ANDA Refuse-to-Receive Pitfalls and How to Avoid Them

A review of FDA expectations

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The generic drug industry is highly competitive and to be among the first on the market can make the difference between a generic product's success and failure. Submitting a comprehensive and scientifically sound Abbreviated New Drug Application (ANDA) is essential to passing the hurdles of FDA review.

FDA has issued many guidance on ANDA submissions that are publicly available. These documents provide a roadmap for product development, quality assurance and regulatory affairs professionals. 21 CFR 314.101 provides the regulatory authority by which FDA may Refuse-to-Receive (RTR) an ANDA.[1] This article will review FDA expectations, summarize commonly received RTRs from some of the major categories, and provide points to consider when developing and submitting the required data.

The first hurdle that an ANDA must pass is for FDA to receive it. This isn't as easy as just transmitting an ANDA to FDA. FDA's "Guidance for Industry—ANDA Submissions—Refuse-to-Receive Standards (December 2016, Rev. 2)" (RTR Guidance),[2] and Office of Generic Drugs "Manual of Policies and Procedures—Filing Review of Abbreviated New Drug Applications (MAPP 5200.14; September 1, 2017),"[3] outline ANDA acceptance requirements and highlight deficiencies that may cause FDA to RTR an ANDA

Table 1.

Fiscal Year	Number of RTRs	Number Submitted	Percentage
FY 2013 (Oct. 2012 – Sept. 2013)	150	968	15%
FY 2014 (Oct. 2013 – Sept. 2014)	173	1473	12%
FY 2015 (Oct. 2014 – Sept. 2015)	236	539	44%
FY 2016 (Oct. 2015 – Sept. 2016)	246	852	29%
FY 2017 (Oct. 2016 – Aug. 2017)	130 (142 projected for FY 2017 based upon prior 2017 trends)	1090 (1189 projected for FY 2017 based upon prior 2017 trends)	12% (12% projected for FY 2017 based upon prior 2017 trends)

An RTR decision indicates that FDA has determined that an ANDA is not substantially complete. A substantially complete ANDA, as defined in 21 CFR 314.101(b)(1), is "an ANDA that on its face is sufficiently complete to permit a substantive review."[4] The RTR Guidance goes on to state,"In FY 2015, the five most frequent bases for an RTR determination were (in order of frequency): inadequate stability data; incomplete information request response; inadequate dissolution; drug product was not qualitatively and quantitatively (Q1/Q2 same) the same as the reference listed drug (RLD); and failure to respond to information request within the prescribed timeframe."

Table 1 contains information reported by the FDA in its annual"Activities Report of the Generic Drug Program"[5] regarding ANDA RTRs over the past several years. According to this information, 2017 appears to show a decrease in the percentage of RTRs compared to recent years.

The RTR Guidance lists in each section the major elements required to be substantially complete. Below are selected items from the RTR Guidance that will be explored further. The complete list can be found in the RTR Guidance.

A frequent issue related to general items is errors related to the Form FDA 356h. A firm is required to submit the Form FDA 356h as a fillable form with all the required information and with an electronic signature. If the applicant does not have an electronic signature they can sign a printed version of the completed form and create a PDF scan. However, they must submit both the unsigned completed fillable form and the signed completed PDF forms to the application.

Another general RTR point is related to Submission, Format, and Organization of the application. There are specific requirements in the FDA guidance"Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications—Guidance for Industry (April 2017, Rev. 4),"[6] which provide explicit guidance on the electronic format of the application. This was published on May 5, 2015 and went into effect as of May 5, 2017. Many ANDAs receive an RTR for items such as lack of hyperlinking the Table of Contents or for book-

marking of any document longer than five pages.

The selection of the appropriate inactive ingredients and quantities to conform to the requirements for Qualitative and Quantitative (Q1/Q2) sameness and Inactive Ingredient database (IIG) limits is a critical consideration in development of an ANDA formulation. Deviation will require justification that may or may not result in an RTR. We have come across Information Requests specific to the justification of inactive ingredients above the allowable limits that give only seven calendar days to provide enough information so the application can be accepted for review. This is not an ideal time to start developing an appropriate rationale. The RTR Guidance provides explicit instances for justification regarding inactive ingredients.

Regarding Q1/Q2 sameness, there are guidance related to specific dosage forms. For example, in accordance with 21 CFR 320.22(b)(1), parenteral drug products, in addition to ophthalmic and otic solutions, may be eligible for a waiver of bioequivalence (BE) studies, provided that their formulations are considered Q1/Q2 same as the RLD (other than exception ingredients such as buffers, antioxidants or preservatives). For ophthalmic solutions, the RTR Guidance indicates that it is critical to also complete and include the BE table Comparative Physicochemical Data of Ophthalmic Solution Drug Products in Module 2.7, otherwise it will result in an RTR.

Setting specifications for impurities has been well understood through ICH and FDA guidance. Yet there are still RTR deficiencies cited by FDA as published in the FDA guidance "ANDA Submissions—Refuse to Receive for Lack of Justification of Impurity Limits (August 2016)."[7] Typical deficiencies leading to an RTR decision include: (1) failing to provide justification for proposed limits in drug substances and drug products for specified identified impurities that are above qualification thresholds; (2) failing to provide justification for proposed limits for specified unidentified impurities that are above identification thresholds; and (3) proposing limits for unspecified impurities (e.g., any unknown impurity) that are above identification thresholds.

Stability requirements are outlined in the FDA's draft guidance,"ANDA Submissions—Content and Format of Abbreviated New Drug Applications (June 2014)."[8] At the time of its issuance, the draft guidance represented a significant change in the stability requirements by requiring a minimum of six months (180 days) accelerated and room temperature stability on three batches—three pilot scale or two pilot scale and one small scale. Understandably, there was a sharp increase in RTRs around the time this draft guidance was issued.

A more recent increase in RTRs has been seen regarding scored tablets. The relevant reference regarding tablet scoring is FDA's "Guidance for Industry—Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (March 2013)" (Scoring Guidance).[9] The Agency is looking for consistent scoring to allow the patient to adjust the dose by splitting the tablet, in the same manner as the RLD, without encountering problems related to dose. The Agency's concerns with splitting a tablet included variations in the tablet content, weight, disintegration, or dissolution and stability. We have seen RTRs for lack of the required 90-day pharmacy bottle stability on the split tablets, a lack of comparison of split tablets to the RLD for tablet content, weight, and disintegration as well as a lack of data from both mechanically split and hand split tablets.

RTRs have been received for the lack of comparative dissolution between the scored test product and the scored RLD. The Scoring Guidance states that if the RLD is functionally scored then the test product must be scored in the same configuration. There is the expectation that the dissolution studies must be conducted on the split tablets for both the proposed drug product and the RLD. This testing needs to be performed on 12 split portions in the same test media as is used for the whole tablet dissolution studies. This is commonly overlooked.

A recent increase in RTRs is related to ANDA applicants requesting a waiver of BE studies based on the Biopharmaceutics Classification system (BCS) for Immediate Release tablets. The waiver is generally acceptable for lower strengths based on *in-vivo* and *in-vitro* comparative studies on the higher strength to the RLD/RS. However, the requirement for comparative *in-vitro* dissolution must still be met on all strengths, not only on the reference strength. The comparison must be performed on 12 tablet individual dissolution of test versus RLD in all dissolution media. The data needs to be generated on the submission batches and be presented in summary tables in module 2.7 in both PDF and word format.

In addition to the major categories, Appendix A of the RTR Guidance includes specific examples of what the FDA will consider a minor filing deficiency. One or two minor deficiencies will not be a cause for an RTR but the RTR Guidance is very clear that 10 or more minor deficiencies will result in an RTR.

Conclusion

21 CFR 314.101 provides the regulatory authority by which FDA may RTR an ANDA. Generally, a major deficiency is one that in FDA's judgment cannot be easily remedied. A minor deficiency is one that in FDA's judgment can be easily remedied. FDA will allow the applicant a prescribed time period to provide a response. If FDA determines that an ANDA contains 10 or more minor deficiencies or one or more major deficiencies, FDA will consider such an application not sufficiently complete to permit a substantive review, and will result in a RTR.

There have been several guidance documents issued by FDA elaborating on the requirements for ANDA filing suitability. In addition, FDA has published Q&A documents answering questions they have received from industry on these topics. In this current environment of transparency, as well as accessibility using online search engines, an RTR for an ANDA should be a rare event. Yet, according to the numbers provided by FDA, there are still a significant number of RTRs each year. It is important for Product Development, Quality and Regulatory professionals to understand every aspect of relevant guidance documents related to their product and generate the necessary data for a high quality ANDA submission to avoid an RTR. **CP**

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