ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017

Generics

ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers

Guidance for Industry

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ANDA Submissions – Refuse-to-Receive Standards: Questions and Answers Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This draft guidance is intended to assist applicants preparing to submit to FDA abbreviated new drug applications (ANDAs) and certain prior approval supplements (PASs) to ANDAs.[2] This guidance provides answers to questions we have received from applicants regarding the guidance for industry, *ANDA Submissions—Refuse-to-Receive Standards* (RTR Standards guidance)[3] and the filing review process, in general. The questions and answers address general issues about the organization of an ANDA, filing decisions made by FDA, the review of and deficiencies related to Drug Master Files (DMFs), product quality, and bioequivalence (BE) and clinical reviews, and are intended to clarify the deficiencies that may cause FDA to refuse to receive (RTR) an ANDA. An RTR decision indicates that FDA has determined that an ANDA is not a substantially complete application (i.e., that the ANDA, on its face, is not sufficiently complete to permit a substantive review).[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For purposes of this guidance, the use of the term ANDA will mean ANDAs *and* PAS submissions to ANDAs, as described in the introduction.

[3] The RTR Standards final guidance was issued in September 2014 (see Guidance for Industry on [ANDA] Submissions—Refuse-to-Receive Standards; Availability, 79 FR 55813, September 17, 2014). A revised final guidance was posted to FDA's web site on May 26, 2015, which contained minor changes to clarify text, improve readability, and reference the Office of Pharmaceutical Quality, which was established after the original guidance posted in September 2014. A subsequent revised final version was posted to FDA's website on December 21, 2016. This most recent revised guidance contains further clarifications of policy and minor changes in policy to benefit applicants.

[4] 21 CFR 314.101(b)(1) and 314.3(b).

the word *should* in Agency guidances means that something is suggested or recommended, but not required.[5]

II. BACKGROUND

Pursuant to the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA),[6] the Office of Generic Drugs (OGD) is tasked with a number of activities, including the development of "enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program…."[7] Enhanced RTR standards are important because the practice of submitting an ANDA that is not sufficiently complete to permit a substantive review and then "repairing" it in the course of an extended review period that needs several cycles of FDA response and applicant repair is inherently inefficient and wasteful of resources. In addition, ANDAs that are not sufficiently complete to permit a substantive review generate extra reviews and letters.

FDA evaluates each submitted ANDA individually to determine whether the ANDA can be received. The receipt of an ANDA means that FDA made a threshold determination that the ANDA is a *substantially complete application*, that is, an ANDA that on its face is sufficiently complete to permit a substantive review.[8] Sufficiently complete means that the ANDA contains all the information required under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and does not contain a deficiency described in 21 CFR 314.101(d) and (e).[9]

Our regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in other cases, RTR an ANDA.[10]

III. QUESTIONS AND ANSWERS

A. Scope

Q1: To which generic drug product submissions do this guidance and the RTR Standards guidance apply?

[5]At various points in this guidance, it is noted that when a particular type of deficiency is identified in an ANDA, FDA *will* RTR the ANDA. These statements are included for purposes of transparency, and do not create legal obligations, on applicants, or on FDA. This means that FDA generally will RTR an ANDA on the grounds described in this guidance. This guidance does not preclude the possibility that an ANDA applicant may be able to demonstrate, in particular circumstances, that the regulatory requirements for receiving an ANDA have been met even when, as described in this guidance, FDA would generally find that the ANDA is not a substantially complete application and RTR the submission.

[6] Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III).

[7] See Generic Drug User Fee Act Program Performance Goals and Procedures: http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[8] See 21 CFR 314.101(b)(1) and 314.3(b).

[9] 21 CFR 314.3(b).

[10] See 21 CFR 314.101(d)-(e).

This guidance and the RTR Standards guidance apply to original abbreviated new drug applications (ANDAs) and certain prior approval supplements (PASs) to ANDAs consistent with our current practices, including those in which the applicant is seeking approval of a new strength[11], reformulation of a drug product that does not require a new original ANDA submission, return of a discontinued product to the market, and Rx-to-OTC switches for all conditions of use.[12]

B. Responding to Deficiencies and RTR Determinations

Q2: Does an applicant have an opportunity to correct deficiencies identified during the filing review?

The guidance for industry, *ANDA Submissions—Refuse-to-Receive Standards*, memorializes many of the standards that FDA historically has applied in its RTR determinations and sets forth several minor deficiencies that may be corrected and major deficiencies that may result in an RTR determination. FDA, in its discretion, may provide applicants with the opportunity to correct deficiencies that are minor in nature as identified in an Information Request (IR) within seven calendar days. If the applicant successfully corrects the minor deficiencies within seven calendar days, the ANDA submission will be received and retain the original submission date.

If information is missing, the type of data missing determines FDA's RTR decisions. If FDA determines a deficiency is major, but that deficiency could be corrected quickly, it does not obviate the fact that the ANDA lacked that data in the first instance. This would result in an RTR determination and the ANDA, if resubmitted, would not retain the original submission date.

Q3: An applicant receives an IR listing minor deficiencies identified during the filing review. The IR states that the response is due within seven calendar days. What happens if the applicant fails to submit the responses within this time frame?

If an ANDA applicant receives an IR from FDA listing minor deficiencies identified during the filing review, and the requested information is not submitted and received within seven calendar days, FDA will RTR the ANDA. Responses to IRs should completely address all outstanding issues identified in the IR. Responses to IRs should be formatted and submitted following current electronic Common Technical Document (eCTD) specifications, submission structure recommendations, file format, and version recommendations (see guidance for industry on *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*).

[11] A PAS for a new strength includes a change in strength of a solid oral dosage form product, ; change in concentration for a parenteral dosage-form product; change in vial size, fill volume, and/or package size to a parenteral dosage-form product (i.e., total drug content); change in concentration of an oral liquid, ophthalmic, otic, transdermal, or topical drug product,

[12] Once this guidance is finalized, FDA will revise the introduction to this guidance and the RTR Standards Guidance so that the PASs that currently are subject to filing review and within the scope of these guidances are clearly identified.

Q4: An applicant receives an RTR determination and provides a response to some of the deficiencies. Will the response be accepted as a resubmission?

No, FDA will not accept a partial response to an RTR determination. If FDA issues an RTR determination, an applicant may either correct all deficiencies identified therein by resubmission of a complete ANDA (i.e., a new application that remedies the major deficiencies and any and all minor deficiencies identified in the RTR letter) or withdraw the application under 21 CFR 314.99. (If the applicant takes no action, FDA may consider the ANDA withdrawn after one year.)[13]

If the applicant's response to RTR determination is incomplete or otherwise inadequate and therefore does not remedy FDA's determination that the ANDA is not a substantially complete application, FDA will RTR the resubmission.

Q5: An applicant receives an RTR determination. The applicant resubmits the ANDA and provides a response to each deficiency, but the applicant receives a subsequent RTR determination. Why did FDA RTR the resubmission?

FDA may RTR a resubmission for multiple reasons including, but not limited to, the failure to provide a comprehensive response to the deficiencies identified in the RTR letter and failure to follow the current recommendations relevant to filing (e.g., recommendations set forth in RTR guidances and in product-specific bioequivalence guidances) in effect at the time of resubmission.

Q6: An applicant receives an RTR determination and seeks assistance in developing a resubmission. Will FDA assist the applicant in responding to the deficiencies?

FDA does not provide specific guidance to applicants on how to remedy an ANDA that has received an RTR determination. If an applicant has concerns regarding the content of an RTR determination letter, the applicant should contact FDA via the email address identified in the correspondence. If an applicant has general questions about generic drug development (e.g., quantitative and qualitative (Q1/Q2) issues),[14] FDA recommends that the applicant submit a controlled correspondence to FDA at genericdrugs@fda.hhs.gov.[15] An applicant may submit questions and request general information regarding the preparation of submissions in electronic format to esub@fda.hhs.gov.

Q7: How long does an applicant have to request reconsideration of an RTR determination?

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[13] 21 CFR 314.101(b)(3).

[14] See, generally, guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance webpage at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[15] See guidance for industry *Controlled Correspondence Related to Generic Drug Development.* If the applicant's general question pertains to a drug product for which the applicant has submitted an ANDA that was subsequently refused for receipt, the applicant should reference the RTR determination in the controlled correspondence.

The Agency believes that seven calendar days provides an applicant sufficient time to review FDA's regulatory action and determine whether the applicant would like to pursue a request for reconsideration. It also ensures that applicants submit requests for reconsideration of recent Agency regulatory actions. Like minor deficiencies, any matters that will be challenged should be reviewed, analyzed, and addressed within seven calendar days.

The Agency recognizes that an applicant will require some time to identify, coordinate, and compile the information necessary to submit a response to the RTR determination; however, in an effort to streamline reviews and enable timely inspections, the Agency needs to define an acceptable time frame in which to challenge an RTR determination. For example, if an applicant receives an RTR determination 60 days after the application is submitted and submits a successful request for reconsideration one month after the RTR determination was made, the Agency will have lost one month of application review time and the Agency's ability to ensure timely inspections may be jeopardized.

Q8: If an applicant requests reconsideration of an RTR determination, should the applicant resubmit the ANDA including responses to the deficiencies identified in the RTR correspondence with the request for reconsideration?

The applicant may either submit only a request for reconsideration or a request for reconsideration with the resubmitted ANDA (i.e., a new submission that provides a comprehensive response to the deficiencies identified in the RTR letter). If an applicant only submits a request for reconsideration, the applicant does not pay an additional GDUFA fee and the ANDA will remain in RTR status, meaning that no technical review will commence.

If an applicant prefers to resubmit the ANDA while the request for reconsideration is pending, the applicant should provide a resubmission and remit any applicable user fees.[16] This will initiate the filing review for the ANDA as resubmitted. The applicant should identify that the resubmission is related to a pending request for reconsideration on the resubmission cover page. To facilitate review, submit all supporting information provided for the request for reconsideration in the resubmission, along with complete responses to any other deficiencies identified in the RTR correspondence. While the FDA is evaluating the request for reconsideration, the ANDA will remain in RTR status and no technical review will commence. The applicant will be notified when a decision on the request for reconsideration has been made.

Q9: Will FDA accept an unsolicited filing amendment submitted during filing review to correct a deficiency identified by the ANDA applicant?

FDA will not review any unsolicited amendment submitted by the applicant, other than an administrative amendment identifying a change in contact information or ownership, while the ANDA is pending filing review.[17] For example, an amendment containing data

[16] See Section 744B(a)(3)(E) of the FD&C Act.

[17] FDA will note the submission of any amendments containing patent certifications during filing review.

that should have been included in the original submission will not be reviewed during the filing review or considered when making the determination of whether the ANDA is a substantially complete application.

Q10: How does the GDUFA Amendment Tier structure impact the filing review?

The Amendment Tier program associated with GDUFA I will generally not impact the filing review. FDA will communicate minor filing deficiencies that may be remedied to an applicant. The applicant's response to these deficiencies is not considered a "solicited amendment," which is an amendment submitted in response to a complete response letter that sets a new goal date for the ANDA.[18] The applicant's submission of a response to minor deficiencies identified during the filing review will not impact the GDUFA performance goal date for the ANDA, provided that adequate responses to such minor deficiencies are received within seven calendar days. The reauthorization of GDUFA does not include the Amendment Tier program.[19] The types of amendments and review goals associated with the GDUFA II apply only to submissions that have been received for review (i.e., review goals do not apply to submissions pending filing review).

C. General Deficiencies

Q11: If a typographical error (or "typo") is the basis for a major deficiency resulting in an RTR determination, will FDA rescind its RTR decision if the applicant identifies the typographical error and provides a corrected submission?

FDA will not rescind the RTR determination if a typographical error is the basis for a major deficiency and the applicant informs FDA of the error and provides a corrected submission. When compiling an ANDA, applicants should ensure that all relevant data and information necessary to support the substantive review is correctly transcribed into appropriate sections of the ANDA. When performing a filing review, the Agency will assume that the information transcribed in an ANDA is correct. The Agency must move expeditiously through the filing process to ensure that FDA is able to meet its commitment to review and act on ANDAs within specified GDUFA performance metric goal dates.

A typographical error that may result in a major deficiency due to an applicant's lack of quality control is not limited to a numerical value; the error may involve an alphabetical letter, symbol, or other text.

> *Example*: In guidance, FDA recommends that ANDAs contain the initiation date for each stability study conducted, along with individual pull dates (removal from the storage chamber and preferably identified in MM/DD/YYYY or

[18] See GDUFA Program Performance Goals and Procedures (GDUFA I Commitment Letter) available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[19] See GDUFA Reauthorization Performance Goals and Program Enhancement Fiscal Years 2018-2022 (GDUFA II Commitment Letter) available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

YYYY/MM/DD format) for each stability time point, so FDA can verify that each study covers the recommended six-month (180-day) minimum hold time. If the applicant provides a date that does not confirm a 180-day hold time as a result of a typographical error, FDA will RTR the ANDA. A demonstration by the applicant that the basis of the RTR was caused by a typographical error will not be sufficient to rescind the RTR determination for this type of deficiency.

Example: In guidance, FDA recommends that ANDAs contain information concerning Long-Term Storage Stability coverage in the applicable row of the Study Information Bioequivalence table. These data are necessary to ascertain adherence to appropriate storage temperatures and duration. If the applicant provides a date or temperature (including temperature range) that does not confirm proper storage conditions or duration as a result of a typographical error, FDA will RTR the ANDA. A demonstration by the applicant that the basis of the RTR was caused by a typographical error will not be sufficient to rescind the RTR determination for this type of deficiency.

Example: In guidance, FDA recommends that a threshold value for a particular variable should be >60 units. In the ANDA, the applicant uses a symbol that indicates it does not meet the threshold value (e.g., <60 units). As a result of this typographical error, FDA will RTR the ANDA. A demonstration by the applicant that the basis of the RTR was caused by a typographical error will not be sufficient to rescind the RTR determination for this type of deficiency.

Q12: Will FDA RTR an ANDA that does not contain a patent certification that is consistent with the regulations?

FDA will treat as a minor deficiency an applicant's failure to include a patent certification or statement that is consistent with section 505(j)(2)(A)(vii) and (viii) of the FD&C Act and 21 CFR 314.94(a)(12) and 314.96(d).

Q13: Will FDA RTR an ANDA if the submission contains a section or information in a language other than English and the applicant does not provide an English translation?

FDA will identify untranslated content, which must be translated into English,[20] in an IR. Failure to provide the requested translations will result in an RTR. Moreover, it is incumbent upon the applicant to ensure that any and all untranslated content in the ANDA submission, including all sections of the document (e.g., headers, titles), is translated into English. Therefore, should FDA discover additional untranslated content in the ANDA submission after an IR response has been submitted, the ANDA will be refused for receipt.

[20] See 21 CFR 314.101(d)(5).

FDA will accept an ANDA with the English translation on a page next to the original text. FDA recommends that the translation be printed in size 12 type to facilitate review. The applicant should use its best judgment in determining how to fit the necessary information on a page without impacting the reviewer's ability to read the information.

Q14: If the point of contact for the ANDA is out of the office, how will the applicant receive filing deficiencies from FDA?

FDA will notify the point of contact for the ANDA (i.e., the applicant's responsible official for applicants located in the U.S. or the U.S. Agent, if applicable), as identified on the Form FDA 356h in the ANDA file via the primary method for communication for deficiencies, which is secure email. Once notified, the applicant has seven calendar days to satisfactorily correct the identified deficiencies. In the event that FDA receives an out-of-office message when communicating deficiencies by email to the point of contact, FDA will not contact any person not identified on Form FDA 356h. FDA recommends that applicants provide an email address on the Form FDA 356h that is checked regularly, even if the designated point of contact is out of the office, to ensure that all communications from FDA are received in a timely manner.

We recommend that applicants notify the Agency of any change in the point of contact for the ANDA as soon as practicable by submitting an administrative amendment to the ANDA file.

D. Drug Master File (DMF) Review and Deficiencies

Q15: Will FDA RTR an ANDA referencing a Type II active pharmaceutical ingredient (API) DMF that has not been listed on the Available for Reference List[21] as of the date the ANDA is submitted to FDA?

FDA will RTR an ANDA that relies on a Type II API DMF that has not been deemed available for reference[22] at the time the filing review for such ANDA is completed. In determining whether a Type II API DMF is available for reference by an ANDA, FDA will consider those materials submitted by the relevant DMF holder as of the date that the ANDA is submitted to FDA.

Q16: Will FDA review a Type IV DMF for the formulation of flavoring agents, coloring agents, and/or imprinting inks that are referenced in an ANDA during the filing review?

[21] Type II API DMFs for which applicable fees have been paid and that have been found complete are listed on an Available for Reference list on FDA's Web site available at: http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf. FDA encourages applicants to consult the Available for Reference list to confirm that FDA has determined that a Type II API DMF is available for reference.

[22] Available for reference indicates that the DMF fee has been paid within the required payment period and the DMF has not failed an initial completeness assessment. See sections 744B(a)(2)(D) and 744B(g)(2) of the FD&C Act.

FDA will review a Type IV DMF for flavoring and coloring agents and imprinting inks that are referenced in an ANDA to determine if the formulation or information on the formulation is readily available therein. Information will be considered readily available if the Right of Reference letter clearly indicates the exact location of the relevant information within the DMF, including 1) the page number and the date of submission to the DMF if such DMF is a paper or a hybrid submission or 2) the eCTD sequence number and submission date if such DMF number is fully electronic (i.e., electronically submitted in eCTD format). If any of the information identified in numbers 1 or 2 above is missing from the Right of Reference letter, FDA will contact the applicant to request submission of a revised Right of Reference letter that includes the missing information. The applicant may have the supplier or DMF holder submit the information directly to FDA. If the requested information is not provided within seven calendar days from notification, FDA will RTR the ANDA.

Q17: Will FDA review a Type IV DMF for an excipient to determine whether it contains pharmacology/toxicology (pharm/tox) data to support its use in a proposed drug product?

FDA will review a Type IV DMF for an excipient to determine whether it contains pharm/tox data to support its use in a proposed drug product, provided the pharm/tox data is readily available therein. Information will be considered readily available if the Right of Reference letter clearly indicates the exact location of the relevant information within the DMF, including 1) the page number and the date of submission to the DMF if such DMF is a paper or a hybrid submission or 2) the eCTD sequence number and submission date if such DMF number is fully electronic (i.e., electronically submitted in eCTD format). If any of the information identified in numbers 1 or 2 above is missing from the Right of Reference letter, FDA will contact the applicant to request submission of a revised Right of Reference letter that includes the missing information. Alternately, the applicant may have the supplier or DMF holder submit the information directly to FDA. If the requested information is not provided within seven calendar days from notification, FDA will RTR the ANDA.

E. Product Quality Deficiencies

1. Stability Data

Q18: Will FDA RTR an ANDA that fails to use two API lots to manufacture three batches of each strength of a proposed product?

Yes, FDA will consider an applicant's failure to use two API lots to manufacture three batches of each strength of a proposed product a major deficiency.

Q19: Will FDA RTR an ANDA if the applicant fails to provide certain stability study information to support worst-case orientation?

FDA will RTR the ANDA if the applicant fails to provide the recommended stability study information. An applicant should provide three pilot-scale batches or two pilot-scale and one small-scale batch with both accelerated and long-term data provided for each batch covering a period of no less than six months (i.e., 180 days), in all cases, in the upright orientation and, for liquids, solutions, semi-solids, and suspensions in the worst-case orientation as well. For each of these batches, the applicant should provide three time points (e.g., 0, 3, and 6 months) that cover the recommended hold time (i.e., 6 months) for the data for both worst-case and non-worst-case orientations.

If an ANDA contains stability data for studies conducted under intermediate conditions, the applicant should provide the full complement (i.e., 6 months' worth) of failed accelerated data at three time points (e.g., 0, 3, and 6 months) and repeat the intermediate stability study for each of the three batches of the strength for whichever batch failed, including intermediate data in both the worst-case and upright orientations.[23] The recommendation for the submission of intermediate data for all three batches if an applicant's accelerated data show a significant change or failure of any attribute in one or more batches also applies to drug products for which orientation is not a consideration and that do not require worst-case orientation data.[24]

2. Packaging Configurations

Q20: Will FDA RTR an ANDA if the proposed packaging is inconsistent with the condition(s) of use approved for the reference listed drug (RLD)?

Yes, FDA will RTR an ANDA if the proposed packaging is inconsistent with the condition(s) of use approved for the RLD. For example, if the RLD is approved for a 14-day course of treatment, repeated at a specific interval, and is marketed in 14-count packages, the ANDA should propose marketing containers that are consistent with the approved condition(s) of use.

3. Batch Records

Q21: The guidance for industry *ANDA Submissions - Refuse to Receive Standards* states that FDA will RTR an ANDA if batch records are not provided. Should an applicant submit commercial (i.e., blank) batch records if no scale-up is proposed?

An applicant should submit the commercial (i.e., blank) batch records, even if the applicant does not propose scale-up for the commercial batches. The submission of the commercial batch records is in addition to the executed batch records submitted pursuant to 21 CFR 314.50(d)(1)(ii)(*b*).

Q22: Will FDA RTR an ANDA that references batch records previously submitted by an applicant in another ANDA?

[23] See guidances for industry, *ANDA Submissions – Refuse to Receive Standards*, *ANDAs: Stability Testing of Drug Substances and Products*, and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers.*

[24] See guidance for industry *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers*.

Yes, FDA will RTR an ANDA that references batch records previously submitted by an applicant in another ANDA. When an applicant submits individual ANDAs for drug products containing the same active ingredient, each ANDA should have its own independent basis for approval.[25]

4. Over-the-Counter Drug Products

Q23: Will FDA RTR an ANDA for an over-the-counter (OTC) two-piece, hard gelatin capsule product that does not contain information indicating that it is sealed using an acceptable tamper-evident technology in conformance with tamper-evident packaging requirements?

Yes, FDA will RTR an ANDA for an OTC two-piece hard gelatin capsule product that is not sealed using an acceptable tamper-evident technology because that product fails to conform to the tamper-evident packaging requirements for OTC products in 21 CFR 211.132. The regulations require, for products covered by 21 CFR 211.132, that an OTC two-piece hard gelatin capsule product for retail sale be sealed using an acceptable tamper-evident technology.

Q24: Will FDA RTR an ANDA for a partial Rx-to-OTC switch that references data in the applicant's approved ANDA for the prescription drug product?

In general, an applicant submitting an ANDA for an Rx-to-OTC switch where fewer than all conditions of use were switched to OTC status ("partial Rx-to-OTC switch") may reference data on the proposed product from an approved ANDA or ANDA that has been received for the prescription drug product that the ANDA applicant also owns instead of conducting new in vivo and in vitro studies to establish BE to the RLD for the OTC product. However, each Rx-to-OTC switch is unique and the requirements for ANDA applicants are based on the characteristics of the OTC RLD including formulation, packaging, conditions of use, among others, and any other requirements specific to OTC products. For example, if the OTC RLD has a different formulation from the Rx RLD, the ANDA applicant will likely need to produce new batches and new BE data. Certain changes in packaging may also result in ANDA applicants needing to produce new batches, with this packaging change also potentially requiring additional data to support BE. An applicant that is referencing an approved ANDA should provide BE summary tables in Module 2.7 in the proposed ANDA.

In order to avoid an RTR determination, an applicant may submit a controlled correspondence regarding the ability to reference an existing ANDA in a new ANDA for a partial Rx-to-OTC switch.

5. Inactive Ingredients[26]

[25] 21 CFR 314.101(d)(3).

[26] OGD's Division of Filing Review (DFR) reviews the list of inactive ingredients and determines whether the inactive ingredients were identified in the Inactive Ingredient Database (IID) and justified for the proposed use

Q25: If an application references a general listing from the Inactive Ingredient Database (IID) and does not include a justification for the grade of excipient, will FDA identify the lack of justification as a deficiency at filing?

FDA will RTR an ANDA that lacks a justification in its original ANDA submission for the grade of an inactive ingredient when referencing a nonspecific or different grade of an inactive ingredient that is available in various grades.[27] An ANDA that references a general IID listing or an IID listing for a different grade of an inactive ingredient but fails to provide any justification for the specific grade is not a substantially complete application because FDA has no basis on which to review the safety of the specific grade of the inactive ingredient in the proposed drug product.

An applicant using a specific grade of an inactive ingredient should justify the use of that grade, and may not cite to a different grade or a nonspecific listing as support for the safety of the inactive ingredient in the proposed drug product without providing additional justification. Grades of an inactive ingredient may differ in chemical or physical properties and may affect the safety profile of a drug product. Some inactive ingredients have grades or variations that may not have undergone a full safety evaluation in a previously approved product. Some variations may rely, in part, on a finding of safety for an approved drug product that contains a similar grade of the inactive ingredient. The applicant's justification should identify the differences between the grades of the inactive ingredient and address any implication of the change in grade on the safety of the proposed drug product using a data-driven approach. Whether the safety of a proposed grade of the inactive ingredient, in the context of the currently proposed drug product, is supported by a different grade of the inactive ingredient included in a previously approved drug product will be evaluated during the technical review of the ANDA.

An applicant may submit a controlled correspondence during product development regarding the specific grade of an inactive ingredient that the applicant proposes to use in the proposed drug product and reference the correspondence in the ANDA.

Q26: Will FDA RTR an ANDA that fails to provide an IID reference for an inactive ingredient for the particular route of administration for the proposed drug product or that provides an IID reference for the inactive ingredient for a different route of administration than the route of administration for the proposed drug product?

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based on the IID. Accordingly, FDA will RTR an ANDA if the proposed limits for a particular inactive ingredient exceed those identified in the IID without justification supporting this higher level. Also, for an IID listing that differs from the proposed inactive ingredient in nomenclature, molecular weight, viscosity, grade, etc., applicants should provide justification for citing the IID listing as the basis for its proposed level of use. Absent such justification, DFR will RTR an ANDA for a proposed product that contains the new inactive ingredient.

[27] For some inactive ingredients available in various grades, the IID may contain a listing for the inactive ingredient with grade unspecified (i.e., the IID listing is nonspecific).

FDA will generally consider an applicant's failure to provide an IID reference for an inactive ingredient for the particular route of administration for the proposed drug product or an applicant's provision of an IID reference for an inactive ingredient for a different route of administration than the route of administration for the proposed drug product (e.g., referencing an IID listing for an inactive ingredient for an oral route of administration for a sublingual or buccal tablet) as a minor deficiency, provided FDA is able to validate the level of use.[28] If FDA cannot validate the level of use and the applicant has not provided justification for its level of use within the original ANDA submission, then FDA will RTR the ANDA.

Generic drug products should use inactive ingredients that have previously been included in an FDA-approved product at or below the proposed maximum daily exposure, in a similar clinical context, and by the same route of administration. Applicants should consider the safety of inactive ingredients in their generic drug product. A justification may include supportive information from the IID, a controlled correspondence response from OGD, published literature, evidence of safe use in FDA-approved drug products with a similar context of use, or other relevant and science-based safety information. If a justification cites published literature, the applicant should submit a copy of the publication(s) in its ANDA.

If an inactive ingredient is unqualified for the corresponding route of administration of the proposed drug product (unless it is a physical mixture of components that are not novel), FDA will RTR the ANDA because there is no prior evidence of safe use in an FDA-approved drug product. An inactive ingredient without prior evidence of safe use in an FDA-approved drug product is considered novel. Use of a novel excipient generally will require submission of a new drug application (NDA) under section 505(b) of the FD&C Act.

6. Impurity Data

Q27: The guidance for industry *ANDA Submissions – Refuse to Receive for Lack of Justification of Impurity Limits* indicates that FDA will RTR an ANDA that fails to provide justification for certain impurities above specified thresholds. How does FDA review ANDAs at filing to determine if sufficient justification is provided in the application?

During the filing review, FDA will determine if the ANDA: 1) proposes limits in drug substances and drug products for specified identified impurities that are above qualification thresholds; (2) proposes limits for specified unidentified impurities that are above identification thresholds; and/or (3) proposes limits for unspecified impurities (e.g., any unknown impurity) that are above identification thresholds. If any of these factors are met, FDA will review the ANDA to determine if the applicant has provided a justification for these proposals.

[28] Level of use is used in this guidance to describe the amount per dosage unit as represented in the IID.

If the ANDA does contain a justification, the application will be received, assuming there are no deficiencies leading to an RTR determination. The sufficiency of the justification will be reviewed during the technical review of the ANDA. If the ANDA does not contain a justification for the proposed limits, FDA will RTR the application.

7. Dissolution Testing

Q28: What is the proper location for comparative (test product and RLD) half-tablet dissolution data?

FDA recommended half-tablet dissolution test data should be contained in Module 2.7 of the ANDA. The failure to perform the recommended half-tablet dissolution studies (i.e., test product and RLD) or the failure to correctly place such dissolution data in Module 2.7 is considered a major deficiency.

8. Scoring and Conditions of Use

Q29: Will FDA RTR an ANDA containing a statement that the score mark is non-functional?

The scoring configuration of a generic drug product generally should be the same as the RLD to demonstrate that the test product can be administered in a manner consistent with the dosing recommendations of the RLD. An applicant should include a comparison of the test product to the RLD for any proposed scoring configuration of the generic drug product. FDA will RTR an ANDA that contains as justification an applicant's statements that the score mark is non-functional when the RLD labeling contains dosing recommendations consistent with the dose delivery enabled by the score mark.

F. BE and Clinical Deficiencies

Q30: Will FDA RTR an ANDA if the ANDA deviates from the recommendations identified in a product-specific guidance (or BE guidance)?

As a general matter, ANDA applicants should consult the BE recommendations for specific products on FDA's Web page for product-specific recommendations on conducting recommended in vivo and/or in vitro studies for generic drug development[29]. FDA will RTR an ANDA that deviates from any study or standard described or recommended in a product-specific recommendation without providing justification (i.e., a demonstration that the alternate approach proposed by the applicant meets applicable statutory and regulatory requirements) for the deviation. For example, if an applicant does not perform dissolution testing in all types of media as recommended in the product-specific recommendation, the applicant should provide a justification for its testing methods to avoid a major deficiency determination. In general, dissolution test methods for particular products are provided in FDA's product-specific BE recommendations.

[29] Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Q31: Will FDA RTR an ANDA if the ANDA does not contain the data sets as recommended or does not otherwise follow recommendations identified in a product-specific recommendation?

FDA considers an applicant's failure to provide data sets (as distinguished from stability studies) or definition files (e.g., type of data recommended, format, and file structure) as recommended in product-specific recommendations to be a minor deficiency.

Certain product-specific recommendations suggest additional information or data to support the studies recommended therein (e.g., testing the minimum amount of antimicrobial activity against a microorganism, providing adequate measurements at time points identified in the guidance). Failure to submit this additional information to support the recommended studies would be considered a major deficiency in the absence of a justification (i.e., a demonstration that the alternate approach proposed by the applicant meets applicable statutory and regulatory requirements).

As noted in the product-specific recommendations, applicants can use an alternate approach if it satisfies the requirements of the applicable statutes and regulations. Applicants who wish to discuss an alternate approach are encouraged to contact OGD by submitting a controlled correspondence. The ANDA submission should indicate if the applicant is proposing to use an alternate approach to certain product-specific recommendations and identify any discussions with OGD, if applicable, related to the proposed alternate approach. The justification for the proposed alternate approach should be provided in Module 2.7 of the ANDA.

Q32: Where should an applicant place long-term storage stability (LTSS) data? Will failure to provide this information cause FDA to RTR an ANDA?

An applicant should provide LTSS coverage and data location in Bioequivalence Summary Table 10. As indicated in the table, the applicant should specify the exact location of the LTSS study reports and data in Module 5.3.1.4. The applicant should state the Module, Section, Subsection, and pages. We recommend that the applicant also include a hyperlink in addition to the exact location.

FDA will generally classify an applicant's failure to provide LTSS data in Summary Table 10 as a minor deficiency, provided the applicant has provided LTSS data in Module 5.3.1.4. If the applicant fails to provide the LTSS data in Module 5.3.1.4, but provides the LTSS data in Summary Table 10, this omission will be considered a minor deficiency. However, if an applicant fails to include the LTSS data in Summary Table 10 and fails to provide supporting data in Module 5.3.1.4, FDA will RTR the ANDA.

Q33: Will FDA RTR an ANDA that makes reference to BE data previously submitted by that applicant in another ANDA?

An applicant may reference BE data submitted in another ANDA, as long as the ANDA being referenced has been received for review. FDA recommends that an ANDA

referencing an ANDA that has been received provide, at minimum, the BE summary tables.

Q34: Should an applicant provide summary tables in an ANDA for other studies?

Depending on the type of study conducted, the applicant should provide appropriate summary tables for each applicable study within their submission. To facilitate submission of this data, FDA has developed summary table templates to be utilized by applicants and FDA has posted these tables to FDA's Web page.[30] Generally, failure to provide the data in a summary table would be considered a minor deficiency. However, if an applicant fails to provide the tables in Module 2 and the underlying data in Module 5, this omission is considered a failure to submit a passing study and would result in an RTR determination.

Q35: How should the study reports be submitted in Module 5 to ensure that an ANDA contains information to support an in vivo BE or clinical endpoint BE study, or statistical data and/or design? Would the omission of these reports be considered a major or minor deficiency?

Clinical study reports should be provided as more than one document pursuant to the International Conference on Harmonization guideline for industry *E3: Structure and Content of Clinical Study Reports*. Omission of any of these reports would be considered a minor deficiency. The individual documents that should be included in a study report are listed below:

- Synopsis 10 (E3 2)
- Study report (E3 1, 3 to 15)
- Protocol and amendments (E3 16.1.1)
- Sample case report forms (E3 16.1.2)
- List of IECs or IRBs (E3 16.1.3) and consent forms
- List and description of investigators (E3 16.1.4) and sites
- Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer (E3 16.1.5)
- Listing of patients receiving test drug(s) from specified batch (E3 16.1.6)
- Randomization scheme (E3 16.1.7)
- Audit certificates (E3 16.1.8) and reports
- Documentation of statistical methods (E3 16.1.9) and interim analysis plans
- Documentation of interlaboratory standardization methods of quality assurance procedures if used (E3 16.1.10)
- Publications based on the study (E3 16.1.11)
- Important publications referenced in the report (E3 16.1.12)
- Discontinued patients (E3 16.2.1)

[30] See Abbreviated New Drug Application (ANDA) Forms and Submission Requirements page available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm.

- Protocol deviations (E3 16.2.2)
- Patients excluded from the efficacy studies (E3 16.2.3)
- Demographic data (E3 16.2.4)
- Compliance and/or drug concentration data (E3 16.2.5)
- Individual efficacy response data (E3 16.2.6)
- Adverse event listings (E3 16.2.7)
- Listing of individual laboratory measurements by patient (E3 16.2.8)
- Case report forms (E3 16.3)
- Individual patient data listings (Case Report Tabulations) (E3 16.4)
    - Data tabulations
        - Data tabulations datasets
        - Data definitions
        - Annotated case report form
    - Data listing
        - Data listing datasets
        - Data definitions
        - Annotated case report form
    - Analysis datasets
        - Analysis datasets
        - Analysis programs
        - Data definitions
        - Annotated case report form
    - Subject profiles
    - IND safety reports