outside of range (temperature) for samples storage temperature conditions. Regulatory Strategic Recommendations for ANDA Module 2: (To prevent major and minor deficiencies or comments) It is required to include dissolution data (profile) for whole tablets (RLD and Test) and split tablets (RLD and Test) – for scored tablets (12 units in recommended media and time points) along with CofAs (certificates of analysis) in a single document. The summary-biopharm document should be prepared by utilizing FDA recommended tables in a single document (for all studies) with the required hyperlinks to the applicable documents.

Microbiological Assessment: The drug product release-specification may include, sometimes, microbiological attributes as a default requirement. However, it is not necessary to perform micro testing as part of routine finished-product release-testing for the drug-product utilizes the dry mix process. The elimination or non-inclusion of micro testing in finished-product release-speciation brings substantial cost savings to the generic industry, when it is not necessary based on the controls in the upstream operations, controls in the facility, and formulation ingredients etc. As noted in this study, microbiological assessment report may be presented as a standalone document or summarized under justification of limits. However, it is advised to prepare a standalone microbiological assessment report by utilizing an approved protocol for the drug-product or SOP. The evaluation should embrace the below items at the minimum.

Review the ingredients utilized in the drug-product formulation and their release specification regarding the microbial quality attributes. If the formulation ingredient is susceptible to microbiological load, there should have been a micro testing as part of release specification. Review the facility air handling qualification and periodic air quality monitoring programs. There should have been periodic air quality assessment in place as part of cGMP requirements. Review the Purified Water and Potable Water quality assessments and monitoring programs at the site. There should have been periodic Purified Water quality assessment in place as part of cGMP requirements. Review the equipment cleaning and sanitation procedures. There should have been final wiping of the equipment contact surfaces with 70% IPA and also equipment cleaning validation in place regarding microbiological assessment of the equipment surfaces as part of cGMP requirements. In addition to the above controls in place, consider testing for Water Activity of the final formulation either as part of product-development or utilizing the exhibit batch samples. There are certain requirements to be met for the water activity results to conclude that the drug product do not or may not support the microbiological proliferation. Refer to the USP for specific limits. Additionally, as part

of data generation strategies (in case the FDA requires the data), place the packaged product in stability studies utilizing a standalone stability protocol exclusively for microbiological assessment of the drug-product at release (To), 6 months and 24 months' stability time points. The microbiological assessment protocol and data may be retained at the site for future FDA inspections or can be submitted in a response to FDA deficiencies, if requested.[2]

Stratified Samples Content Uniformity Assessment: The drug-product in-process control may include, when necessary, stratified samples content-uniformity as a default requirement. In such circumstances (low dose), it is advised to utilize the principles outlined in the ASTM E2810/E2709 for sampling-plans and acceptance-criterion to be applied for the stratified content-uniformity for the exhibit-batches The summary of stratified content uniformity assessment can be discussed either in a standalone report or covered under submission batch results section. The following sampling-plans and acceptance-criterion may be utilized for in-process stratified-samples content-uniformity during exhibit-batches and process validation batches:

Sampling Plan: Collect 7 Tablets each from 20-time intervals throughout compression run. Samples should be placed in separate bottles (20 x 7). Test 3 tablets from each location for content uniformity[3.] ANDA Module-3 – Drug-Substance Sections: Deficiencies: The following deficiency is regarded as a major deficiency pertaining to Drug Substance Sections: Key Starting Ingredient: Initial material selected for synthesis of substance is not meeting standard[3]. Regulatory Strategic Recommendations for ANDA Module 3 - DS: (To prevent major and minor deficiencies or comments) It is expected to present entire synthesis starting with the correct designated starting material in the MF or DMF. The MF or DMF must describe the steps and sites associated with manufacturing, synthesis or production of intermediates. ANDA filing firm should summarize some sections in ANDA considering text available from open MF part as oppose to referencing MF. The specific sections requiring to re- summarize are 1) properties 2) structure and 3) nomenclature. In some cases, MF may list ordinary impurities with a limit of 2% allowed in the past. Careful assessment is needed for limits selected and must meet current standards. Sometimes, the MF holder may start substance synthesis utilizing intermediate material purchased from an outside vendor and such vendor details are not included in MF. FDA may inspect outside vendor sites responsible for synthesis of intermediate materials[4]

ANDA Module-3 Drug-Substance Sections:

3.2.S.1 General Information

General Properties, Nomenclature, Structure: Present summaries in table format (from the open part of the MF/DMF). Do not refer directly to the DMF.

3.2.S.2 Manufacture

Manufacturer Info: Include name, address, contact, US Agent (if applicable), DUNS#, FEI#, and required declarations (e.g., cGMP, debarment, TSE/BSE, melamine-free, GMO, residual solvents). Organize as a single, bookmarked document.

Manufacturing Process & Related Sections: For process description, materials control, intermediates, development, and validation—include a statement referring to the DMF.

3.2. S.3 Characterization Structure Elucidation: Summarize techniques (IR, NMR, MS, XRD) from the open part of the MF/DMF.

Impurities: Summarize all impurity data (organic, residual solvents, genotoxins) from the open part of the MF/DMF.

3.2. S.4 Specification - Include drug substance specifications and a CofA from the manufacturer in one document with a table of contents and bookmarks.

Follow USP and vendor specs—whichever is stricter—especially for impurity limits. Align in-house tests (e.g., particle size) with vendor data to avoid inconsistencies. Review USP PF and general chapters to prevent post-filing queries. ANDA Module 3 – Drug Product Sections: Deficiencies: The following deficiencies are regarded as major deficiencies pertaining to Drug Product Sections: Inactive Ingredients: excipient quantity utilized in

formulation is outside of amount allowed. Stability: some batch sizes and study conditions are not per standards. Packing Considerations: packaged amounts not meeting the standard quantities per regulations Batch Records: unexecuted and submission batch records are missing in ANDA. Method Validation / Verification Reports: Method validation / verification reports are not provided.

Regulatory Strategic Recommendations for ANDA Module 3-DP: (To prevent major and minor deficiencies or comments)

Inactive Ingredients- Use the same administration route from the IID; oral, buccal, and sublingual are considered different. For tablets, refer to the highest amounts listed under "tablets and capsules," not liquids. List all excipients in flavors, colors, coatings, and inks, ensuring quantities are within IID limits.

Stratified Content Uniformity: Perform stratified sampling during compression of all exhibit batches to meet content uniformity criteria. Use ASTM standards as preferred by the FDA. USP <905> and PQRI provide alternative strategies suitable for post-validation testing.

Stability Studies: Provide 6-month accelerated and long-term data for three batches (two pilot-scale, one small-scale) using two API lots. Include "date placed on stability" and pull dates at 0, 3, and 6 months. Continue ACC studies even if failures occur, and include intermediate data if needed.

Batch Size & Packaging Strategy: To avoid RTR and reduce cost, submit two pilot batches (≥10% of commercial batch or 100,000 units) and one lab-scale batch (≥25% of pilot or 25,000 units). Fully package the small-scale batch and portions of the pilot batches to total 100,000 units in proposed containers.

ANDA Module 3 Drug-Product Sections:

3.2.P.1 – Description and Composition - Include a summary of the test drug description, composition comparison with the RLD, and a list of inactive ingredients within IIG limits. Address elemental impurities. Reference controlled correspondences or tox reports if needed.

3.2.P.2 – Pharmaceutical Development- Provide a drug development summary, including XRD studies (if applicable), with table of contents and bookmarks.

Elemental Impurities Report - Include an assessment of elemental impurities from ingredients and equipment, supported by supplier statements. Submit as a single, bookmarked document.

Compliance Options: Direct tablet testing

Paper assessment (preferred) – avoids costs related to testing, validation, and instrumentation. This approach includes background, source evaluation, and impurity calculations, removing the need for lab testing.

ANDAModule 5 –Bioequivalence & Clinical Summaries Sections: Deficiencies: Following deficiencies are regarded as major deficiencies pertaining to Module 5 Bioequivalence and Clinical Summaries Sections: Failed In-Vivo BE Study: An ANDA should include passing in-vivo BE (bioequivalence) study. However, the applicants also require presenting information regarding failed BE study, where conducted.

Inadequate Dissolution: Dissolution between RS and Test not presented as per standards. Miscellaneous Factors: The BE (bioequivalence) Study Information table is incomplete. Missing Cases Reports Forms in ANDA.[5]

CONCLUSION:

This study highlights the prevalent regulatory deficiencies encountered in Abbreviated New Drug Application (ANDA) submissions, emphasizing both technical and administrative pitfalls that can significantly delay generic drug approvals. Through a comprehensive review of FDA guidance, Refusal-to-Receive (RTR) letters, and real-world submission case studies, it is evident that common issues span across multiple modules—from missing administrative documentation (e.g., Form 356h, GDUFA fee receipts) and inadequate module organization, to technical oversights in stability data, bioequivalence studies, impurity limits, and method validations. A recurring theme in the findings is the lack of alignment with current FDA expectations regarding document format,

content uniformity protocols, dissolution profile requirements, and complete bioequivalence data reporting. These gaps not only increase the regulatory burden but can also compromise the timeliness of generic drug market entry, ultimately impacting patient access to affordable treatments. To mitigate these deficiencies, the study recommends a proactive, strategic approach that includes: ·Utilizing FDA pre-submission meetings and guidance documents as core planning tools. ·Implementing Quality-by-Design (QbD) principles during development stages. Conducting thorough internal and third-party audits prior to submission. Preparing comprehensive microbiological and elemental impurity assessments in advance. Reporting both successful and failed bioequivalence studies transparently, including case report forms and complete summary tables. By adopting these best practices, ANDA applicants can significantly improve submission quality, reduce review cycles, and enhance regulatory outcomes. This ultimately supports the overarching goal of increasing the availability of safe, effective, and affordable generic medications to the public.

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