
ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry

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

**December 2016
Generics**

Revision 2

Contains Nonbinding Recommendations

ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov*

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**December 2016
Generics**

Revision 2

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	GENERAL POLICY	3
	A. Form FDA 356h (356h).....	4
	B. Submission, Format, and Organization	4
	C. Non-Payment of GDUFA Obligations.....	4
	D. Lack of a Designated U.S. Agent for a Foreign Applicant	5
	E. Citing a Pending Suitability Petition as a Basis of Submission.....	5
IV.	REVIEWS FOR API	6
	A. Starting Material.....	6
	B. Sterility Assurance Data.....	6
V.	PRODUCT QUALITY DEFICIENCIES	6
	A. Inactive Ingredients	6
	B. Inadequate Stability.....	9
	C. Packaging Amount Considerations	10
	D. Batch Records	10
	E. Method Validation/Verification Reports	10
	F. Special Consideration for Transdermal Patches.....	11
	G. Scoring and Conditions of Use.....	12
	H. Microbiology Considerations.....	13
VI.	BIOEQUIVALENCE AND CLINICAL DEFICIENCIES.....	14
	A. Failed In Vivo BE Studies	14
	B. Alternate BE Studies.....	14
	C. Q1/Q2 Sameness Requirement for Consideration of an In Vivo BE Study Waiver	15
	D. Inadequate Dissolution Data (In Vitro Studies).....	15
	E. Miscellaneous Factors.....	16
VII.	DISPUTE OF A REFUSE-TO-RECEIVE DECISION	17
	APPENDIX A: EXAMPLES OF MINOR DEFICIENCIES.....	1

ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry¹

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist applicants preparing to submit to FDA abbreviated new drug applications (ANDAs) and prior approval supplements (PASs) to ANDAs for which the applicant is seeking approval of a new strength of the drug product.² The guidance highlights deficiencies that may cause FDA to refuse to receive (RTR) an ANDA.³ An RTR decision indicates that FDA determined that an ANDA is not substantially complete.⁴ A substantially complete ANDA is “an ANDA that on its face is sufficiently complete to permit a substantive review.”⁵

This guidance is not meant to be a comprehensive list of the deficiencies that may or will lead to an RTR determination by FDA. Instead, this guidance identifies certain deficiencies and certain recurrent deficiencies that in FDA’s experience have led FDA to RTR an ANDA. This guidance also describes how FDA will assess deficiencies identified during FDA’s filing review to determine whether an ANDA should be received. We note that industry is aware of many of the standards described in this guidance because FDA has historically applied many of these standards in its RTR determinations.

FDA’s guidance documents, including this guidance, generally do not establish legally enforceable responsibilities. Instead, guidances describe FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

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

² For purposes of this guidance, the use of the term “ANDA” will mean ANDAs and new-strength PAS submissions.

³ An RTR determination should not be confused with a refuse-to-approve determination.

⁴ 21 CFR 314.101(b)(1).

⁵ 21 CFR 314.3(b).

Contains Nonbinding Recommendations

The use of the word “should” in Agency guidances means that something is suggested or recommended, but not required.⁶

II. BACKGROUND

Pursuant to the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA),⁷ 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...”⁸ 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.⁹ 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).¹⁰

Our regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in others, RTR an ANDA that does not satisfy the criteria for a threshold determination that the application is substantially complete.¹¹

⁶ At various points in this guidance, it is noted that when a particular type of deficiency in an ANDA is seen, FDA *will* RTR the ANDA. It is important to understand that these statements do not create legal obligations, on applicants or on FDA, but rather are included for purposes of transparency. This means that FDA, in the normal course, 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 in the normal course find the application not sufficiently complete to permit a substantive review and RTR it.

⁷ Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III).

⁸ See Generic Drug User Fee Act Program Performance Goals and Procedures: <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

⁹ See 21 CFR 314.101(b)(1) and 314.3(b).

¹⁰ 21 CFR 314.3(b).

¹¹ See 21 CFR 314.101(d)-(e).

Contains Nonbinding Recommendations

Between Fiscal Years (FY) 2013 to 2015, FDA refused to receive 379 ANDAs for reasons other than failure to pay a GDUFA fee. Of all original ANDA submissions, FDA refused to receive:

- 14% in FY 2013
- 10% in FY 2014
- 14% in FY 2015¹²

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 the same (Q1/Q2 same) as the reference listed drug (RLD); and failure to respond to information request within the prescribed timeframe). .

III. GENERAL POLICY

FDA considers the nature (e.g., major or minor) of the deficiencies, including the number of deficiencies in the ANDA, in determining whether an ANDA is incomplete on its face.¹³ During FDA's filing review of a submitted ANDA, FDA will determine if there are any major or minor deficiencies. Generally, a major deficiency is one that in FDA's judgment is significant in nature such as certain deficiencies found in 21 CFR 314.101(d) or 21 CFR 314.101(e);¹⁴ other major deficiencies are discussed in this and other guidances. Numerous minor deficiencies (discussed below) also constitute a major deficiency. A major deficiency will result in a determination by FDA that the ANDA is incomplete on its face under 21 CFR 314.101(d)(3), and FDA will therefore RTR an ANDA containing a major deficiency.

A minor deficiency is one that in FDA's judgment is minor in nature and can be easily remedied.¹⁵ As a result, FDA will allow the applicant a prescribed time period (described below in this section) to provide a response to such deficiencies. In particular, if FDA determines that an ANDA contains fewer than ten minor deficiencies (i.e., nine deficiencies or fewer), FDA will notify the applicant of the deficiencies, by phone, fax, or through the primary method for communication, which is email. FDA, in its discretion, provides applicants with the opportunity to correct minor deficiencies or amend the ANDA, within seven (7) calendar days.¹⁶ If within 7 calendar days the requested information is not received, FDA will RTR the ANDA. However, if

¹² See FY 2015 Performance Report to Congress for the Generic Drug User Fee Amendments, available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM493026.pdf>.

¹³ 21 CFR 314.101(d)(3).

¹⁴ Pursuant to 21 CFR 314.101(d), FDA "may" not consider an ANDA to be received if any of the deficiencies under that regulation applies. FDA will determine on a case-by-case basis whether a deficiency under certain provisions of § 314.101(d) is a major or minor deficiency, in accordance with the principles described in this guidance.

¹⁵ Though the focus of this guidance is to highlight major deficiencies, select minor deficiencies are listed in Appendix A — the list is not a comprehensive list of minor deficiencies.

¹⁶ The response period will begin the day after notification is provided. If the 7th calendar day falls on a Saturday, Sunday, or Federal holiday, the deadline for amending the ANDA to correct the deficiencies will be the next day that is not a Saturday, Sunday, or Federal holiday.

Contains Nonbinding Recommendations

FDA determines that an ANDA contains ten or more minor deficiencies or one or more major deficiencies, FDA will not consider the ANDA to be a substantially complete application under 21 CFR 314.101(b)(1). In such cases, FDA will notify the applicant that FDA considers the ANDA not to have been “received.” If the applicant decides to submit additional materials to correct the deficiencies, the resulting amended ANDA will be considered a new ANDA submission, received as of the date the amended ANDA is submitted (if deemed substantially complete), and the applicant will be required to pay a new ANDA fee. If an ANDA is not received and the applicant takes no action, FDA may consider the ANDA withdrawn after 1 year.¹⁷ An ANDA applicant’s failure to take action after a refuse-to-accept decision on an ANDA may be considered a request by the applicant to withdraw the ANDA, unless the applicant requests an extension of time in which to resubmit the ANDA.¹⁸ There may be circumstances, however, under which an exception to, or a waiver of, a regulatory requirement may be granted. FDA will consider the merits of such circumstances on a case-by-case basis.¹⁹

The following sections discuss deficiencies that FDA considers to be major deficiencies. A selection of minor deficiencies is provided in Appendix A.

A. Form FDA 356h (356h)

An ANDA must contain a completed application form (i.e., Form FDA 356h). If this form is not included, or is not signed, which indicates that the applicant is not attesting to the material contained in the application, FDA will RTR the ANDA.²⁰

B. Submission, Format, and Organization

The ANDA should be formatted according to the eCTD format, and it should be submitted electronically for GDUFA metric goals to apply to the ANDA.²¹ Under Section 745A(a) of the FD&C Act, electronic submissions of applications to FDA will be required at least 24 months after the issuance of the final guidance for industry, *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (the eCTD guidance), which published on May 5, 2015. Accordingly, the electronic submission of ANDAs in a format specified by FDA is required as of May 5, 2017.²²

C. Non-Payment of GDUFA Obligations

¹⁷ 21 CFR 314.101(b)(3)(iii).

¹⁸ *Abbreviated New Drug Applications and 505(b)(2) Applications*; Final Rule, 81 FR 69580, 69622 (October 6, 2016).

¹⁹ 21 CFR 314.99(b).

²⁰ 21 CFR 314.101(d)(1).

²² To ensure receipt of an electronic submission, please follow the current eCTD specifications as provided in FDA’s Data Standards Catalog available at <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls>.

²² To ensure receipt of an electronic submission, please follow the current eCTD specifications as provided in FDA’s Data Standards Catalog available at <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls>.

Contains Nonbinding Recommendations

FDA will RTR an ANDA in certain cases if there are outstanding user fee obligations²³:

- If an applicant fails to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application²⁴
- If an ANDA references a Type II active pharmaceutical ingredient (API) Drug Master File (DMF) that is not on the public *available for reference* list because of non-payment of the GDUFA DMF fee²⁵
- If an ANDA references a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)²⁶
- If the applicant is the owner of or is affiliated with the owner of a facility on the facility arrears list²⁷
- If the applicant is listed on the backlog arrears list²⁸
- If the applicant is affiliated with an applicant on the backlog arrears list.²⁹

In all of these cases, FDA will RTR an ANDA for nonpayment of GDUFA user fee obligations. Upon satisfaction of all applicable user fee obligations, CDER's Office of Management will issue a formal correspondence to the applicant indicating the adjusted receipt date (i.e., the date on which all outstanding user fee obligations were satisfied in full) for which the ANDA is eligible.

D. Lack of a Designated U.S. Agent for a Foreign Applicant

FDA will RTR an ANDA if a foreign applicant does not designate a U.S. agent. If the person signing the application form (i.e., Form FDA 356h) does not reside or have a place of business within the United States, the application form is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.³⁰

E. Citing a Pending Suitability Petition as a Basis of Submission

If an applicant submits a copy of, or refers to, a pending suitability petition, FDA will RTR the ANDA because it lacks a legal basis for the submission.³¹ An ANDA can rely on a suitability petition as a basis of submission only after the petition has been approved by FDA. ANDAs can be submitted for drug products that differ from the listed drug, provided that a suitability petition requesting a change is submitted pursuant to section 505(j)(2)(C) of the FD&C Act and in

²³ See [Generic Drug User Fee Amendments of 2012; Public Law 112-144, Title III](#). See also <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319567.htm> and the guidance for industry *Generic Drug User Fee Amendments of 2012: Questions and Answers Related to User Fee Assessments*.

²⁴ Section 744B(g)(3) of the FD&C Act.

²⁵ Section 744B(g)(2) of the FD&C Act.

²⁶ Section 744B(g)(4)(A)(ii) of the FD&C Act.

²⁷ Section 744B(g)(4)(A)(i) of the FD&C Act.

²⁸ Section 744B(g)(1) of the FD&C Act.

²⁹ *Id.*

³⁰ 21 CFR 314.94(a)(1) (incorporating by reference 21 CFR 314.50(a)(1), (3), (4), and (5)).

³¹ 21 CFR 314.101(d)(3).

Contains Nonbinding Recommendations

accordance with 21 CFR 314.93 and 10.30, **and** the suitability petition is approved by FDA. The changes (from the RLD) that can be requested in a suitability petition are:

- Change in route of administration
- Change in dosage form
- Change in strength
- One active ingredient is substituted for one of the active ingredients in a listed combination drug

An applicant who wishes to rely on an approved suitability petition as the basis of submission for an ANDA can do so by identifying the listed drug cited in the approved petition as the basis for the ANDA, subject to the limitation described in 21 CFR 314.93(f)(2).³² In addition, the docket number and a copy of FDA's correspondence approving the petition must be included in the ANDA submission.³³

IV. REVIEWS FOR API

A. Starting Material

FDA will RTR an ANDA if the active pharmaceutical ingredient (API) review, whether in an ANDA or in a referenced drug master file (DMF), reveals that the starting material for the API is not justified according to the principles in the ICH Q11 guidance.^{34,35}

B. Sterility Assurance Data

FDA will RTR an ANDA if the API review, whether in an ANDA or a referenced DMF, reveals that sterility assurance data are missing for a sterile API.³⁶

V. PRODUCT QUALITY DEFICIENCIES

A. Inactive Ingredients³⁷

1. Inactive Ingredients Exceeding the Inactive Ingredient Database Limit

FDA will RTR an ANDA if the submission proposes to use an inactive ingredient at a level that exceeds any of the inactive ingredient database (IID) listings without the justification described

³² 21 CFR 314.94(a)(3)(i).

³³ 21 CFR 314.94(a)(3)(iii).

³⁴ See International Conference on Harmonisation (ICH) (2012), *Q11 Development and Manufacture of Drug Substances* (Chemical Entities and Biotechnological/Biological Entities).

³⁵ 21 CFR 314.50(d)(1)(i).

³⁶ 21 CFR 314.50(d)(1)(i) and 21 CFR 314.50(d)(1)(ii).

³⁷ In general, although considered supportive, GRAS certification, FEMA certification, DMF authorization, or composition are not considered sufficient justification to support safety of an inactive ingredient or level at which it is used in the drug product.

Contains Nonbinding Recommendations

below.^{38,39} Applicants can justify inactive ingredient levels by reference to the IID, which is a listing of inactive ingredients and their maximum levels of use (per dosage unit or percent composition), arranged by either route of administration or dosage form.⁴⁰ An inactive ingredient is considered justified, for receipt purposes, if the proposed level is at or below the amount indicated in the IID for the corresponding route of administration of the drug product. If an applicant wishes to use an inactive ingredient at a level per unit that is higher than what is proposed in the IID, options are available to facilitate receipt of the ANDA:

- Submit complete pharmacology/toxicology information.

In the draft guidance, FDA described the type of pharmacology/toxicology information that should be submitted for ANDA submissions that propose to use an inactive ingredient at a level that exceeds any of the IID listings to avoid FDA refusing-to-accept the ANDA. After additional consideration, FDA believes that this issue bears further evaluation, and the Agency is not prepared to offer its current thinking on this subject at this time. The Agency anticipates addressing this issue in a separate guidance.

- Cite a specific example of a CDER-approved drug product.

Applicants should cite a specific example of a CDER-approved drug product that contains the inactive ingredient at or above the proposed level of use⁴¹ for the appropriate route of administration.

- Refer to an FDA controlled correspondence response.

Applicants should refer to a controlled correspondence in which FDA issued a response indicating that the proposed level of use is acceptable for receipt purposes.⁴² Applicants should calculate the maximum daily intake (MDI) for the inactive ingredient and provide the name of the RLD, if applicable. No more than three inactive ingredient queries should be submitted per controlled correspondence.

Inactive ingredient justification for oral liquid drug products should not be based on a listed percentage in the IID. This is because the components of liquid dosage forms are generally expressed in terms of milligrams per milliliter (% w/v), and as a result, the amount of inactive ingredient delivered per dose cannot be properly ascertained by simply comparing the % w/v composition of a particular inactive ingredient to a threshold percentage in the IID. Instead, the

³⁸ If the inactive ingredient is determined to be a novel inactive ingredient for the corresponding route of administration of the drug product (unless it is a physical mixture of components found in the IID and within acceptable IID maximum levels), FDA will RTR the ANDA. Use of a novel inactive ingredient will generally require submission as a 505(b)(2) application.

³⁹ 21 CFR 314.94(a)(9)(ii).

⁴⁰ See <http://www.accessdata.fda.gov/scripts/cder/jig/index.cfm>.

⁴¹ That is, amount per dosage unit or maximum daily intake (MDI) that is based on the calculated maximum daily dose (MDD) of the active ingredient in the drug product.

⁴² Controlled correspondences are submitted via e-mail through GenericDrugs@fda.hhs.gov. See <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120610.htm> for more information.

Contains Nonbinding Recommendations

applicant should calculate the amount of inactive ingredient that is delivered per dose or per day (MDI) based on dosing recommendations indicated in the RLD label. In addition, the applicant should justify the calculated amount based on an amount-per-unit IID listing that corresponds to an oral dosage form (e.g., solid oral dosage form). Alternatively, for the ANDA to be considered for receipt, one of the previously discussed options in this section can be used.

Inactive ingredients that are included in powders for oral suspension should be justified as described in the preceding paragraph, with calculations of amounts delivered per dose based on the dry powder composition (i.e., prior to reconstitution).

When justifying inactive ingredients for semi-solid and topical dosage forms, applicants can refer to listed percentages in the IID. However, the percent concentration of each inactive ingredient should be converted into an amount expressed in one of the following forms: mg/mL, mg/g, mL/mL, etc.

2. Changes to Non-Exception Inactive Ingredients in Parenteral, Ophthalmic, and Otic Products

FDA will RTR an ANDA if certain concerns with respect to non-exception inactive ingredients are not addressed in the ANDA.⁴³

Parenteral drug products generally must contain the same inactive ingredients and in the same concentration as the RLD.⁴⁴ However, specific changes (from the RLD drug product) are permitted for certain inactive ingredients (i.e., preservatives, buffers, and antioxidants), which are considered exception inactive ingredients. Applicants should identify and characterize the differences and should submit information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.⁴⁵ This justification is a critical aspect of the exception inactive ingredient allowance and should be provided in the ANDA to support the proposed exception inactive ingredient change.

For all other inactive ingredients, an ANDA whose subject is a parenteral drug product must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD, with certain allowable differences permitted under 21 CFR 314.94(a)(9)(iii).⁴⁶ Before submitting an ANDA, the applicant can submit a controlled correspondence to request a Q1/Q2 evaluation of proposed formulations to minimize the risk of FDA refusing-to-accept the ANDA.⁴⁷ Even if an inactive ingredient is determined to be quantitatively the same as the RLD, the proposed concentration should be justified with reference to the IID in the event that it falls within the upper limit of the Q1/Q2 threshold. In other words, if an inactive ingredient is demonstrated to be quantitatively

⁴³ 21 CFR 314.94(a)(9)(ii).

⁴⁴ 21 CFR 314.94(a)(9)(iii).

⁴⁵ Id.

⁴⁶ Id. (Also, quantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration. That is, sameness as discussed herein does not suggest an exact value, but rather a range of values).

⁴⁷ As with other inactive ingredient queries, FDA requests that the applicant submit no more than three proposed formulations for evaluation per controlled correspondence. See, guidance for industry *Controlled Correspondence Related to Generic Drug Development*.

Contains Nonbinding Recommendations

the same as the RLD (*same* implies $\geq 95\%$ but $\leq 105\%$ of the RLD concentration or amount) yet exceeds the IID limit for the applicable route of administration, FDA will RTR the ANDA.⁴⁸

An ANDA concerning an ophthalmic drug product should be Q1/Q2 the same as the RLD with respect to all of its components, or include data from appropriate BE studies.⁴⁹ Despite a similar allowance (to parenteral products) provided for ophthalmic drug products in 21 CFR 314.94(a)(9)(iv), FDA has determined that, as a scientific matter, any qualitative or quantitative deviations from the RLD should be accompanied by an appropriate in vivo BE study or studies.

For otic drug products, differences with respect to the types of inactive ingredients listed in 21 CFR 314.94(a)(9)(iv) are permitted, provided that these differences are identified and characterized and information is submitted demonstrating that these differences do not affect the safety or efficacy of the proposed drug product.

B. Inadequate Stability

1. Number of Batches and Length of Studies

FDA will RTR an ANDA if certain batch size and study recommendations are not satisfied.^{50,51} The 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 6 months (180 days), with data from three time points (e.g., 0, 3, and 6 months).⁵² However, if 6 months of accelerated data show a significant change⁵³ or failure of any attribute in one or more batches, the applicant should also include 6 months of intermediate⁵⁴ stability studies at the time of submission.

The initiation date for each of the stability studies, along with individual pull dates (removal from the storage chamber) for each stability time point should also be provided as part of the data to verify that each study covers the recommended 6-month (180 days) minimum hold time.

⁴⁸ The assumption should not be made that any listed IID concentration incorporates the 105% Q1/Q2 allowance.

⁴⁹ See 21 CFR 320.22(b)(1). An applicant proposing to submit an ANDA for a non-Q1/Q2 same ophthalmic drug product is strongly urged to contact the Division of Bioequivalence for guidance prior to submitting an application.

⁵⁰ ANDAs submitted and date-stamped by the Agency prior to June 20, 2014 (the date of implementation of FDA stability guidance), will be evaluated for filing review purposes using ANDA stability recommendations in place prior to June 20, 2014.

⁵¹ 21 CFR 314.50(d)(1)(i) and 21 CFR 314.50(d)(1)(ii).

⁵² Guidance for industry ANDAs: *Stability Testing of Drug Substances and Products*. See also FDA's guidance for industry ANDAs: *Stability Testing of Drug Substances and Products, Questions and Answers*.

⁵³ The ICH guidance for industry entitled *Q1A(R2) Stability Testing of New Drug Substances and Products* defines "significant change" as one or more of the following (as appropriate for the dosage form): (1) a 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures; (2) a degradation product's exceeding its acceptance criterion; (3) failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, harness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; (4) failure to meet acceptance criterion for pH; and (5) failure to meet the acceptance criteria for dissolution for 12 dosage units.

⁵⁴ Intermediate storage condition testing does not apply to drug products intended for storage in a refrigerator.

Contains Nonbinding Recommendations

2. Container Orientation

FDA will RTR an ANDA if both worst-case scenario and non-worst-case stability data adhering to the recommendations described in section V.B.1 and this section are not submitted for the described drug product batches: liquids, solutions, semi-solids, and suspensions.⁵⁵

C. Packaging Amount Considerations

FDA will RTR an ANDA if the ANDA does not package a minimum (threshold) amount of the finished drug product in the container/closure systems that are proposed for marketing, as discussed in FDA's guidance for industry *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers*.⁵⁶ Also as discussed in the guidance, the threshold amount that should be packaged is governed by the specific dosage form (e.g., solid oral dosage forms, oral powders/solutions/suspensions, parenteral drug products, ophthalmic/otic drug products, transdermal patches, and topicals such as creams/lotions/gels and inhalation solutions/nasal sprays) of the finished drug product that is the subject of the ANDA submission.

To qualify the dosage units that are packaged toward the applicable threshold, the following three recommended criteria for each container/closure configuration should be satisfied:

- Stability data (as described in section V.B.1 of this guidance).
- Container/closure system information should be submitted in ANDA section 3.2.P.7. If bracketing or matrixing is used, an ANDA should include the container/closure system information applicable to configurations that were excluded from stability studies because of bracketing or matrixing.
- Container and carton (if applicable) labeling for each packaging configuration containing dosage units to be counted in the overall packaged total should be provided in section 1.14.1 of the ANDA.

D. Batch Records

FDA will RTR an ANDA if blank and executed batch records are not provided, regardless of whether commercial scale-up is proposed.⁵⁷ For example, both commercial (blank) and executed (pilot) batch records for the pilot batches that are manufactured to support an ANDA should be submitted, along with any accompanying reconciliation sheets.

E. Method Validation/Verification Reports

⁵⁵ See 21 CFR 314.94(a)(9)(i) stating that ANDAs must include chemistry, manufacturing, and controls information required under 21 CFR 314.50(d)(1).

⁵⁶ 21 CFR 314.50(d)(1)(ii).

⁵⁷ 21 CFR 314.50(d)(1)(ii)(b).

Contains Nonbinding Recommendations

FDA will RTR an ANDA if method validation/verification reports are not provided.⁵⁸ It is critical that method validation/verification reports for all analytical methods be provided in sections 3.2.S.4.3 and 3.2.P.5.3 of the ANDA, for both the drug substance (API) and drug product, respectively. That is, for drug products for which a relevant official United States Pharmacopeia (USP) drug product monograph exists, verification⁵⁹ of the USP analytical procedures should be provided. Verification should also be submitted for methods used from outside sources, such as a Type II API DMF holder, unless the methods have been fully validated in house. For any in-house methods used, validation of the analytical procedure should be submitted in either of the appropriate sections of the ANDA (i.e., sections 3.2.S.4.3 or 3.2.P.5.3). In-house methods used in lieu of USP methods should be compared to the USP method to support a demonstration that the in-house method is sufficient.

In addition, for ANDAs not submitted electronically⁶⁰, the applicant should submit three copies of the method validation/verification package for the API, the drug product, or both.⁶¹

F. Special Consideration for Transdermal Patches

FDA will RTR an ANDA for a transdermal patch if the ANDA does not address certain special considerations.^{62,63}

- **Matrix Systems**

ANDAs for matrix transdermal systems should be supported by stability data on three batches of drug product manufactured from three distinct laminates, where each batch of laminate is made using different lots of API, adhesives, backing, and/or other critical elements in the drug product. If an applicant is seeking approval for multiple strengths of a particular drug product, the applicant can choose to use a bracket approach by manufacturing three batches of the highest and lowest strengths and at least one batch of each of the bracketed strengths. An example is given below.

- Laminate Batch # 1 (pilot-scale): All strengths (highest, lowest, and bracketed)
- Laminate Batch # 2 (pilot-scale): Highest and lowest strengths
- Laminate Batch # 3 (pilot- or small-scale): Highest and lowest strengths

- **Reservoir Systems**

⁵⁸ 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

⁵⁹ EP (European Pharmacopoeia)/BP (British Pharmacopoeia)/JP (Japanese Pharmacopoeia) methods may be allowed, for which, in many cases, verification (versus full validation) may suffice.

⁶⁰ On May 5, 2017, the electronic submission of ANDAs in a format specified by FDA will be required. See discussion in section III.B.

⁶¹ 21 CFR 314.50(e)(2)(i).

⁶² 21 CFR 314.50(d)(1).

⁶³ In addition to the considerations identified in this section, FDA has provided recommendations on the submission of studies evaluating the adhesive performance of a Transdermal Delivery System (TDS) or topical patch in support of an ANDA in the guidance for industry Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs. The recommendations provided in the guidance will supersede the recommendations related to adhesion studies provided in individual product-specific recommendations published before the guidance was issued. Accordingly, FDA will RTR an ANDA for failure to follow the recommendations in the guidance once the final guidance is issued.

Contains Nonbinding Recommendations

Applicants are strongly encouraged to consult the Office of Lifecycle Drug Products, within the Office of Pharmaceutical Quality before making a decision to develop a reservoir transdermal system product. ANDAs for reservoir transdermal systems should be supported by stability data on three batches of drug product manufactured from three distinct reservoir gels. Each batch of drug product should use different lots of API, adhesives, gel excipients, backing membrane, rate controlling membrane, and/or other critical elements in the drug product. If multiple strengths of a reservoir transdermal system are prepared from reservoir gels containing different concentrations of API, three batches of each strength should be manufactured. A bracket approach is usually not acceptable.

G. Scoring and Conditions of Use

1. Functional Scoring Configurations That Are Inconsistent With the RLD

FDA will RTR an ANDA if there are inconsistencies in the scoring configuration between the RLD and the test product and those inconsistencies have not been reviewed and approved by FDA before submission of the ANDA. Scoring configurations often facilitate dose titration and other patient-specific regimens that would be imprecise because of the difficulty of splitting an unscored tablet (for more information, see FDA's guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (Tablet Scoring guidance)). FDA's Tablet Scoring guidance recommends that the "scoring configuration of generic drug products should be the same as the RLD" and so demonstrate that the test product can be administered in a manner consistent with the dosing recommendations of the RLD.

Inconsistencies in scoring configuration between the RLD and the test product may not facilitate this demonstration. For example, if an RLD 10 mg tablet is scored to enable administration of a 5 mg dose (and a 5 mg dose is supported by the label) and the test product is unscored and does not offer a 5 mg strength, an ANDA applicant will be unable to demonstrate that the test product can be administered in a manner consistent with the dosing recommendations of the RLD.

Conversely, if the ANDA product (e.g., 10 mg) is manufactured with a score mark and the RLD 10 mg tablet is unscored and the label indicates no recommended dose lower than 10 mg, the test product offers the potential for delivering a dose (5 mg) that is not reflected in the label, which would be considered a new dosing regimen. As a result, an ANDA applicant will be unable to demonstrate that the test product would be administered *only* in a manner consistent with the dosing recommendations of the RLD.

2. Fill Volumes for Parenteral Drug Products That Differ From the RLD

FDA will RTR an ANDA whose subject is a parenteral drug product if its fill volume deviates from the RLD drug product and the deviation is not permitted.^{64,65} ANDA parenteral (injectable) drug products should contain the same concentration and total drug content per

⁶⁴ That is, alterations beyond overfill allowances that are within USP recommendations in a relevant drug product monograph.

⁶⁵ See generally 21 CFR 314.50(d)(1).

Contains Nonbinding Recommendations

container as the RLD. Therefore, a deviation from the fill volume (total drug content) of the RLD parenteral drug product may constitute a change in strength. A change in strength must first be approved via the suitability petition process (see section III.F of this guidance) before it can be proposed in an ANDA submission.

3. Differences in Packaging and/or Labeling That May Be Associated With the Safe/Effective Use of the Drug Product

FDA will RTR an ANDA on a case-by-case basis if the ANDA contains differences in packaging and/or labeling from the RLD that may be associated with safe/effective use of the drug product.⁶⁶ Generally, if the RLD is packaged with certain labeling in a manner to ensure its proper administration, the test product should be packaged and labeled similarly. For example, an RLD product may incorporate labeling on its packaging that contains a combination of visual and/or typographical aids, beyond the direct label text, to facilitate patient compliance and safety. Blister packaging is an example of such packaging, whereby certain drug products communicate crucial patient information directly on the blister carton (and/or the blister itself) to both improve patient compliance and reduce the incidence of harm or injury that may result from improper administration of the drug product. A blister carton may also better allow any supplemental patient information to be attached directly to it, which in turn ensures that each patient receives the necessary drug product information upon dispensing from a pharmacy. Such a proposed product should generally be packaged similarly to the RLD to account for these considerations.

4. Other Inconsistencies

FDA will RTR an ANDA if the ANDA contains certain other inconsistencies. In accordance with 21 CFR 314.94(a)(4), an ANDA must include a statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the RLD. However, there are certain exceptions (e.g., for labeling differences permitted pursuant to an approved suitability petition that is cited as an ANDA's basis of submission (see section III.F for further details)). Any other proposed condition-of-use changes would not be acceptable. Examples of proposed condition-of-use changes may include, but are not limited to, citing a sprinkle capsule dosage form as a basis of submission but producing a capsule that cannot be administered in the same manner as the RLD, or proposing alterations to either the amount of active ingredient delivered per dose or the dosing regimen such that neither are consistent with those described in the RLD labeling.

H. Microbiology Considerations

Generally, FDA will RTR an ANDA if it contains certain deficiencies related to microbiology considerations.

An ANDA should contain all sterility assurance validation studies for terminally sterilized drug products and aseptically filled drug products, as described below⁶⁷:

⁶⁶ 21 CFR 314.94(a)(8).

⁶⁷ 21 CFR 314.50(d)(1).

Contains Nonbinding Recommendations

1. Terminally sterilized drug products
 - Validation of production terminal sterilization process
 - Validation of depyrogenation of product containers and closures
 - Validation of container-closure package integrity
2. Aseptically filled drug products
 - Validation of the sterilizing grade filters (bacterial retention studies)
 - Validation of the sterilization of sterile bulk drug or product contact equipment, components, containers, and closures
 - Validation of the depyrogenation of product containers and closures
 - Validation of the aseptic filling process/line/room (media fills/process simulations)
 - Validation of container-closure package integrity

In addition, an ANDA should include at the time of submission, at minimum, summaries of validation studies.

VI. BIOEQUIVALENCE AND CLINICAL DEFICIENCIES

As a general matter, ANDA applicants should refer to FDA's "Product Specific Recommendations for Generic Drug Development" website for Bioequivalence (BE) guidances regarding recommended in vivo and/or in vitro BE and other recommended studies.⁶⁸

A. Failed In Vivo BE Studies

FDA will RTR an ANDA if only a failed in vivo BE study is submitted.⁶⁹ FDA regulations require applicants to submit information on failed BE studies.⁷⁰ Typically, a failed study is one that does not satisfy the 90% confidence interval (CI) criterion (e.g., falls outside of the 0.8-1.25 acceptance criterion limits) for either the area under curve (AUC) or peak plasma concentration (C_{max}) parameter. If this occurs for highly variable drug products, the applicant may submit a study using a replicate study design and analyze data using a reference-scaled average (RSA) approach for the failed parameter. Applicants should refer to FDA's "Product Specific Recommendations for Generic Drug Development" website for BE guidances or submit BE guidance requests for proposed products to GenericDrugs@fda.hhs.gov.

B. Alternate BE Studies

⁶⁸ FDA's BE recommendations for specific products can be found at <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm>.

⁶⁹ It is also recommended that a brief CMC summary of any failed studies be included in the Pharmaceutical Development report.

⁷⁰ 21 CFR 314.94(a)(7)(i).

Contains Nonbinding Recommendations

FDA will RTR an ANDA if the ANDA contains one or more in vivo studies that were not recommended in the BE guidance, without adequate justification.⁷¹ Adequate justification should include justification for an approach that deviates from FDA posted guidance, including data (Module 2.7 and Module 5) and appropriate references. Applicants should refer to FDA's "Product Specific Recommendations for Generic Drug Development" website for BE guidances or submit BE guidance requests for proposed products to Generic.Drugs@fda.hhs.gov.

C. Q1/Q2 Sameness Requirement for Consideration of an In Vivo BE Study Waiver

Certain drug products may be eligible for a waiver from conducting in vivo BE studies typically required to support an ANDA. For example, in accordance with 21 CFR 320.22(b)(1), parenteral drug products, in addition to both ophthalmic and otic solutions, may be eligible for a waiver of BE studies, provided that their formulations are considered Q1/Q2 same as the RLD.⁷² If such a drug product is determined not to be Q1/Q2 same as the RLD, FDA will RTR the ANDA based on the determination that the drug product is ineligible for a waiver because of permissible formulation differences.⁷³

For ophthalmic solutions, it is critical to also complete and include the BE table Comparative Physicochemical Data of Ophthalmic Solution Drug Products⁷⁴ in Module 2.7 of the ANDA submission to further support the waiver request. This table captures key information/data relevant to both the test product and the RLD. If this table is omitted, FDA will RTR the ANDA despite a determination that the test formulation is Q1/Q2 same as the RLD.⁷⁵

D. Inadequate Dissolution Data (In Vitro Studies)

For any recommended dissolution study, it is critical that appropriate comparison data (i.e., test product and RLD) be provided.⁷⁶ If there is evidence within the ANDA that the appropriate dissolution studies were not conducted or a supplemental study is omitted, FDA will RTR the ANDA.

The BE guidances discussed in this section contain important details about the types of dissolution studies appropriate for the RLD and test products, along with information on waiver of an in vivo BE data requirement for any additional strengths for which approval is sought.⁷⁷ In addition, these BE guidances may reference dissolution methods available through FDA's Web site that are specific to a particular drug product.⁷⁸

⁷¹ 21 CFR 314.94(a)(7).

⁷² In such instances, bioequivalence is considered to be self-evident.

⁷³ 21 CFR 314.94(a)(7).

⁷⁴ BE tables can be found on FDA's Web site at the following location:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf>

⁷⁵ 21 CFR 314.94(a)(7).

⁷⁶ 21 CFR 314.50(d)(1).

⁷⁷ See 21 CFR 320.22(d)(2)(ii).

⁷⁸ For examples of FDA-recommended dissolution methods, see <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>.

Contains Nonbinding Recommendations

Other suggested types of comparative (i.e. test product and RLD) supplemental dissolution studies include:

- Alcohol dose-dumping
- Half-tablet dissolution for modified-release drug products with functional score marks⁷⁹ performed for each strength of test and RLD in the recommended media, or quality control (QC) media if there is no recommendation (alcohol dose-dumping studies are not recommended for half-tablet dissolution studies)
- Any other product-specific dissolution study described in the BE recommendations for the relevant product

E. Miscellaneous Factors

1. Study Information BE Table⁸⁰

FDA will RTR an ANDA if the Study Information BE table is incomplete.⁸¹ The Study Information BE table compiles important information about study type and site locations and should be placed in Module 2.7 of the ANDA (along with the other BE summary tables). Applicants should provide the requested information regarding sample storage and long-term storage. Receipt of the ANDA is also predicated on the following information that is captured in the table:

- The number of days of long-term storage stability (LTSS) coverage should be equal to or more than the number of days for sample storage duration.
- The temperature (°C) reported for LTSS coverage should be within or less than the temperature range for sample storage.

2. Waiver of In Vivo BA or BE Studies for BCS Class I Drugs

If the applicant requests a Biopharmaceutics Classification System (BCS) Class 1 BA/BE waiver, FDA will RTR the ANDA if any of the data needed to support such a waiver request are missing from the ANDA at the time of submission.⁸² Applicants should refer to FDA's guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* for details regarding waivers of any required in vivo bioavailability (BA) or BE studies for a BCS Class 1 drug substance.

⁷⁹ A functional score mark enables delivery of a dose that is supported by RLD labeling.

⁸⁰ A copy of this BE table can be found on FDA's Web site at the following location: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf>.

⁸¹ 21 CFR 314.94(a)(7).

⁸² 21 CFR 314.94(a)(7).

Contains Nonbinding Recommendations

3. Office of Bioequivalence and Office of Pharmaceutical Quality Receipt Evaluations

FDA will RTR an ANDA, in certain cases, based on the recommendations of DBE, the Division of Clinical Review (DCR), and/or the Office of Pharmaceutical Quality. Deficiencies in these modules are generally associated with, but not limited to, various concerns with an in vivo BE or clinical endpoint BE study, or statistical data and/or design.

4. Drug-Device Combination Products

On a case-by-case basis and in consideration of preliminary evaluations performed by consultant offices, FDA will RTR an ANDA for a drug-device combination product if a device used to deliver the drug is not sufficiently similar to the device used to deliver the RLD. Any device used to deliver the drug should be similar enough to that used with/for the RLD so as to ensure, at a minimum, safe and proper administration of the product without the need for retraining by a health care professional and to ensure that its performance characteristics, operating principles, and critical design attributes will result in a product that will perform the same as the RLD under the conditions of use described in the labeling. In addition, the patient instructions in the labeling, as it concerns use of the device, should meet the same labeling requirement for ANDAs.⁸³

5. Missing Case Report Forms

FDA will RTR an ANDA if a clinical study conducted does not contain copies of individual case report forms for patients enrolled in the study.⁸⁴ Applicants should provide a random selection of at least 10% of all case report forms for any study that enrolls patients. Applicants should also include all case report forms for subjects removed from study analysis for any reason. In addition, applicants should provide copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug-related or not, including patients receiving reference drugs or placebo, consistent with 21 CFR 314.50(f)(2).

VII. DISPUTE OF A REFUSE-TO-RECEIVE DECISION

If an applicant disagrees with or wishes to discuss an RTR decision, the applicant should submit its concerns first to the email address identified in the RTR letter. If FDA's subsequent response does not resolve the matter, a teleconference can be scheduled with the applicant, a Division of Filing Review (DFR) Team Leader, DFR Supervisor, and, if needed, the appropriate division director. If the matter still remains unresolved, the applicant can use the dispute resolution procedure (see 21 CFR 314.103 and guidance for industry *Formal Dispute Resolution: Appeals Above the Division Level*).

⁸³ Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314(a)(8)(iv).⁸⁴ 21 CFR 314.101(d)(3).

⁸⁴ 21 CFR 314.101(d)(3).

Contains Nonbinding Recommendations

APPENDIX A: EXAMPLES OF MINOR DEFICIENCIES

1. An ANDA is required to contain either an environmental assessment (EA) or a claim of categorical exclusion.⁸⁵ Pursuant to 21 CFR 25.15(a) and in reference to FDA's guidance for industry *Environmental Assessment of Human Drug and Biologics Applications* (EA guidance), all applications or petitions requesting FDA action require the submission of either (1) an EA or (2) a claim of categorical exclusion, as defined in 21 CFR 25.31.⁸⁶ A claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that to the applicant's knowledge, no extraordinary circumstances exist.⁸⁷ If FDA does not receive an EA or claim of categorical exclusion made by the applicant within 7 calendar days of notification of the omission(s), FDA will RTR the ANDA.
2. An ANDA must contain an accurate and complete English translation of each part of the application that is not in English.⁸⁸ This requirement includes the translation of all sections of the document (e.g., headers, titles). FDA will accept an ANDA with the English translation on a blank page next to the original text. FDA recommends that the translation be legible in size 12 font. 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. If FDA does not receive English translation of each part of the application that is not in English within 7 calendar days of notification of the omission(s), FDA will RTR the ANDA.
3. An ANDA must contain either a daily elemental iron calculation for products that contain iron⁸⁹ or a statement that the amount of elemental iron ingested per day does not exceed 5 milligram (mg), in accordance with 21 CFR 73.1200(c). A daily elemental iron calculation should be included in module 3.2.P.1 in addition to all other inactive ingredient justification data/information. If FDA does not receive either the calculation or aforementioned statement within 7 calendar days of notification of the omission(s), FDA will RTR the ANDA.
4. An applicant should complete the Pharmacy Bulk Package Sterility Assurance table⁹⁰ for pharmacy bulk packages and place this table in section 1.14.1.4 of Module 1 of the ANDA. If FDA does not receive the completed table within 7 calendar days of notification of the omission, FDA will RTR the ANDA.
5. An applicant should include *all* of the facility information that is listed in Modules 3.2.S.2 and 3.2.P.3.1 (drug substance and drug product, respectively) of the application in Field 29 of the 356h form, using continuation pages for Field 29 when needed.⁹¹ FDA will notify the applicant if there are any facilities listed in either of the aforementioned modules of the

⁸⁵ 21 CFR 314.101(d)(4).

⁸⁶ See the EA guidance for information as to which types of drug products require an EA

⁸⁷ 21 CFR 25.15(a).

⁸⁸ 21 CFR 314.101(d)(5).

⁸⁹ 21 CFR 314.50(d)(1)(i).

⁹⁰ <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf>.

⁹¹ 21 CFR 314.101(d)(1).

Contains Nonbinding Recommendations

ANDA that are not captured in Field 29 and/or on its continuation pages. If FDA does not receive a revised 356h form within 7 calendar days of notification of the facility omission(s), FDA will RTR the ANDA.

6. If there is a patent listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book) for the RLD, the ANDA must include a patent certification as to that patent, with one exception. If the patent is a *method of use* patent and the labeling of the RLD includes uses that are not covered by the patent, an ANDA applicant may be able to submit⁹² a patent statement⁹³ explaining that the method of use patent does not claim any of the uses in the proposed labeling of the ANDA product. If the applicant submits such a patent statement, the proposed labeling in the ANDA must not include methods of use (or indications) that are covered by the use codes in the Orange Book for the patent in question. Where a listed patent claims the drug substance and/or drug product and one or more methods of use, the applicant may provide a "split certification" to the patent (i.e., the applicant provides a statement that the applicant is not seeking approval for one or more methods of use claimed by the patent based on the use code(s) listed in the Orange Book (sometimes referred to as a "section viii" statement) and a patent certification to the remaining claims). If, upon filing review of such an ANDA, OGD determines that the labeling submitted in the ANDA *does* refer to a use described in such use codes, OGD will not provide guidance or suggestions as to how the proposed labeling should be amended. Instead, OGD will inform the applicant that it must either revise its labeling or withdraw the patent statement. If, within 7 calendar days of being informed of this issue, an applicant fails to withdraw the patent statement or revise the proposed labeling so as not to refer to the use claimed by the patent, FDA will RTR the ANDA.
7. The listed drug that is relied on as the ANDA's basis of submission is ordinarily the drug product that is designated as the RLD in the Orange Book.⁹⁴ If a listed drug that is not designated the RLD is cited as the basis of submission for an ANDA, FDA will notify the applicant of the error. If the correct information is not submitted within 7 calendar days, FDA will RTR the ANDA.
8. For those ANDAs using APIs that do not make reference to a Type II API DMF, an evaluation of the API information presented within Module 3 (drug substance)⁹⁵ of the application will be performed. Any deficiencies⁹⁶ will be communicated to the ANDA applicant for correction. If a response to the API deficiencies is not received within 7 calendar days, FDA will RTR the ANDA.

⁹² Pursuant to section 505(j)(2)(A)(viii) of the FD&C Act and 21 CFR 314.94(a)(12)(iii), and also referred to as a "Section viii carve-out."

⁹³ See Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions; Final Rule, 59 FR 50338, 50347 (Oct. 3, 1994).

⁹⁴ 21 CFR 314.94(a)(3).

⁹⁵ Specifically, section 3.2.S.2 and its accompanying subsections, though this does not preclude review of the other sections and subsections that make up 3.2.S so that the completeness of the API section in its entirety may be assessed.

⁹⁶ Note that the minor deficiencies found during the API review are not counted against the total for all other ANDA deficiencies, as described in the introduction to Section III.

Contains Nonbinding Recommendations

9. In accordance with 21 CFR 314.94(a)(8)(iv), an ANDA's proposed labeling must be the same as the labeling approved for the RLD, except for (1) changes required because of differences approved under a petition filed under 21 CFR 314.93, or (2) because the drug product and the RLD are produced or distributed by different manufacturers. Differences between the applicant's proposed labeling and labeling approved for the RLD can include differences in expiration date, formulation, bioavailability or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the FD&C Act. Applicants must submit a side-by-side comparison of the RLD and the proposed labeling.⁹⁷ In accordance with 21 CFR 314.94(d)(1)(iii), the content of labeling must be submitted in an electronic format that FDA can process, review, and archive. FDA periodically issues and updates its guidance on how to provide electronic submissions.⁹⁸ If responses to these deficiencies are not received within 7 calendar days of being informed of these issues, FDA will RTR the ANDA.

⁹⁷ See 21 CFR 314.94(a)(8)(iv).

⁹⁸ See guidance for industry *Providing Regulatory Submissions in Electronic Format—Content of Labeling*.