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)

May 2015
Generic Drugs

Revision 1

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TABLE OF CONTENTS

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ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA, or the 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 implementing 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 an ANDA.[3] A refuse-to-receive decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review.[4]

This guidance is not meant to be a comprehensive list of the deficiencies that may or will lead to a refuse-to-receive determination by FDA. Instead, this guidance identifies certain deficiencies and certain recurrent deficiencies that in FDA's experience have led FDA to refuse-to-receive 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 refuse-to-receive determinations.

FDA's guidance documents, including this guidance, 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 is prepared by 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 new-strength PAS submissions.

[3] A refuse-to-receive determination should not be confused with a refuse-to-approve determination.

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

The use of 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 refuse-to-receive 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 sufficiently complete to permit a substantive review.[8] Our regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in others, refuse-to-receive an ANDA.[9]

Generally, FDA will not receive an ANDA unless it contains the information required under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)), as specified in more detail in 21 CFR 314.101 and other regulations, for example[10]:

- 21 CFR 314.50
- 21 CFR 314.94
- 21 CFR 320.21
- 21 CFR 320.22

[5] At various points in this guidance, it is noted that when a particular type of deficiency in an ANDA is seen, FDA *will* refuse-to-receive 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 refuse to receive 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 refuse to receive it.

[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).

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

[10] In certain cases, other statutes or regulations may apply.

Recent data underscore the need for improvement in the quality of original ANDA submissions. For example, between 2009 and 2012, FDA refused to receive 497 ANDAs. Of all ANDA submissions, FDA refused to receive:

- 12% in 2009
- 18% in 2010
- 15.5% in 2011
- 9.4% in 2012[11]

In 2012, of the 100 ANDAs that FDA refused-to-receive, 40 were refused because of serious bioequivalence (BE) deficiencies; 36 because of serious chemistry deficiencies; 13 because of format or organizational flaws; 6 because of clinical deficiencies; 4 because of inadequate microbiology (sterility assurance) information; and 1 was refused because an incorrect reference listed drug (RLD) was cited as the basis of submission. Despite evidence that the majority of deficiencies are related to BE and product quality standards (chemistry, manufacturing, controls (CMC)), FDA believes that clarification of these and certain other deficiencies (as discussed below) will help improve the overall quality of ANDA submissions.

III. GENERAL POLICY

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 cannot be easily remedied, such as certain deficiencies found in 21 CFR 314.101(d) or 21 CFR 314.101(e);[12] other major deficiencies are discussed in this and other guidances. A major deficiency will not permit a substantive review of the ANDA by FDA under 21 CFR 314.101(b)(1), and FDA will therefore refuse-to-receive the ANDA.

A minor deficiency is one that in FDA's judgment can be easily remedied.[13] 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 ten or more minor deficiencies or one or more major deficiencies, FDA will consider such an application not sufficiently complete to permit a substantive review 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."[14] If the applicant decides to submit additional materials to correct the deficiencies,

[11] The 2012 figures are based on incomplete data.

[12] 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 [emphasis added]. As a result, on a case-by-case basis, FDA will determine whether a deficiency under that regulation is a major or minor deficiency.

[13] 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.

[14] 21 CFR 314.101(b)(3).

the resulting amended ANDA will be considered a new ANDA submission, received as of the date the amendment to the ANDA is received, and the applicant will be required to pay a new GDUFA fee.[15]

However, 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, usually by phone, email, or fax. If the applicant subsequently satisfactorily amends the ANDA to correct the identified deficiencies within 7 calendar days and FDA makes the determination to receive the application as amended, the application will be considered received as of the date on which it was first submitted to FDA.[16] If within 7 calendar days the requested information is not received, FDA will refuse-to-receive the ANDA.

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.[17]

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, FDA will refuse-to-receive the ANDA.[18]

B. Organization/Format

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.[19] FDA will refuse-to-receive an ANDA that is submitted as a single, continuous, unbookmarked PDF file.[20]

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[15] If FDA refuses-to-receive an ANDA for reasons other than failure to pay GDUFA fees, a refund of 75% of the application fee paid for that ANDA will be made to the applicant (section 744B(a)(3)(D) of the FD&C Act (21 U.S.C. 379j-42)). The resubmission of that ANDA will be subject to a full application fee (section 744B(a)(3)(E) of the FD&C Act).

[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.

[17] 21 CFR 314.99(b).

[18] 21 CFR 314.101(d)(1).

[19] See Generic Drug User Fee Act Program Performance Goals and Procedures at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf and the draft guidance entitled, *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* for details. When finalized, this guidance will represent FDA's current thinking on this topic.

[20] 21 CFR 314.50(l)(5).

C. Non-Payment of GDUFA Obligations

FDA will refuse-to-receive an ANDA in certain cases if there are outstanding user fee obligations[21]:

- If an applicant fails to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application [22]
- If an ANDA references a Type II active pharmaceutical ingredient (API) Drug Master File (DMF) that is not deemed *available for reference* because of non-payment of the GDUFA DMF fee [23]
- If an ANDA references a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)[24]
- If the applicant is the owner of or is affiliated with the owner of a facility on the facility arrears list[25]
- If the applicant is listed on the backlog arrears list[26]
- If the applicant is affiliated with an entity on the backlog arrears list[27]

In all of these cases, FDA will refuse-to-receive 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 refuse to receive 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

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[21] 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 draft guidance for industry, *Generic Drug User Fee Amendments of 2012: Questions and Answers*. When finalized, this guidance will represent FDA's current thinking on this topic.

[22] Section 744B(g)(3) of the FD&C Act.

[23] Section 744B(g)(2) of the FD&C Act.

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

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

[26] Section 744B(g)(1) of the FD&C Act.

[27] Id.

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.[28]

E. Failure to Provide Environmental Assessment or Claim of Categorical Exclusion

FDA will refuse-to-receive any ANDA that fails to provide either an environmental assessment (EA) or a claim of categorical exclusion.[29] Pursuant to 21 CFR 25.15(a) and in reference to FDA's guidance for industry entitled *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.[30]

F. 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 refuse-to-receive the ANDA because of the lack of 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 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.[32] In addition, the docket number and a copy of FDA's correspondence approving the petition must be included in the ANDA submission.[33] For more information about which suitability petitions are available as a basis of submission for an ANDA, see FDA's Web site.[34]

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[28] 21 CFR 314.94(a)(1) (incorporating by reference 21 CFR 314.50(a)(1), (3), (4), and (5)).

[29] See 21 CFR 314.101(d)(4).

[30] See the EA guidance for information as to which types of drug products require an EA.

[31] 21 CFR 314.101(d)(3).

[32] 21 CFR 314.94(a)(3)(i).

[33] 21 CFR 314.94(a)(3)(iii).

[34] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120944.htm.

IV. REVIEWS FOR API

A. Starting Material

FDA will refuse-to-receive 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.[35,36]

B. Sterility Assurance Data

FDA will refuse-to-receive 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.[37]

V. CHEMISTRY, MANUFACTURING, AND CONTROL DEFICIENCIES

A. Inactive Ingredients

1. Inactive Ingredients Exceeding the Inactive Ingredient Database Limit

FDA will refuse-to-receive 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 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, three options are available to facilitate receipt of the ANDA:

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

[36] 21 CFR 314.50(d)(1)(i).

[37] 21 CFR 314.50(d)(1)(i) and 21 CFR 314.50(d)(1)(ii).

[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 refuse to receive 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/iig/index.cfm.

- 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-receive 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 use[41] 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 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).

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[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.

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 refuse-to-receive 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.[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-receive the ANDA.[47] However, even if an inactive ingredient is determined to be quantitatively the same as the RLD in a controlled correspondence response, 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 the same as the RLD (*same* implies ≥95% but ≤105% of the RLD concentration or amount) yet exceeds the IID limit for the applicable route of administration, FDA will refuse-to-receive 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

[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.

[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.

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.

3. Elemental Iron Levels

FDA will refuse-to-receive an ANDA if a daily elemental iron calculation is not included for products that contain iron.[50] In accordance with 21 CFR 73.1200(c), the amount of elemental iron ingested per day must not exceed 5 milligram (mg). A daily elemental iron calculation should be included in module 3.2.P.1 in addition to all other inactive ingredient justification data/information.

B. Inadequate Stability

1. Number of Batches and Length of Studies

FDA will refuse-to-receive an ANDA if certain batch size and study recommendations are not satisfied.[51,52] 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.[53] However, if 6 months of accelerated data show a significant change[54] or failure of any attribute in one or more batches, the applicant should also include 6 months of intermediate[55] 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

[50] 21 CFR 314.50(d)(1)(i).

[51] 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.

[52] 21 CFR 314.50(d)(1)(i) and 21 CFR 314.50(d)(1)(ii).

[53] 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*.

[54] 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.

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

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.

2. Container Orientation

FDA will refuse-to-receive an ANDA if horizontal or inverted (i.e., worst-case scenario) accelerated 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.[56] However, these drug products should also be evaluated for stability in the upright (or vertical) position. For routine stability studies, the applicant should pick the worst-case orientation for the study.

C. Packaging Amount Considerations

FDA will refuse-to-receive 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*.[57] 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:

- Accelerated 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

[56] 21 CFR 314.50(d)(1).

[57] 21 CFR 314.50(d)(1)(ii).

FDA will refuse-to-receive an ANDA if batch records are not provided.[58] 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. Furthermore, batch records, either commercial or executed, should contain an accurate and complete English translation of any portion of an application that is not printed or written in English.[59]

E. Method Validation/Verification Reports

FDA will refuse-to-receive an ANDA if method validation/verification reports are not provided.[60] To clarify: 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, verification[61] 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 electronically, the applicant should submit three copies of the method validation/verification package for the API, the drug product, or both.[62]

F. Special Consideration for Transdermal Patches

FDA will refuse-to-receive an ANDA for a transdermal patch if the ANDA does not address certain special considerations.[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

[58] 21 CFR 314.50(d)(1)(ii)(*b*).

[59] 21 CFR 314.101(d)(5).

[60] 21 CFR 314.50(d)(1) and 314.94(a)(9)(i).

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

[62] 21 CFR 314.50(e)(2)(i).

[63] 21 CFR 314.50(d)(1).

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

Applicants are strongly encouraged to consult the Division of Chemistry 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 refuse-to-receive an ANDA if there are inconsistencies in the scoring configuration between the RLD and the test product that 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 refuse-to-receive 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 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 refuse-to-receive 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 refuse-to-receive 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

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

[65] 21 CFR 314.50(d)(1).

[66] 21 CFR 314.94(a)(8).

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 refuse-to-receive 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 below[67]:

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.

The Pharmacy Bulk Package Sterility Assurance table[68] should be completed for pharmacy bulk packages and placed in section 1.14.1.4 of Module 1 of the ANDA.

[67] 21 CFR 314.50(d)(1).

[68] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf.

VI. BIOEQUIVALENCE AND CLINICAL DEFICIENCIES

As a general matter, ANDA applicants should consult the BE recommendations Web page on FDA's Web site for product-specific guidance on conducting recommended in vivo and/or in vitro studies.[69]

A. Failed In Vivo BE Studies

FDA will refuse-to-receive an ANDA if only a failed in vivo BE study is submitted.[70] FDA regulations require applicants to submit information on failed BE studies.[71] Typically, a failed study is one that does not satisfy the 90% confidence interval (CI) criterion (i.e., 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 should submit a study using a replicate study design and analyze data using a reference-scaled average (RSA) approach for the failed parameter. Alternatively, applicants should consult the BE recommendations Web page for product-specific study information, or contact OGD's Division of Bioequivalence (DBE) via a BE Guidance Request for further guidance, if needed.

B. Alternate BE Studies

FDA will refuse-to-receive an ANDA if the ANDA contains a non-recommended in vivo study without adequate justification.[72] 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. We encourage applicants to consult the BE recommendations Web page for product-specific study information or to contact OGD's Division of Bioequivalence via a BE Guidance Request for further guidance, if needed.

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.[73] If such a drug product is determined not to be Q1/Q2 same as the RLD, FDA will refuse-to-receive the

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

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

[71] 21 CFR 314.94(a)(7)(i).

[72] 21 CFR 314.94(a)(7).

[73] In such instances, bioequivalence is considered to be self-evident.

ANDA based on the determination that the drug product is ineligible for a waiver because of unpermitted formulation differences.[74]

For ophthalmic solutions, it is critical to also complete and include the BE table Comparative Physicochemical Data of Ophthalmic Solution Drug Products[75] 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 refuse-to-receive the ANDA despite a determination that the test formulation is Q1/Q2 same as the RLD.[76]

D. Inadequate Dissolution Data (In Vitro Studies)

For any recommended dissolution study, it is critical that appropriate comparison data be provided.[77] If there is evidence within the ANDA that the appropriate dissolution studies were not conducted or a supplemental study is omitted, FDA will refuse-to-receive the ANDA. For tablets that are scored, applicants should submit data as recommended in FDA's guidance for industry entitled *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.

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.[78] In addition, these BE guidances may reference dissolution methods available through FDA's Web site that are specific to a particular drug product.[79] Finally, other suggested types of supplemental dissolution studies include:

- Alcohol dose-dumping
- Half-tablet dissolution for drug products with functional score marks[80]
- Any other product-specific dissolution study described in the BE recommendations for the relevant product

[74] 21 CFR 314.94(a)(7).

[75] 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.

[76] 21 CFR 314.94(a)(7).

[77] 21 CFR 314.50(d)(1).

[78] See 21 CFR 320.22(d)(2)(ii).

[79] For examples of FDA-recommended dissolution methods, see http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm.

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

E. Miscellaneous Factors

1. Study Information BE Table[81]

FDA will refuse-to-receive an ANDA if the Study Information BE table is incomplete.[82] 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 coverage should be equal to or more than the number of days for sample storage duration.

- The temperature (°C) reported for long-term storage stability 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 refuse-to-receive the ANDA if any of the data needed to support such a waiver request are missing from the ANDA at the time of submission.[83] 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.

3. DBE, DCR, Office of Pharmaceutical Quality Receipt Reviews

FDA will refuse-to-receive 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 (e.g., inappropriate or inadequate clinical endpoint, inappropriate indication for use, inadequate sampling, failure to measure appropriate active drug or active metabolites in PK sampling, use of an inappropriate patient population, or allowance of inappropriate concomitant medications).

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[81] 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.

[82] 21 CFR 314.94(a)(7).

[83] 21 CFR 314.94(a)(7).

4. Sameness Criterion for Devices

On a case-by-case basis, FDA will refuse-to-receive 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.[84]

5. Missing Case Report Forms

FDA will refuse-to-receive an ANDA if a clinical study conducted does not contain copies of individual case report forms for patients enrolled in the study.[85] 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).

[84] Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314(a)(8)(iv).

[85] 21 CFR 314.101(d)(3).

VII. DISPUTE OF A REFUSE-TO-RECEIVE DECISION

If an applicant disagrees with or wishes to discuss a refuse-to-receive decision, the applicant should present its concerns first to the contact person named in the refuse-to-receive letter. If this does not resolve the matter, a teleconference can be scheduled with the applicant, the contact person, a supervisory consumer safety officer, 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*).

APPENDIX A: EXAMPLES OF MINOR DEFICIENCIES

1. 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.[86] FDA will notify the applicant if there are any facilities listed in either of the aforementioned modules of the 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 refuse-to-receive the ANDA.

2. 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 reference listed drug (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 submit[87] a patent statement[88] 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. 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 refuse-to-receive the ANDA.

3. 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.[89] 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 refuse-to-receive the ANDA.

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[86] 21 CFR 314.101(d)(1).

[87] 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."

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

[89] 21 CFR 314.94(a)(3).

4. 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)[90] of the application will be performed. Any deficiencies[91] 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 refuse-to-receive the ANDA.

5. 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.[92] 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.[93] If responses to these deficiencies are not received within 7 calendar days of being informed of these issues, FDA will refuse-to-receive the ANDA.

[90] 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.

[91] 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.

[92] See 21 CFR 314.94(a)(8)(iv).

[93] Guidance for industry *Providing Regulatory Submissions in Electronic Format—Content of Labeling*.