Guidance for Industry

ANDA Submissions — Refuse-to-Receive Standards

DRAFT GUIDANCE

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

October 2013
Generic Drugs

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ANDA Submissions — Refuse-to-Receive Standards

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors preparing to submit to the Food and Drug Administration (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 describes what should be included in an ANDA and highlights serious deficiencies that may cause FDA to *refuse to receive* an ANDA.[3] A refuse-to-receive decision indicates that FDA has determined that an ANDA is incomplete on its face, usually because of omissions. This guidance is not meant to be all-inclusive and does not offer explicit guidance on minor deficiencies that may be found in an ANDA submission. FDA currently is applying many of these standards in its refuse-to-receive determinations.

This guidance is organized according to FDA's *ANDA Filing Checklist for Completeness and Acceptability of an Application* (ANDA checklist), which is an internal checklist FDA reviewers use when evaluating the completeness of ANDAs. FDA makes the ANDA checklist available to the public for transparency purposes and to help sponsors gain an understanding of FDA's review process.

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.

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[1] This guidance has been prepared by the Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] From now on, the use of the term *ANDA* will be understood to include ANDAs and new strength PAS submissions.

[3] This should not be confused with a *refuse-to-approve determination.*

The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.[4]

II. BACKGROUND

With the enactment of the Generic Drug User Fee Act of 2012 on July 9, 2012,[5] the Office of Generic Drugs (OGD) was tasked with a number of activities, including development of "enhanced refusal to receive standards for ANDAs and other related submissions by the end of year 1 of the program…."[6]

Recent data underscore the need for improvement in the quality of original ANDA submissions. Between 2009 and 2012, OGD 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[7]

In 2012, of the 100 ANDAs that OGD refused to receive, 40 were refused because of serious bioequivalence 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 because an incorrect reference listed drug was cited. Despite evidence that the majority of deficiencies are related to bioequivalence and product quality (chemistry, manufacturing, controls—CMC) standards, FDA believes that clarification of all criteria will help improve the overall quality of ANDA submissions. Any major deficiency, regardless of how it is categorized, hinders the efficiency of the review process.

FDA evaluates each incoming ANDA individually to determine whether its format and content meet threshold criteria to permit a substantive review and can thus be *received* by FDA.[8] Our

[4] 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 sponsors, 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 deficient and refuse to receive it.

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

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

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

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

regulations at 21 CFR 314.101 provide the bases on which FDA may and must refuse to receive an application.[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), as specified in more detail in the following regulations[10]:

- 21 CFR 314.94
- 21 CFR 314.50
- 21 CFR 314.101
- 21 CFR 320.21
- 21 CFR 320.22

There may be circumstances, however, under which an exception to, or a waiver of, a regulatory requirement may be granted. The merits of such circumstances will be considered on a case-by-case basis.

FDA's ANDA checklist captures the essential statutory and regulatory requirements for receiving ANDA submissions. The ANDA checklist is formatted to mirror the organization of the Electronic Common Technical Document (eCTD),[11] and it can be downloaded from FDA's website.[12]

> *Note:* The ANDA checklist is updated quarterly so if you are referring to the checklist, it is important to make sure you have the most up-to-date version.

This guidance describes what should be included in an ANDA submission. It identifies and explains deficiencies that would lead FDA to refuse to receive an ANDA. The overall goal of this guidance is to help sponsors increase the quality of their ANDA submissions.

III. GENERAL POLICY

Regulations at 21 CFR 314.101(b)(3) state that, if FDA considers an ANDA not to have been received under 21 CFR 314.101(d)-(e), FDA will notify the applicant and the applicant may elect to withdraw the ANDA, amend it to correct the deficiencies, or take no action.

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

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

[11] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf.

[12] See the ANDA checklist on FDA's web site at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM151259.pdf.

FDA intends to work with an applicant if FDA determines that an ANDA contains *fewer than ten* minor[13] deficiencies. In such a case, FDA will notify the applicant by phone, e-mail, or fax. If the applicant satisfactorily amends the ANDA to correct the identified deficiencies within five (5) business 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. If within five business days the requested information has not been submitted, FDA will refuse to receive the ANDA.

However, if FDA determines that an ANDA contains *ten or more* minor deficiencies, or one or more major deficiencies, FDA will consider the ANDA on its face to not contain the information required in section 505(j) of the FD&C Act and 21 CFR 314.94 and, therefore, be incomplete. In such cases, FDA will send a letter refusing to receive the ANDA. The sponsor may decide to submit additional materials to correct the deficiencies, but the resulting amended ANDA will be considered a new ANDA submission, received as of the new date and requiring a new GDUFA fee.[14]

The following sections discuss deficiencies that FDA considers to be of a major nature. As described below, major deficiencies can lead to FDA refusing to receive an ANDA.

A. Form FDA 356h (356h)

An application must contain a completed application form (i.e. Form FDA 356h). If this form is not included, FDA will refuse to receive the ANDA.[15] The 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. 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 five business days of notification of the facility omission(s), FDA will refuse to receive the ANDA.

B. Organization/Format

The ANDA should be formatted according to the eCTD format, and it should be submitted electronically.[16] In some cases, FDA will accept hybrid applications (paper/electronic

[13] FDA considers *minor* deficiencies to be deficiencies FDA determines to be easily remedied.

[14] 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 application will be made to the applicant (section 744B(a)(3)(D)). The resubmission of that application will be subject to a full submission fee (section 744B(a)(3)(E)).

[15] 21 CFR 314.101(d)(1).

[16] FDA has issued a draft guidance, *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* for details. Once finalized, this guidance will represent FDA's perspective on this issue.

Note: FDA guidance documents are available at http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm. Guidances are updated and

combinations) (e.g., a paper ANDA that includes electronic labeling and electronic copies of Modules 2.3 and 2.7). PDF files should be converted from MS Word documents, rather than submitted as scanned documents, for these are often large files that are difficult to open and navigate. Moreover, scanned PDFs do not facilitate the review process because they lack user-friendly manipulation tools that are available for properly converted PDFs. FDA will refuse to receive an ANDA that is submitted as a single, continuous, unbookmarked PDF file.

Applicants are advised to follow the eCTD format and to use appropriate folders and subfolders, into which corresponding files should be placed. All sections and subsections should be included. If a folder or subfolder is not applicable to a submission, simply include a document as a placeholder indicating that the section is *not applicable*. FDA will also refuse to receive ANDAs containing duplicate files or datasets when distinct or specific information is requested. Electronic ANDA submissions should include a statement that a letter of non-repudiation is on file with FDA, pursuant to 21 CFR 11.100, to validate electronic signatures.

C. Non-Payment of GDUFA Obligations

There are certain conditions under which outstanding user fee obligations will result in FDA refusing to receive an ANDA:

- If a sponsor fails to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application
- If an application references a Type II active pharmaceutical ingredient (API) DMF that is not on the public *available for reference* list because of non-payment of the GDUFA DMF fee
- If an application references a facility on the facility arrears list for failure to pay the GDUFA facility fee(s)
- If the sponsor of the application is affiliated with the owner of a facility on the facility arrears list
- If the sponsor of the application is listed on the backlog arrears list
- If the sponsor of the application is affiliated with an entity on the backlog arrears list

In all of these cases, the FDA will refuse to receive an ANDA until such time that all user fee obligations have been satisfied. Upon satisfaction of all applicable user fee obligations, CDER's Office of Management will issue a formal correspondence 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

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revised regularly. To make sure you have the most recent version of a guidance, be sure to check the guidance website.

Foreign applicants whose responsible official, representative, or signer does not reside within the United States must designate a U.S. agent as a point of contact to ensure that FDA Form 356h has been countersigned by a U.S. agent.[17] Apart from the requirement of a U.S. signatory, there is a practical consideration to having a domestic representative. Because of global time differences, communication efforts between FDA and a foreign applicant's official residing outside of the United States can be challenging.

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

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), any application or petition requesting FDA action requires either (1) an environmental assessment or (2) a claim of categorical exclusion, as defined in 21 CFR 25.31. Failure to provide either one or the other of these documents within the ANDA submission will result in a refuse-to-receive decision. [18] See the EA guidance for information as to which types of drug products require an EA.

F. Failure to Ensure that Proposed Labeling Is Consistent with a Patent Statement

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[19] a patent statement,[20] 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 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 five business 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.

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[17] See 21 CFR 314.90(a)(1) (incorporating by reference 21 CFR 314.50(a)(1), (3),(4), and (5)).

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

[19] Pursuant to 505(j)(2)(A)(viii) and 21 CFR 314.94(a)(12)(iii) and also referred to as a "Section viii carve-out."

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

G. Citing an Incorrect or Unfounded Basis of Submission

ANDAs must have a basis of submission in accordance with 21 CFR 314.94(a)(3). There are two instances in which FDA will refuse to receive an ANDA over the basis of submission:

1. Incorrect basis of submission

The listed drug that is relied upon as the ANDA's basis of submission is ordinarily the drug product that is designated as the RLD in the Orange Book. 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 five business days, FDA will refuse to receive the ANDA.

Note: An applicant may ask FDA to designate a second RLD through a citizen petition, submitted in accordance with 21 CFR 10.20 and 10.30. However, the requested alternate RLD cannot be cited as a basis of submission until after FDA has granted the citizen petition.

2. Unfounded basis of submission

ANDAs may 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 approved by FDA. Requested changes from the listed drug product allowed by statute are:

- One active ingredient in a combination-ingredient drug product
- Change in dosage form
- Change in strength
- Change in route of administration

However, an ANDA may rely on a suitability petition as a basis of submission *only* after the petition has been approved by FDA. If an applicant submits a copy of, or refers to, a *pending* suitability petition, OGD will refuse to receive the ANDA because of the lack of a legal basis for the submission.

An applicant who wishes to rely on an approved suitability petition as the basis of submission for an ANDA may do so by identifying the listed drug cited in the approved petition as the basis for the ANDA.[21] In addition, the docket number and a photocopy of the approved petition must be included in the ANDA submission.[22] For more information about which suitability petitions are available for reference as a basis of submission for an ANDA, see FDA's website.[23]

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

[22] See 21 CFR 314.94(a)(3)(iii).

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

IV. LABELING DEFICIENCIES

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 may 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 505(j)(5)(F) of the FD&C Act. Applicants must submit a side-by-side comparison of the RLD and the proposed labeling.[24]

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.[25]

V. TYPE II API DRUG MASTER FILE AND API REVIEW DEFICIENCIES

A. Type II API Drug Master File Is Considered an Invalid Reference

FDA will refuse to receive an ANDA referencing a Type II API drug master file (DMF) if the GDUFA fee obligation for the Type II API DMF has not been paid within 20 days of notice from FDA to the ANDA applicant that that fee has not been paid.[26]

If the date the Type II API DMF was submitted to FDA is after the date that the ANDA was submitted, FDA will refuse to receive the ANDA.

B. Reviews for APIs

1. APIs with a Type II API DMF reference

Type II API DMFs for which the required fee has been paid undergo an initial completeness assessment (CA).[27] An ANDA that relies on a Type II API DMF for which the initial CA

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

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

[26] http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319567.htm. Also, Section 744B(g)(2) of FD&C Act.

determination is "incomplete" at the time FDA is to make a receipt decision will result in FDA refusing to receive the ANDA.[28]

2. APIs without a Type II API DMF reference

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)[29] of the application will be performed. Any deficiencies[30] will be communicated to the ANDA applicant for correction. If a response to the API deficiencies is not received within five business days, FDA will refuse to receive the ANDA.

3. Starting material

FDA will not receive an ANDA if the API review, whether in an ANDA or in a referenced DMF, reveals that the starting material for the API is improperly designated.

4. Sterility assurance data

FDA will not receive an ANDA if the API review, whether in an ANDA or in a referenced DMF, reveals that sterility assurance data are missing for a sterile API.

VI. CHEMISTRY, MANUFACTURING, AND CONTROL DEFICIENCIES

A. Inactive Ingredients

1. Inactive ingredients exceeding the inactive ingredient database (IID) limit

Applicants can justify inactive ingredient (excipient) levels by reference to the IID, which is a listing of excipients and their maximum levels of use (per dosage unit or percent composition), arranged by either route of administration or dosage form.[31] An excipient is considered justified,

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[27] FDA issued a draft guidance for industry on *Initial Completeness Assessments for Type II API DMFs under GDUFA*. Once finalized, this guidance will represent FDA's thinking on this topic.

[28] Type II API DMFs for which applicable fees have been paid and that have been found complete are listed on an Available For Reference list on FDA's website. See http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.pdf.

[29] 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.

[30] 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 of Section III.

[31] See http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

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 test drug product. If an applicant wishes to use an excipient at a level per unit that is higher than what is proposed in the IID, three avenues are available for receipt:

- Submit complete pharmacology/toxicology information

  Applicants should submit complete pharmacology/toxicology (pharm/tox) information (not only summaries or listings of data available in the literature) in the ANDA as recommended in FDA guidance. FDA's guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* suggests two studies — one rodent, one non-rodent — with inclusion of full data. Also, the studies should be conducted over a time period that is consistent with the regimen of the drug product (i.e., acute versus chronic administration). The maximum daily intake (MDI) of the inactive ingredient should also be calculated based on the maximum daily dose (MDD) of the active ingredient. Any pharm/tox information should be submitted as a PDF document (if the ANDA is a paper submission).

- Cite a specific example of a CDER-approved drug product that contains the inactive ingredient at or above the proposed level of use[32] for the appropriate route of administration

- Submit a Control Correspondence requesting an evaluation of the proposed level of use prior to submission of the ANDA[33]

  Calculate the MDI for the excipient and provide the name of the RLD, if applicable. No more than three excipient queries should be submitted per control document. Finally, pharm/tox information should not be submitted for evaluation in a Control Correspondence. Such content will be evaluated solely within the context of the ANDA submission.

If an ANDA submission proposes to use an inactive ingredient at a level that exceeds any of the IID listings without the support described in the above bullet points, FDA will refuse to receive the ANDA.

Regarding excipient justifications for oral liquid drug products, FDA recommends that the justification not be based on a listed percentage in the IID. Instead, the applicant should calculate the amount of inactive ingredient that is delivered per dose or per day (MDI) — based

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[32] That is, amount per dosage unit or MDI that is based on the calculated MDD of the active ingredient in the drug product.

[33] Control 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.

on dosing recommendations indicated in the RLD label — and justify the calculated amount based on an amount-per-unit IID listing that corresponds to a solid oral dosage form.

Because the components of liquid dosage forms are generally expressed in terms of milligrams per milliliter (%w/v), the amount of inactive ingredient delivered per dose cannot be properly ascertained by simply comparing the %w/v composition of a particular excipient to a threshold percentage in the IID. Furthermore, 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).

2. Changes to non-exception excipients

Parenteral drug products generally must contain the same inactive ingredients and in the same concentration as the RLD.[34] However, specific changes[35] are permitted for injectable drug products: preservatives, buffers, and antioxidants may differ from those contained in the RLD drug product (exception excipients), *provided that the differences are characterized and information is submitted demonstrating that the differences do not compromise the safety or efficacy of the drug product.*[36] This justification is a critical aspect of the exception excipient allowance and should be provided in the ANDA to support the proposed exception excipient change.

For all other inactive ingredients, an ANDA injectable drug product must be qualitatively and quantitatively the same (Q/Q same) as the RLD.[37] The applicant can submit a Control Correspondence to request a Q/Q evaluation of proposed formulations before an ANDA submission to minimize the risk of FDA refusing to receive the ANDA.[38] But even if an excipient 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 Q/Q threshold. In other words, if an inactive ingredient is demonstrated to be quantitatively the same as the RLD, yet exceeds the IID limit for the applicable route of administration, FDA will refuse to receive the ANDA.

Despite a similar allowance provided for *ophthalmic* drug products by 21 CFR 314.94(a)(9)(iv), FDA has determined that as a scientific matter, we will not accept any qualitative or quantitative deviations from the RLD in the absence of an appropriate in vivo bioequivalence study or

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[34] See 21 CFR 314.94(a)(9)(iii).

[35] Referred to as *exception excipients*.

[36] See 21 CFR 314.94(a)(9)(iii).

[37] Id. (Also, quantitative sameness generally is defined as a concentration that is within 95-105% of the RLD concentration).

[38] As with other inactive ingredient queries, OGD requests that the applicant submit no more than three proposed formulations for evaluation per Control document.

studies. Thus, an ANDA ophthalmic drug product should be Q/Q the same as the RLD with respect to all of its components, or include data from appropriate bioequivalence studies, for the ANDA to be received by FDA.[39] However, differences with respect to the types of inactive ingredients listed in 21 CFR 314.94(a)(9)(iv) are permitted for otic drug products, provided that these differences are characterized and information is submitted demonstrating that they do not compromise the safety or efficacy of the drug product.

3. Elemental iron levels

In accordance with 21 CFR 73.1200(c), the amount of elemental iron ingested per day may not exceed 5 milligram (mg). A daily elemental iron calculation should be included in module 3.2.P.1 along with all other excipient justification data/information.

B. Inadequate stability

1. Number of batches and length of studies

Three pilot-scale batches or two pilot-scale plus one small-scale batch are recommended, with both accelerated and long-term data provided for each batch covering a period of no less than six months.[40] Intermediate stability studies can also be conducted and included in the ANDA as per FDA's guidance for industry on stability testing.[41] The initiation date for 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 six-month (168 days) minimum hold time. If any of these conditions are not satisfied, FDA will refuse to receive the ANDA.

2. Container orientation

Stability studies for liquid drug products (e.g., ophthalmics, otics, and oral solutions) should be conducted with the container positioned in both the vertical *and* horizontal (or inverted) orientation to maximize contact of the drug product with all components of the container/closure materials, thereby simulating possible storage scenarios. Therefore, if horizontal or inverted

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

[40] Guidance for industry *ANDAs: Stability Testing of Drug Substances and Products.* See also FDA's draft guidance for industry, ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers. Once finalized, that guidance will reflect the Agency's thinking on Stability Testing for ANDAs.

Note: FDA guidance documents are available at http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm. Guidances are updated and revised regularly. To make sure you have the most recent version of a guidance, be sure to check the guidance website

[41] Ibid.

accelerated stability data adhering to the recommendations described in section VI.B.1, above, at minimum, are not submitted for liquid drug products, FDA will refuse to receive the ANDA.

C. Packaging Amount Considerations

To be considered for receipt, ANDAs should package a minimum (threshold) amount of the finished drug product in container/closure systems that are proposed for marketing. The threshold amount that should be packaged is governed by the specific dosage form of the finished drug product that is the subject of the ANDA submission. In the subsections that follow (sections 1, 2, and 3), current thinking is presented related to various dosage forms. However, applicants should always consult existing FDA guidance to be sure they have the most up-to-date information. See for example, FDA's guidance *ANDAs: Stability Testing of Drug Substances and Products*.[42]

1. Solid oral dosage forms

The minimum amount of solid oral dosage forms to be packaged for receipt of an ANDA is 100,000 units in containers/closures proposed for marketing, unless FDA has provided prior permission to package a smaller quantity (see next page for more information on exceptions). Packaged dosage units will be qualified toward the 100,000-minimum if the following three criteria are satisfied:

- Accelerated stability data (as described under section VI.B.1 of this guidance) are provided for each packaging configuration listed in the packaging reconciliation as containing dosage units making up the overall packaged total. However, bracketing or matrixing is permissible. To use either of these approaches, FDA recommends sponsors refer to FDA's stability guidance and the International Conference on Harmonisation (ICH) guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.*

- Adequate container/closure information for any pack size covered by the first bullet point is submitted in the ANDA in section 3.2.P.7. If bracketing or matrixing is used, it is important *not* to omit the container/closure information applicable to those configurations that were excluded from stability studies because of bracketing or matrixing.

- Container and carton labeling (if applicable) 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.

For the dosage units contained in bulk packaging to be counted toward the 100,000 minimum, the second and third bullet points, above, should be satisfied. With regard to the appropriate supportive stability, applicants can submit six months' worth of controlled room temperature stability data (conducted in the proposed bulk package components) in lieu of accelerated data,

[42] FDA has issued a draft guidance titled *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers.* Once finalized, this guidance will represent the Agency's current thinking on this topic.

provided a statement affirming that the bulk-packaged dosage units will be repackaged within six months is included on the bulk package labeling. Otherwise, accelerated stability data as recommended in the first bullet point and/or a clear and explicit description of shipping condition monitoring should be submitted.

As previously noted, there are circumstances in which packaging less than 100,000 solid oral dosage units is considered acceptable:

- The reference product has an orphan drug exemption.
- The reference product is a controlled substance.
- The exhibit batch size is equivalent to the commercial batch size, and a commitment is provided that affirms there will be no scale-up postapproval without a PAS.

In general, the applicant should provide a commitment that the commercial batch size will be equivalent to the exhibit batch size and that there will be no scale-up postapproval without an approved PAS.

Cost of the drug substance alone is not adequate justification for producing and packaging a smaller batch size.

2. Parenteral drug products

No less than 10% of the manufactured batch of drug product should be packaged in each vial size proposed in the ANDA submission, in accordance with the fill volumes established in the RLD label.

3. Transdermal drug products

For transdermal products, the packaged amount recommended for ANDA receipt is 25,000 units per laminate (minimum of three). See section VI.F for more information on manufacturing recommendations for transdermal drug products.

D. Batch Records

Both commercial (blank) and executed (pilot) batch records for the pilot batches that are manufactured to support the ANDA should be submitted, along with any accompanying reconciliation sheets. Furthermore, if the batch records, either commercial or pilot, contain any portion that is printed or written in a foreign language, an accurate and complete English translation of the same is required.[43]

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

E. Method Validation/Verification Reports

It is critical that method validation/verification reports for all analytical methods be provided for both the drug substance (API) and drug product, in sections 3.2.S.4.3 and 3.2.P.5.3 of the ANDA, respectively. That is, for drug products for which a relevant official United States Pharmacopeia (USP) drug product monograph exists, *verification*[44] of the USP analytical procedures should be provided. Verification should also be submitted for methods transferred 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). 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.[45] 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.

F. Special Consideration for Transdermal Patches

ANDAs for transdermal patches should be supported by three lots of drug product manufactured from three distinct laminates, where each lot of laminate is made using different combinations of sources of API/adhesives/backing and/or other critical elements in the patch matrix. If an applicant is seeking approval for at least three different strengths of a particular drug product, each of three strengths can be manufactured from only one laminate batch (rather than three), as long as each strength is cut from a different laminate resulting in three distinct lots of drug product.

G. Scoring and Conditions of Use

1. Scoring configurations that are inconsistent with the RLD's

FDA's guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (*Tablet Scoring*) recommends that the "scoring configuration of generic drug products should be the same as the RLD." This is especially important when considering dosing recommendations. 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), whereas 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 consistent with the dosing recommendations of the RLD. Moreover, 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 the *Tablet Scoring* guidance).

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

[45] 21 CFR 314.50(e)(2)(i).

If the ANDA product (e.g., 10 mg) is manufactured with a score mark, whereas 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. FDA will refuse to receive an ANDA if there are inconsistencies in the scoring configuration between the RLD and test product that have not been reviewed and approved by FDA before submission of the ANDA.

2. Fill volumes for parenteral drug products that differ from the RLD

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.G.2 of this guidance) before it can be proposed in an ANDA submission. Thus, any unapproved alteration of fill volume[46] from that of the RLD drug product will result in FDA refusing to receive the ANDA.

3. Differences in packaging that may be associated with the safe/effective use of the drug product

This particular deficiency is one that will likely be considered on a case-by-case basis. Generally, if the RLD is packaged in such a manner as to ensure its proper administration, the proposed product should be packaged in similar fashion. For example, an RLD package may contain 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

In accordance with 21 CFR 314.94(a)(4), an ANDA's proposed label must meet the conditions of use approved for and described in the RLD label, except for any specific indication/method-of-use carve-outs associated with provided patent statements (see section III.F for further details), exclusivities, or labeling differences permitted pursuant to an approved suitability petition that is cited as an ANDA's basis of submission (see section III.G.2 for further details). Any other proposed condition of use changes would not be acceptable. Examples of these may include, but are not limited to, citing a sprinkle capsule dosage form as a basis of submission but

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

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 refuse to receive an ANDA if any of the sterility assurance validation studies are missing from the submission:

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

FDA will refuse to receive an ANDA if it does not also include the full validation studies at the time of submission, even though summaries of any of the above are included.

For pharmacy bulk packages, it is strongly recommended that the Pharmacy Bulk Package Sterility Assurance table[47] be completed and placed in section 1.14.1.4 of Module 1 of the ANDA. Failure to do so will result in FDA refusing to receive the ANDA.

VII. BIOEQUIVALENCE AND CLINICAL DEFICIENCIES

As a general matter, FDA recommends that ANDA applicants consult the bioequivalence (BE) recommendations webpage on FDA's website for product-specific guidance on conducting recommended in vivo and/or in vitro studies.[48]

[47] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm142112.htm.

A. Failed In Vivo BE Studies

FDA regulations require applicants to submit information on failed BE studies.[49] 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 AUC or the C_{max} parameter. If this occurs for highly variable drug products, the applicant can submit a study using a replicate study design and analyze data using a reference-scaled average (RSA) approach for the failed parameter. However, we encourage applicants to consult the BE recommendations webpage for product-specific study information or to contact the Division of Bioequivalence via Control Correspondence for further guidance if needed.

FDA will refuse to receive an ANDA if only a failed study is submitted.[50]

B. Alternate BE Studies

Submitting a non-recommended in vivo study without adequate justification will result in FDA refusing to receive an ANDA. We encourage applicants to consult the BE recommendations webpage for product-specific study information or to contact the Division of Bioequivalence via Control Correspondence for further guidance if needed.

C. Q/Q 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 the 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 Q/Q same as the RLD.[51] If the drug product is determined not to be Q/Q same as the RLD, FDA will refuse to receive the ANDA based on the determination that the drug product is ineligible for a waiver due to unpermitted formulation differences.

For ophthalmic solutions, it is critical to also complete and include the BE table *Comparative Physicochemical Data of Ophthalmic Solution Drug Products*[52] in Module 2.7 of the ANDA submission to further support the waiver request. This table captures key information/data

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

[49] 21 CFR 314.94(a)(7)(i).

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

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

[52] BE tables can be found on FDA's website at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf.

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 Q/Q same as the RLD.

D. Inadequate Dissolution (In Vitro Studies)

The BE guidances mentioned above 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 bioequivalence data requirement for any additional strengths for which approval is sought.[53] Additionally, the BE guidances may reference dissolution methods available through FDA's website that are specific to a particular drug product.[54] Finally, other suggested types of supplemental dissolution studies include:

- Alcohol dose-dumping
- Half-tablet dissolution for modified-release tablets that are scored
- Any other product-specific dissolution study described in the BE recommendations for the relevant product

For any recommended dissolution study, it is critical that the appropriate comparison data be provided (e.g., the current recommendation is that comparison data for 12 individual test units versus 12 individual RLD units be provided (whole-tablet and, where applicable, half-tablet), with each strength of the test product evaluated against the corresponding strength of the RLD). If there is evidence within the ANDA that the appropriate unit studies were not conducted, or a supplemental study has been omitted, FDA will refuse to receive the ANDA.

E. Miscellaneous Factors

1. Study Information BE Table[55]

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). Of particular importance are the information rows regarding sample storage and long-term storage. Without this information, FDA will refuse to receive the ANDA. Also, receipt of the ANDA is predicated on the following information presented in the Study Information BE 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**.**

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

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

[55] A copy of this BE table can be found on FDA's website at the following location: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf.

- The temperature (°C) reported for long-term stability storage 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

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 based on a Biopharmaceutics Classification System (BCS) Class 1 drug substance.

If any of the data needed to support a waiver request are missing from the ANDA at the time of submission, FDA will refuse to receive the ANDA based on insufficient evidence to support a BCS Class 1 BA/BE waiver request. However, FDA may deny a BA/BE waiver request based on a BCS Class 1 drug substance even with inclusion of these data if there are other factors present that would negatively affect the waiver request. Such a decision will result in FDA refusing to receive the ANDA.

3. Nasal aerosols and sprays

Refer to FDA's guidance for industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* for recommendations pertaining to these types of drug products.

4. DBE and DCR receipt reviews

The Division of Bioequivalence (DBE) or Division of Clinical Review (DCR) will perform a preliminary review of certain ANDAs,[56] with respect to information located in Modules 2.7 and 5. Should any major deficiencies be revealed as a result, FDA will refuse to receive the ANDA, based on their recommendations. Deficiencies are generally associated with, but not limited to, flaws in an in vivo BE or clinical endpoint BE study, or statistical data and/or design.

5. Sameness criterion for devices

Any device used to deliver the drug product should be similar to that used with/for the RLD so as to ensure, at a minimum, safe and proper dose administration. Each of these will be considered on a case-by-case basis by the DCR typically by way of its own receipt review.

6. Missing case report forms

FDA will refuse to receive an ANDA for which a clinical study has been conducted that does not contain copies of all individual case report forms for subjects of the study.

[56] Such as, but not limited to, ANDAs for topical, transdermal, nasal spray, and testosterone drug products.

VIII. 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, Regulatory Support Branch Chief, 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*).