INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Optimizing RTR (Refuse To Receive) Filing For Enhanced Regulatory Compliance In Pharmaceutical Submission And Briefing The Analysis Of The USFDA ECTD Publishing

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ARTICLE INFO

Received: 20 May 2024
Accepted: 24 May 2024
Published: 31 May 2024
Keywords:
RTR filing, regulatory compliance, pharmaceutical submission, USFDA, eCTD publishing
DOI:
10.5281/zenodo.11403389

ABSTRACT

The pharmaceutical industry faces stringent regulatory requirements, particularly concerning the submission of Electronic Common Technical Documents (eCTD) to the United States Food and Drug Administration (USFDA). A critical aspect of this process is the Refuse to Receive (RTR) filing, wherein submissions may be rejected due to non-compliance with regulatory standards. This article presents an in-depth exploration of optimizing RTR filing procedures to ensure enhanced regulatory compliance and expedited approval timelines. Through a thorough analysis of USFDA eCTD publishing guidelines and best practices, this study identifies key challenges and proposes actionable strategies for pharmaceutical companies to mitigate RTR risks. By integrating advanced technologies and regulatory intelligence tools, organizations can streamline their submission processes, minimize errors, and ultimately accelerate market access for innovative therapies. This article serves as a comprehensive guide for pharmaceutical professionals navigating the complex landscape of regulatory compliance in drug development and submission.

INTRODUCTION

An FDA RTR (Refuse to Receive) decision includes a finding that an ANDA is not materially complete. A substantially complete ANDA is "an ANDA that, on its face, is sufficiently complete to permit a substantive review." It lists certain deficiencies and some recurring deficiencies that, in the FDA's experience, have caused the FDA to

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

RTR an ANDA. The amended ANDA will be considered a new submission as of the date of submission, and a new ANDA fee will be needed if the applicant chooses to submit additional materials. Seventy-five percent of the filing fee will be returned to the applicant without the need for a formal refund request if the FDA determines that an ANDA was not received for reasons unrelated to nonpayment of fees. If the applicant takes no action within 1 year of a non-receipt, the FDA may consider the ANDA withdrawn.[1,2,3]

Table 1 ANDA Fees as per GDUFA (2024)

	ANDA Fees as per GDUFA (2024)	75% Fees	25% Fees
US Dollar	$ 2,52,453	$ 1,89,339.75	$ 63,113.25
INR	₹ 2,09,23,191.04	₹1,56,92,393.28	₹52,30,797.75

Note: 1 US Dollar equals to 83.06 Indian Rupee

BACKGROUND

The Office of Generic Drugs (OGD) has been tasked with a number of duties following the passage of the Generic Drug User Fee Amendments of 2012 (GDUFA). One of these responsibilities is to develop enhanced guidelines for RTR ANDAs and submit associated applications by the conclusion of the first year of the program. The FDA rejected 379 ANDAs during Fiscal Years (FY) 2013 and 2015 for reasons other than nonpayment of the GDUFA fee. According to frequency, the top five causes for an RTR determination in FY 2015 were as follows:

1. Insufficient data on stability
2. An incomplete answer to the information request
3. Insufficient dissolution
4. The drug product does not match the RLD (Reference Listed Drug) in terms of quality and quantity (Q1/Q2).
5. Not responding to an information request in the allotted amount of time. [1]

LIST OF REQUIREMENTS THAT ARE NOT FULFILLED (CATEGORY WISE) WHICH LEADS TO RTR

Upon filing evaluation of an ANDA, the FDA will identify any major or minor deficiencies. A serious deficiencies is one that the FDA considers to be of a noticeable significance. According to the FDA, a minor deficiencies is one that is easily fixed and of a modest nature. FDA shall advise the applicant of any defects by phone, fax, or email if it determines that an ANDA contains nine or fewer minor deficiencies, or fewer than ten minor difficulties. Applicants may amend or repair any minor errors in the ANDA within seven calendar days, at FDA's discretion. If the requested data is not obtained within seven calendar days, FDA will RTR the ANDA.

Table 2 List of Requirements that are Not Fulfilled (Category Wise) Which Leads to RTR [1,2,3,4,5]

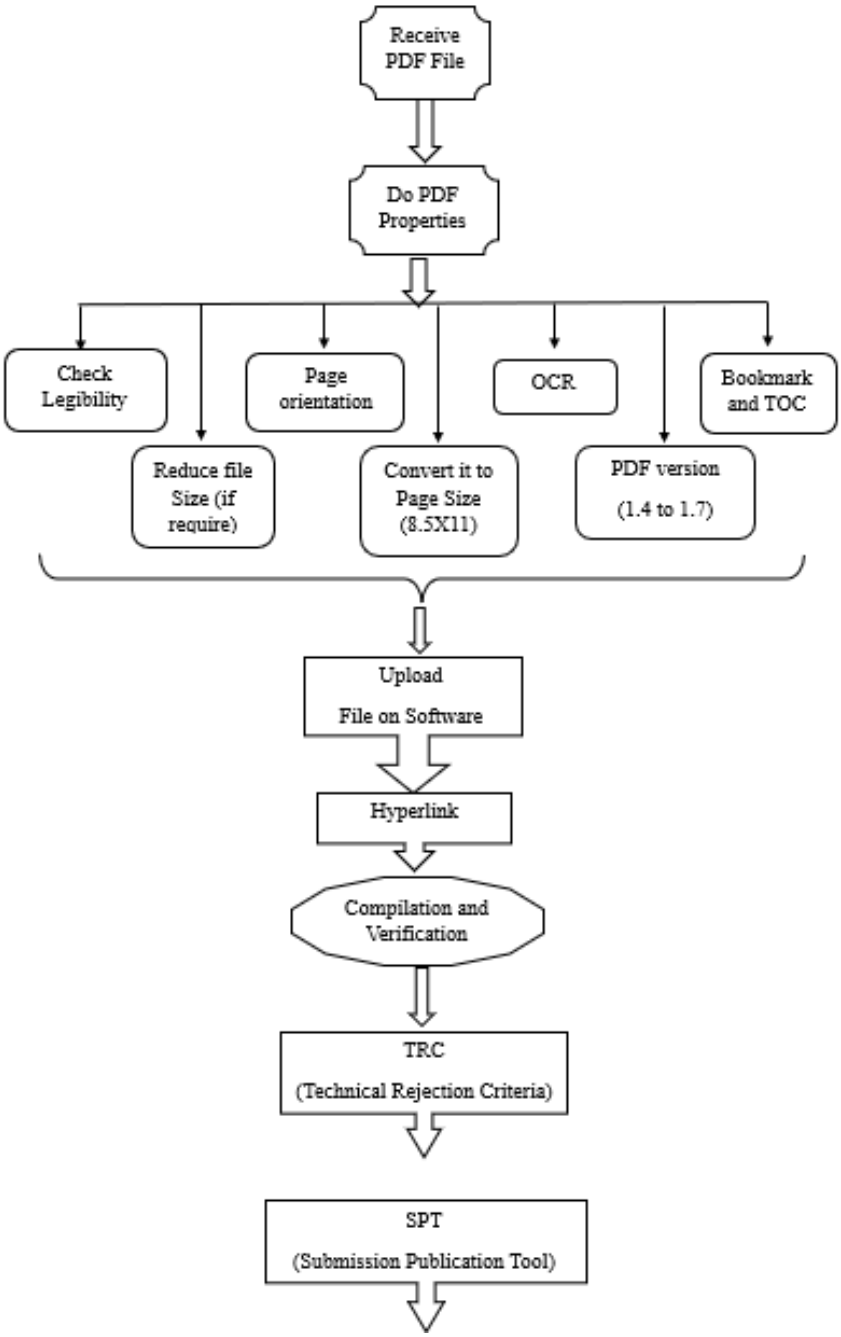
Module	Title	Category (Major/Minor)
General		
-	Application is not presented in English language	Minor
-	Application is not formatted according to the eCTD format	Minor
-	Non-Payment of GDUFA user fee obligation	Major
-	PDF files are not as per PDF specification	Minor
-	Failure to follow the ANDA checklist	Major
-	Lack of legibility in documents/data	Major
-	If product combination, separate section of substance is not provided	Major
Module 1: Administrative Information		

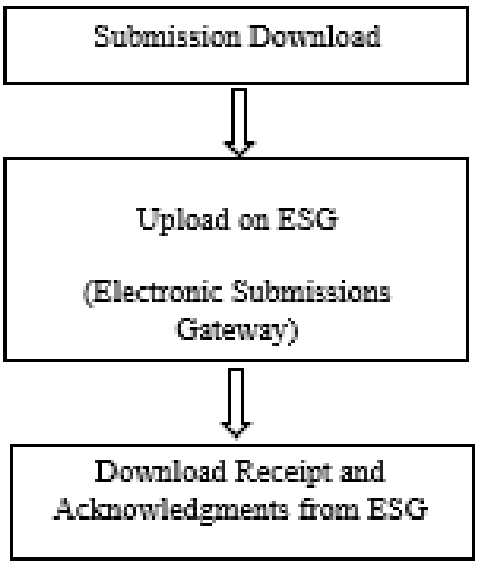
1.1.2	Form 356h is not signed and updated by relevant person	Major
1.3.1.2	"Lack of a designated U.S. agent for a foreign applicant and Letter of Authorization for US Agent is not included"	Major
1.3.3	Debarment Certificate and Conviction statement are not provided	Minor
1.3.4	Financial Disclosure Statement (Form 3454/3455) is not provided	Minor
1.3.5	Relevant Patent and exclusivity certificate is not included	Minor
1.4.2	"Statement of Right of References are not provided" (LOA from DMF Type II, III and IV)	Major
1.12.11	Citing a pending Suitability/Citizen Petition as a Basic of Submission	Major
1.12.12	There is no comparison between RLD and generic drugs	Major
1.12.14	Environmental Analysis or a claim of categorical exclusion is not provided	Minor
1.12.15	Waiver of In-Vivo BA/BE Study is not provided. (Q1/Q2 sameness is not provided. It is for Injections, Otics, Ophthalmic, and some topical products. It is not required for the solid oral dosage forms)	Major
1.14	Container and carton labelling for each packaging configuration are not provided	Major
1.14	variations in the drug product's packaging and/or labeling that could have an impact on its safe or efficient usage	Major
1.14.1.4	"Complete the Pharmacy Bulk Package Sterility Assurance table for pharmacy bulk packages is not provided"	Minor
1.16	Risk Management plan (REMS protocol) is not included If the product is covered under REMS	Major
Module 2: Quality Overall Summary		
2.3	Summary of validation studies are not included	Major
2.7	Study information BE table is incomplete	Major
2.7	CoA for RLD and Test are not provided	Major
Module	**Title**	**Category (Minor/Major)**
2.7	Inadequate dissolution study (in vivo) • Comparative dissolution data between RLD and test are not provided • Alcohol dose dumping (For delayed release dosage form) • Half tablet dissolution data (For functional score tablets) • "Any other product-specific dissolution study described in the BE recommendations for the relevant product"	Major
Module 3: Quality		
3.2.S – Drug Substance		
3.2.S.2.1	Type II DMF is not publicly available for reference (DMF fee has been paid and GDUFA cover sheet attached)	Major
3.2.S.2.1	Initial CA determination API DMF is not completed	Major
3.2.S.2.1	All facility used in the manufacturing and testing are not included in manufacture and form 356h	Minor
3.2.S.2.2	Starting material is not according to ICH Q11guidance.	Major
3.2.S.2.2	Sterile API is used in the submission, sterility assurance data is not included	Major
3.2.S.3.2	Impurity profile is not in FDA recommended table	Major
3.2.S.4.1	Impurity limits are not as per the ICH recommendation	Major

	(If it is higher than the ICH recommendation then appropriate justification is not provided)	
3.2.S.4.3	Method validation/verification/equivalency/transfer reports are not included	Major
3.2.S.4.4	Two distinct lots of API is not used in the manufacturing of finished product	Major
3.2.S.4.5	Justification for impurity specification is not provided in FDA recommended Format	Major
3.2.P – Drug Product		
s3.2.P.1	Inactive ingredients in the composition are not with-in Inactive Ingredients Database (IID) for proposed route of administration	Major
3.2.P.1	"Inconsistencies observed in the scoring configuration between the RLD and test product."	Major
3.2.P.1	Daily elemental Iron calculation is not included	Major
Module	**Title**	**Category (Minor/Major)**
3.2.P.1	Fill volume of generic drug is not same as RLD for parenteral products	Major
3.2.P.1	Same inactive ingredients and same concentration (Q1/Q2) is not there for parenteral products.	Major
3.2.P.3.1	All facility used in the manufacturing and testing are not included in manufacture and form 356h	Minor
3.2.P.3.3	Commercial batch record for the proposed scale-up batches or blank batch record for pilot batches are not included	Major
3.2.P.3.5	"Sterility Assurance validation studied for terminally sterilized drug products are not included • Validation of container closure package integrity • Validation of depyrogenation of product container and closure • Validation of product terminal sterilization process"	Major
3.2.P.3.5	"Sterility assurance validation studies for aseptically filled drug products are not included • Validation of the sterilizing grade filters • Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures • Validation of the depyrogenation of the product containers and closures • Validation of the aseptic filling process/line/room • Validation of container closure integrity"	Major
3.2.P.5.3	Method validation/verification/equivalency/transfer reports are not included	Major
3.2.P.5.1	Impurity limits are not as per the ICH recommendation (If it is higher than the ICH recommendation then appropriate justification is not provided)	Major
3.2.P.5.5	Impurity profile is not in FDA recommended table	Major
3.2.P.5.6	Justification for impurity specification is not provided in FDA recommended Format	Major
3.2.P.7	Proposed packing is not inconsistent with the RLD	Major
3.2.P.8	Inadequate stability	Major

	- Container orientation Number of batch and length of studies	
3.2.P.8	"Accelerated data show a significant change or failure of any attribute then 6M intermediate stability data are not provided in submission."	Major
3.2.P.8	Stability data of drug product are not completed minimum hold time 180 days at the time of the submission.	Major
3.2.R – Regional		
3.2.R	Executed batch records with reconciliation sheets are not provided	Major
3.2.R	Product is not packaged in the container/closure systems that are proposed for marketing in a minimum (threshold) amount of the completed drug product, as indicated in the FDA's guidance for industry ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers.	Major
Module 5: Clinical Study Report		
5.2	Tabular listing of clinical studies	Major
5.3	Supporting data for BCS class 1 is not included if API is BCS class 1 and BE waiver is requested in submission	Major
5.3	Alternate BE studies without any justification	Major
5.3	Provide the Failed in vivo BE studies	Major
5.3	CRF data (at least 10 %) is not included	Major
5.3	The data sets and definition files (ADaM, SDTM) are provided in the submission	Minor
Miscellaneous Factors		
-	Three Drug product batches are not manufactured with three distinct laminates/reservoir gel for transdermal patch.	Major
-	"Each batch of laminates/ reservoir gel is not made using three distinct lots of API, adhesives, gel excipients, backing membrane, rate controlling membrane in transdermal patch"	Major
-	"Device is used to deliver the drug is not sufficiently similar to the device used to deliver the RLD for Drug-device combination product"	Major
-	"Proposed product is ophthalmic solution if yes, BE table comparative physicochemical date of ophthalmic solution drug product is included in module 2.7"	Major

BRIEFING THE ANALYSIS OF THE USFDA ECTD PUBLISHING [6]





CONCLUSION

Compliance with RTR requirements outlined in Table 2 is vital to avoid screening queries and RTR from the agency, ensuring timely acceptance of ANDA, and meeting company goals. Failure to comply results in a 25% loss of the ANDA submission fee and forfeits first-filer status and exclusivity for FTF ANDA submissions. Adhering to RTR requirements is crucial to preventing unnecessary losses. Submission types like NDAs, ANDAs, and BLAs have been in eCTD format since May 5, 2017. IND submissions and Master Files transitioned to eCTD format on May 5, 2018, excluding Type III DAMTs. eCTD offers advantages like streamlined agency management, enhanced readability, and simplified lifecycle management. Following the FDA's PDF Technical Specification Guidance is vital to avoiding screening deficiencies. Compliance with the FDA's Technical Rejection Criteria for Dataset in Module 4 and Module 5 is necessary to prevent submission rejection. ECTD submission packages must be sent via the Electronic Submission Gateway (ESG) to the US agency.

REFERENCES

1. FDA. ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry, December 2016.
2. FDA. ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits Guidance for Industry, August 2016.
3. FDA. ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers Guidance for Industry (Draft), October 2017.
4. FDA. ANDA Submissions — Content and Format Guidance for Industry, September 2018.
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HOW TO CITE: Manisha B. Divraniya, Maitreyi Zaveri, Zuki Patel, Optimizing RTR (Refuse To Receive) Filing For Enhanced Regulatory Compliance In Pharmaceutical Submission And Briefing The Analysis Of The USFDA ECTD Publishing, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 5, 1866-1872. https://doi.org/10.5281/zenodo.11403389