Good ANDA Submission Practices

Guidance for Industry

DRAFT GUIDANCE

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

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Generics

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance is intended to assist applicants preparing to submit to FDA abbreviated new drug applications (ANDAs). This guidance highlights common, recurring deficiencies that may lead to a delay in the approval of an ANDA. It also makes recommendations to applicants on how to avoid these deficiencies with the goal of minimizing the number of review cycles necessary for approval.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Generic Drug User Fee Amendments (GDUFA I)[2] was signed into law on July 9, 2012. Based on an agreement negotiated by FDA and industry,[3] GDUFA I was designed to increase the likelihood that American consumers have timely access to low cost, safe, effective, and high-quality generic drugs and to improve the predictability of the ANDA review process. Under GDUFA I, FDA constructed a modern generic drug program that resulted in a significant and sustained increase in communications between FDA and industry, ANDA regulatory actions, and ANDA approvals.

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

[2] Public Law 112-144.

[3] This agreement is reflected in the Generic Drug User Fee Act Program Performance Goals and Procedures letter, available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

Despite the advances made under GDUFA I, approximately half of all ANDAs with GDUFA review goals required three or more review cycles to reach approval or tentative approval.[4] Multiple review cycles are highly inefficient, require significant resources from applicants and FDA, and delay timely patient access to more affordable generic drugs.

Accordingly, after receiving public input, FDA and industry negotiated a revised agreement, reflected in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 letter (GDUFA II Commitment Letter),[5] and GDUFA was reauthorized (GDUFA II)[6] on August 18, 2017. GDUFA II includes important program enhancements that are designed to improve the predictability and transparency of ANDA assessments[7] and to minimize the number of review cycles necessary for approval. These program enhancements are intended to foster the development of high-quality submissions, ensure the timely resolution of filing reconsideration requests, promote the correction of deficiencies in the current review cycle, and support the development of high-quality resubmissions.

This guidance has been developed as part of FDA's "Drug Competition Action Plan," which, in coordination with the GDUFA[8] program and other FDA activities, is expected to increase competition in the market for prescription drugs, facilitate entry of high-quality and affordable generic drugs, and improve public health. In conjunction with this guidance, FDA is issuing a *Good ANDA Assessment Practices* Manual of Policies and Procedures, which establishes good ANDA assessment practices for the Office of Generic Drugs and the Office of Pharmaceutical Quality to increase their operational efficiency and effectiveness. This guidance and the Manual of Policies and Procedures are intended to build upon the success of the GDUFA program and to help reduce the number of review cycles for an ANDA to attain approval.

This guidance describes common, recurring deficiencies identified during FDA's substantive assessment of an ANDA with respect to (1) patents and exclusivities, (2) labeling, (3) product quality, and (4) bioequivalence (BE).[9] This guidance also provides recommendations to

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[4] A *tentative approval* is a notification from FDA that an ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act) but cannot be approved until the expiration of a period of patent and/or exclusivity protection; until the expiration of a 30-month stay of approval; or, because of a court order in patent litigation, before a specific date. See 21 CFR 314.3(b) and 314.105(d).

[5] The GDUFA II Commitment Letter is available at https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

[6] Pub. Law 115-52.

[7] Going forward, the Office of Generic Drugs and the Office of Pharmaceutical Quality will generally use the term *assessment* in place of *review*. *Assessment* means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

[8] In this guidance, *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

[9] The deficiencies and accompanying recommendations in this guidance are organized by FDA's review disciplines and generally follow the same order as the electronic common technical document. Information on the electronic common technical document format is available at

applicants on how to avoid these deficiencies. FDA comprehensively communicates deficiencies identified during a substantive review[10] of an ANDA in complete response letters.[11] Applicants may address the deficiencies identified by FDA by submitting an amendment to their application.[12]

This guidance does not include a comprehensive list of all of the deficiencies identified during ANDA assessment. In addition, it is each applicant's responsibility to submit a high-quality, complete application that FDA can approve in the first review cycle. FDA strongly encourages applicants to review FDA regulations and all applicable guidances for industry[13] to understand FDA's current thinking on each topic.

III. PATENT AND EXCLUSIVITY DEFICIENCIES

The timing of ANDA approval depends on, among other things, the patent and exclusivity protections for the reference listed drug (RLD) on which the applicant relies in seeking approval. An applicant must provide, in its ANDA, information related to any patents listed for the RLD in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[14] In particular, an ANDA applicant generally must submit to FDA one of four specified certifications regarding the patents for the RLD under section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(2)(A)(vii)).

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https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm153574.htm.

[10] Prior to a substantive review, FDA communicates with ANDA applicants that deficiencies were identified during the filing review of their submitted application either through a notification to the applicants (if fewer than 10 minor deficiencies were identified) or in a refuse-to-receive decision. Please see FDA's guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* for additional information on how FDA conveys to applicants deficiencies identified during the filing review and for a non-exhaustive list of deficiencies that may or will lead to a refuse-to-receive determination by FDA. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] It should be noted that the Agency also issues *discipline review letters*, which are defined in the GDUFA II Commitment Letter as "a letter used to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review." In addition, *information requests* are communications "sent to an applicant during a review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review." GDUFA II Commitment Letter.

[12] For information on amendment classifications and categories, please see FDA's draft guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA*. When final, this guidance will represent FDA's current thinking on this topic.

[13] Applicants may review the Center for Drug Evaluation and Research's Manuals of Policies and Procedures, which are Federal directives and documentation of internal policies and procedures that are made available to the public at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[14] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/.

If the Orange Book does not list a patent for the RLD that, in the opinion of the ANDA applicant and to the best of its knowledge, claims the RLD or that claims a use of such listed drug for which the applicant is seeking approval,[15] the ANDA applicant must certify that such patent information has not been submitted by the new drug application (NDA) holder for listing in the Orange Book (a paragraph I certification).[16]

With respect to each patent listed in the Orange Book for the RLD, the applicant's patent certification must state one of the following:

- That such patent has expired (a paragraph II certification)
- The date on which such patent will expire (a paragraph III certification)
- That such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification)[17]

On or after the date on which FDA has received an ANDA for review,[18] an applicant that has submitted a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner notice of its paragraph IV certification, including a description of the legal and factual basis for the ANDA applicant's assertion that the patent is invalid, unenforceable, or will not be infringed.[19] If a patent is listed at the time an original ANDA is submitted and, in response to a notice of a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the latter of the date of receipt of the notice by any owner of the patent or the NDA holder or such shorter or longer time as the court might order.[20]

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[15] If, in the opinion of the applicant and to the best of its knowledge, there are no patents claiming the RLD that are, or should have been, listed in the Orange Book, the applicant must include in the ANDA a certification in the following form:

> In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this ANDA or that claim a use of the listed drug.

21 CFR 314.94(a)(12)(ii).

[16] 21 CFR 314.94(a)(12)(i)(A).

[17] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[18] 21 CFR 314.101(b).

[19] Section 505(j)(2)(B) of the FD&C Act. See section III.C of this guidance for more information on notice of a paragraph IV certification.

[20] Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i). Note that, in some circumstances, the period of the stay may be 7½ years after the date of approval of the RLD rather than 30 months from the date of the notice. See 21 CFR 314.107(b)(3).

The statute provides an incentive and a reward to ANDA applicants that expose themselves to the risk of patent litigation; the statute does so by granting a 180-day period of exclusivity *vis-à-vis* certain other ANDA applicants to the applicant that is first to file a substantially complete ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification to a listed patent for the RLD (First Applicant).

A. Documentation and Notification of a Legal Action Filing

Applicants that file a paragraph IV patent certification[21] must subsequently amend their ANDA to provide documentation to FDA regarding (1) their notice of certification that was sent to the patent owner(s) and NDA holder and (2) any legal action that has been taken against the applicant under that paragraph IV notice.[22] Specifically, applicants must amend their ANDAs to provide documentation:

- That their notice of a paragraph IV certification was sent on a date that complies with the time frame provided in the regulations for sending this notice

- Of the date that this notice was received by the patent owner(s) and NDA holder

This documentation must be submitted to the ANDA within 30 days after the last date on which the notice was received by the patent owner(s) and NDA holder.[23]

Applicants also must submit documentation "within 14 days of the filing of any legal action filed within 45 days of receipt of the notice of paragraph IV certification."[24] Any submission indicating that legal action was initiated against the applicant should include a complete copy of the civil action. If a legal action was not filed by either the patent owner(s) or the exclusive patent licensee within 45 days of its or their receipt of the notice of the paragraph IV certification, applicants should submit an amendment to their ANDA immediately after the 45-day period elapses stating that no legal action was taken by the patent owner(s) and exclusive patent licensee.

However, applicants have often not submitted to FDA written documentation in a timely fashion:

- Of their timely sending notice of a paragraph IV certification and of the dates that the patent owner(s) and NDA holder received notice of a paragraph IV certification

- That the patent owner(s) and/or exclusive patent licensee have filed a legal action

[21] Paragraph IV patent certifications are described in 21 CFR 314.94(a)(12)(i)(A)(4).

[22] 21 CFR 314.95(e) and 21 CFR 314.107(f)(2).

[23] 21 CFR 314.95(e).

[24] 21 CFR 314.107(f)(2).

- That includes a statement that the patent owner(s) and exclusive patent licensee did not file a legal action within 45 days of receipt of the notice of the paragraph IV certification

Applications that lack all required patent/legal documentation or those that do not respond in a timely manner to a request for information may receive a complete response letter.

B. Resolution or Appeal of a Legal Action

If an applicant submitted a paragraph IV certification, litigation is brought against that applicant, and the court enters a decision in favor of the patent owner(s) and/or NDA holder finding the patent valid and infringed, that applicant must notify FDA of the court's decision within 14 days.[25]

If the applicant appeals the court decision within the time permitted to appeal, the applicant similarly must notify the Agency within 14 days.[26] If the applicant does not appeal the court's decision, the applicant must submit an amendment to change its paragraph IV certification to a paragraph III certification; this amendment must certify that the patent will expire on a specific date, or, if applicable, that the applicant is no longer seeking approval for a method of use claimed by the patent.[27]

Similarly, if the litigation results in a district court decision, a court of appeals mandate, or a settlement order "signed and entered by the . . . district court or court of appeals"[28] that specifies that the patent in question is invalid, unenforceable, or not infringed, the ANDA applicant must submit to the ANDA: a copy of the court judgment, written notification of whether or not there is an appeal within the time for appeal, and/or a copy of any order by the court terminating the 30-month or 7½-year stay of approval. If the litigation is resolved with written consent to approval of the ANDA from the patent owner or the exclusive patent licensee, a copy of that written consent must be submitted.[29]

Timely notification that the court has issued a decision or that the court's decision has been appealed and, when applicable, submission of a timely amendment of the patent certification are necessary for FDA to determine the timing of an ANDA's approval.[30]

C. Notice of a Paragraph IV Certification

An applicant may not provide notice of a paragraph IV certification that was submitted in an original ANDA to the patent owner(s) and NDA holder until that applicant receives a paragraph

[25] 21 CFR 314.107(e)(2).

[26] Id.

[27] 21 CFR 314.94(a)(12)(viii)(A).

[28] 21 CFR 314.107(e)(1).

[29] Id.

[30] See 21 CFR 314.107(b)(3).

IV acknowledgement letter from FDA.[31] Similarly, if an applicant submits an amendment to its ANDA that includes a paragraph IV certification and FDA has not yet informed the applicant that the ANDA was received for review, that applicant must wait to provide notice of its paragraph IV certification to the patent owner(s) and NDA holder until after the applicant has received a formal acknowledgement letter from FDA that the ANDA was received for review.[32] The applicant must send notice of the paragraph IV certification contained in the amendment on or after the date it receives acknowledgement from FDA that the ANDA was received for review; this notice must be sent no later than 20 days after the date of acknowledgement from FDA.[33] If FDA has notified the applicant that it has received the ANDA and the ANDA applicant makes a subsequent amendment that requires a paragraph IV certification (see section III.E of this guidance), the notice must be sent at the same time that the amendment is submitted.[34]

Notice of a paragraph IV certification that was submitted in an original ANDA or in an amendment before FDA has received the ANDA for review is invalid.[35]

D. New or Revised Information in the Orange Book

If a new patent is listed for the RLD after an applicant submits an ANDA or information related to a patent listed for the RLD is revised[36] after an applicant submits an ANDA, that applicant must address these changes to the patent listing for the RLD by submitting an appropriate patent certification or statement for each patent.[37] However, applicants have either:

- Provided "serial submissions" of amendments with paragraph IV certifications and sent multiple notices of paragraph IV certifications in anticipation of a newly issued patent being listed in the Orange Book, which is not permissible under FDA's regulations[38] or

- Failed to submit an appropriate patent certification or statement for each newly listed patent or revised patent information

[31] 21 CFR 314.95(b)(2). An *ANDA acknowledgement letter* is the letter that FDA sends when it has determined that the ANDA can be received for review.

[32] 21 CFR 314.95(b)(1) and 21 CFR 314.95(d)(2).

[33] Id.

[34] 21 CFR 314.95(d)(1). Similarly, if the ANDA applicant submits a supplement to an approved ANDA and that supplement requires a paragraph IV certification, its notice must be sent at the same time that the supplement is submitted to FDA. Id.

[35] 21 CFR 314.95(d)(2).

[36] For example, if a new use code is added to the Orange Book for a currently listed patent for the RLD, the applicant must provide an updated paragraph IV certification or statement to FDA to address the newly listed use code.

[37] 21 CFR 314.94(a)(12)(i) and 21 CFR 314.94(a)(12)(iii).

[38] 81 FR 69610 (Oct. 6, 2016).

An applicant must not submit a paragraph IV certification to the ANDA for a newly listed patent "earlier than the first working day after the day the patent is published in [the Orange Book]."[39] FDA recommends that applicants monitor the Orange Book and address newly listed patents and revised patents in a timely manner to avoid unnecessary delays to ANDA approval.

In addition, ANDA applicants have failed to address new exclusivities for the RLD, which may result in a delay in FDA's approval of an application. FDA recommends that applicants monitor the Orange Book and address exclusivities in a timely manner to avoid unnecessary delays to ANDA approval.

E. Amendments to an Unapproved ANDA

An amendment to an unapproved ANDA must contain either:

- "an appropriate patent certification or statement" or "a recertification for a previously submitted paragraph IV certification" if approval is sought for (1) a new indication or other condition of use, (2) a new strength, (3) an other-than-minor change in product formulation, or (4) a change to the physical form or crystalline structure of the active ingredient or

- A verification statement that states that the amendment does not contain one of the those four types of changes[40]

Applicants, however, have failed to provide either:

- An appropriate patent certification or statement (or recertification) or

- The required verification statement in their amendment to an unapproved ANDA when that amendment did not contain one of the four types of changes described above

To address this requirement, FDA recommends that applicants provide an appropriate patent certification or statement (or recertification) or, if applicable, include a verification statement (stating, e.g., "This amendment does not contain one of the proposed changes under 21 CFR 314.96(d)(1)") in the cover letter of their amendment to an unapproved ANDA.

F. Notification of Commercial Marketing

The 180-day exclusivity period commences upon any First Applicant's commercial marketing of its drug product (including the commercial marketing by the First Applicant of the RLD or an authorized generic).[41] Under either scenario, a First Applicant must submit correspondence to its

[39] 21 CFR 314.94(a)(12)(viii)(C)(1)(ii).

[40] 21 CFR 314.96(d).

[41] Section 505(j)(5)(B)(iv)(II)(aa) of the FD&C Act and 21 CFR 314.3.

ANDA notifying FDA "within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug."[42] If a First Applicant commences marketing of its approved drug product (or the RLD or an authorized generic) and does not notify FDA within this time frame, "the date of first commercial marketing will be deemed [by FDA] to be the date of the drug product's approval."[43]

To address this requirement and avoid losing the benefit of part of the 180-day exclusivity period, FDA recommends that applicants submit the required notification of commercial marketing to FDA within the 30-day time frame.

IV. LABELING DEFICIENCIES

A. Draft Container Labels and Carton Labeling

Generally, an ANDA's labeling must be the same as its RLD's labeling.[44] There are, however, limited exceptions, including an exception for differences caused by the ANDA and RLD being produced or distributed by different manufacturers.[45] These differences between the ANDA's labeling and the RLD's labeling may include differences (e.g., in the expiration date or in the formulation) that were made to comply with current FDA labeling guidelines or other guidance documents.[46] FDA reviews ANDA container labels and carton labeling to make certain that differences from the RLD's labeling do not raise safety concerns.[47] During this review, FDA considers formatting factors such as the font size, style, and color of the required text; the labeling's identification of different product strengths; and other methods used to ensure that the required information is presented with adequate prominence.[48] Applicants sometimes submit draft container labels and carton labeling that do not accurately represent the formatting factors that will be used with the final printed labels and labeling, which makes it challenging for FDA to confirm that the final printed labels and labeling will be adequate.

To ensure that container labels and carton labeling are adequately evaluated for potential deficiencies, FDA recommends that the draft version of container labels and carton labeling "reflect the content as well as an accurate representation of the layout, text size and style, color, and other formatting factors that will be used with the [final printed labeling]."[49] In addition, as explained in the FDA guidance for industry *Acceptability of Draft Labeling to Support ANDA*

[42] 21 CFR 314.107(c)(2).

[43] Id.

[44] Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

[45] Id.

[46] 21 CFR 314.94(a)(8)(iv).

[47] FDA guidance for industry *Acceptability of Draft Labeling to Support ANDA Approval*, at 3.

[48] Id.

[49] Id.

Approval, applicants that "receive approval based on draft labeling are responsible for ensuring the content of the [final printed labeling] is identical to the approved labeling."[50] Failure to receive this approval may render the product misbranded and an unapproved new drug.[51]

B. Color Differentiation for Container Labels and Carton Labeling

Factors such as the color and format of container labels and carton labeling can help differentiate multiple strengths within the same product line as well as multiple products within a company's product line, thereby reducing the likelihood of medication errors. Applicants, however, have submitted container labels and carton labeling for products that lack an adequate differentiation between various strengths and from other drug products.

FDA recommends that applicants ensure that the color and/or format of container labels and carton labeling is adequately differentiated from other pending and approved products in their product line. As noted in FDA's draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, when applying color, applicants "should ensure that the text highlighted by the color has adequate color contrast against the background color."[52] In addition, "[c]olor differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme."[53]

C. Labeling Format

FDA requests that labeling be submitted in Microsoft Word, structured product labeling, and text-based portable document format (PDF) files.[54] Labeling submitted in PDF format should be text based and not scanned to enable the use of search and compare functions. Applicants should also ensure consistency in the content between their different formats (i.e., in their Microsoft Word, structured product labeling, and text-based PDF files). If the text of the labeling differs in any of the three requested formats, applicants may be asked to resubmit their labeling for review.

D. Parenteral Drug Products

1. Package Type

Labeling indicating the package type (i.e., single-dose, multiple-dose, or single-patient-use) for ANDAs of parenteral drug products must be the same as the labeling indicating the RLD's

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[50] Id.

[51] Id.

[52] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 8. When final, this guidance will represent FDA's current thinking on this topic.

[53] Id.

[54] FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*. When final, this guidance will represent FDA's current thinking on this topic.

package type.[55] For example, if the RLD is appropriately labeled and packaged in a single-dose vial, the ANDA should also be labeled and packaged in a single-dose vial.

Applicants have proposed package types for parenteral drug products that differ from those approved for the RLD (e.g., an applicant proposed a single-dose vial when the RLD is packaged in a multi-dose vial), which resulted in a deficiency.

2. Product Strength

A parenteral drug product's strength is critically important information that should be clearly displayed and correctly expressed on the container label to avoid dosing errors, among other reasons. Overdoses have occurred with small-volume parenterals because of end-user failure to determine the total amount of the drug product in the container. As described in FDA's draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*,

> [i]n most cases, the user noticed the concentration (e.g., 10 [milligrams] (mg)/[milliliter] (mL)) but failed to see the net quantity (e.g., 10 mL), which often appears in a different location on the container label. This confusion has led to administration of the entire contents of the container, when only a portion of the total volume was needed.[56]

To avoid confusion, "the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per milliliter enclosed by parentheses."[57] The following format is acceptable:[58]

500 mg/10 mL
(50 mg/mL)

3. Ferrules and Cap Overseals

The ferrules and cap overseals of injectable drug products should clearly and concisely convey cautionary statements that will help prevent imminent, life-threatening situations.[59] In particular, FDA recommends that the text on ferrules and cap overseals either "be limited to important safety messages critical for the prevention of imminent, life-threatening situations" or remain blank.[60] An example of an acceptable cautionary statement is "Warning-Paralyzing Agent."

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[55] Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

[56] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 11.

[57] Id.

[58] Id.

[59] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.* See also U.S. Pharmacopeia (USP) General Chapter <7>.

[60] FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 17.

Applicants should refer to the FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* for further information.

Applicants have submitted proposed labeling for ANDAs covering drug products with integrated ferrules and cap overseals that does not convey safety information critical for the prevention of imminent, life-threatening situations. In other instances, applicants have proposed labeling containing information on ferrules and cap overseals that is not recommended for certain drug products (e.g., some ferrules and cap overseals of injectable drug products have displayed lot numbers, logos, or product names). Applicants should consider the appropriateness of including or excluding such information for drug products with integrated ferrules or cap overseals because this inclusion or exclusion may impact the approvability of a particular application.

In addition, FDA recommends that applicants state in Module 3.2.P.7 of their ANDA submission whether text appears on the ferrule and cap overseal and, if so, what the text is. Applicants should also indicate the color of the ferrule and cap overseal to ensure that the color black, which is to be used only with potassium chloride injectable products, is not used for other drug products.

V. PRODUCT QUALITY DEFICIENCIES

A. Drug Substance

Applicants are required to submit data and information in their ANDAs about the drug substance(s) in their proposed drug products.[61] To satisfy this requirement, FDA regulations permit applicants either to provide this information directly in their ANDA or to reference a drug master file (DMF) in their ANDA.[62] Specifically, in their ANDA, applicants may choose to either (1) include all sections of Module 3.2.S.2 or (2) reference a DMF, which should contain the same information that would have been provided by the applicant in Module 3.2.S.2.

The recommendations in this section apply both to applicants that include all sections of Module 3.2.S.2 in their ANDAs and to DMF holders that submit DMFs to FDA.

The DMF holder is required to notify each person authorized to reference the DMF of any additions, changes, or deletions to any information contained in the DMF.[63] Changes made to a DMF referenced in an ANDA that may impact the safety, efficacy, quality, or substitutability of the drug product (e.g., new facilities added by the DMF holder that need to be addressed by the applicant in an amendment to the ANDA) may be considered *unsolicited amendments* to the

[61] 21 CFR 314.94(a)(5).

[62] 21 CFR 314.420(b).

[63] 21 CFR 314.420(c).

ANDA and therefore may extend existing GDUFA review goals or create new review goals.[64] It is important for applicants to be aware of when amendments will be submitted to the DMF because these amendments may affect the adequacy of the DMF to support approval of the ANDA.

1. Active Pharmaceutical Ingredient Starting Material

In Module 3.2.S.2, DMF holders[65] should include information on the control of materials used in the manufacture of the drug substance and provide a justification for the starting material selection for the process. Often, the designated starting material is a late-stage intermediate, and DMF holders fail to include:

- The route of synthesis to the proposed starting material to support the starting material specification (i.e., the impurity control)
- A discussion on the fate and purge of the potential impurities arising from the starting material manufacturing process
- The carry-over studies of reagents/solvents into the final active pharmaceutical ingredient (API)
- A demonstration of the suitability of analytical methods used to detect impurities in the starting material

Without this information, FDA cannot assess the starting material selection and its impact on both the manufacturing process and the final drug substance quality.

FDA recommends that DMF holders provide sufficient information, in Module 3.2.S.2, on their API starting material, including the information specified in the bulleted list in this section. For recommendations on the justification and selection of starting materials, DMF holders should review the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidances for industry *Q11 Development and Manufacture of Drug Substances* and *Q11 Development and Manufacture of Drug Substances Questions and Answers*.[66]

2. API Manufacturing Process

[64] FDA draft guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA*.

[65] As noted above, the recommendations in section V.A of this guidance also apply to applicants that include all sections of Module 3.2.S.2 in their application but do not reference a DMF.

[66] ICH guidances for industry can be found on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

DMF holders should fully describe, in their DMF, their API manufacturing process, but they have commonly failed to include the following information as part of a complete description of the API manufacturing process:

- A detailed synthetic scheme
- The molar ratios of starting materials/reagents
- The reaction conditions (e.g., time and temperatures)
- A flow chart of the manufacturing process
- The batch size for each step (i.e., input/output of materials)
- The batch blending or mixing operations
- The recovered solvents, reprocessing, and reworking
- Documentation of the consistent manufacture of the claimed polymorphic form

FDA recommends that DMF holders provide complete information in Module 3.2.S.2.2 on their API manufacturing process, including the information in the bulleted list above. DMF holders should include a flow chart for every stage, and if the API is synthetic or semisynthetic, they should provide a complete synthetic scheme from the appropriately supported starting materials.[67]

3. Impurities

a. API characterization information

DMF holders should include characterization information for the API, including information on all potential impurities. In some cases, however, DMF holders have failed to provide information on the identification and purge of impurities (i.e., process impurities and degradants), including those with mutagenic potential.[68]

DMF holders should include a discussion of impurities in Modules 3.2.S.2 and 3.2.S.3. For information on the limits for potentially genotoxic impurities, FDA recommends that DMF holders refer to the ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (ICH M7). Applicants should carefully assess and consider all of the control options outlined in ICH M7.

b. Safety assessment of mutagenic potential for actual and potential impurities

The impurity profile of a proposed generic drug should not pose a greater mutagenic risk than the RLD. DMF holders should provide an assessment of the actual and potential mutagenic

[67] FDA guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*, at 11, and ICH guidances for industry *Q11 Development and Manufacture of Drug Substances* and *Q11 Development and Manufacture of Drug Substances Questions and Answers*.

[68] See the ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

impurities resulting from synthesis or degradation of the drug substance and discuss the corresponding control strategy as outlined in ICH M7. The bulleted list below describes (1) information DMF holders have commonly failed to include about their evaluation of actual and potential genotoxic impurities, and when appropriate, (2) FDA's recommendations on conducting these evaluations:

- An assessment of potential and actual impurities with a risk assessment and a follow-up evaluation of mutagenicity at the time of the DMF submission. For impurities that require an evaluation of the mutagenic potential, a hazard assessment should initially include conducting either (1) literature and database searches on the carcinogenicity and bacterial mutagenicity potential or (2) Quantitative Structure-Activity Relationship ((Q)SAR) and Structure Activity Relationship studies. Failure to include a full evaluation of potential mutagenic risk at the time of the DMF submission can disrupt the review process and prevent the timely review of the ANDA.

- Appropriate spike/purge or purging factor studies performed in a manner representative of the commercial process, with a corresponding validated and fit-for-purpose analytical method to support Options 3-4 described in ICH M7.[69]

- A (Q)SAR evaluation that includes both an expert-based and a statistical-based model for bacterial mutagenicity prediction. (Applicants have supplied a single model or used models without submitting sufficient information on their validation.) Applicants should submit full study reports for *in silico* predictions.[70]

- An appropriately conducted in vitro bacterial reverse mutation assay to address a positive prediction by a (Q)SAR analysis. For these assays, applicants should (1) test neat impurities; (2) test concentrations up to 5,000 micrograms/plate, unless limited by precipitation or cytotoxicity; and (3) adequately document that an impurity is unstable or difficult to synthesize and provide a scientific justification of their due diligence to synthesize the impurity.[71]

4. Specifications for Isolated Intermediates

DMF holders should justify their specification for isolated intermediates so that FDA reviewers can understand why the DMF holder set that specification. The justification should focus on

[69] As described in ICH M7: (1) under Option 3, the DMF holder controls potentially genotoxic impurities upstream at higher than the threshold of toxicological concern with spike/purge data to less than 30% of that threshold and (2) under Option 4, the DMF holder does not use a control based on high chemical reactivity, solubility, and proven process-purging capability.

[70] For additional information, see Amberg, A, L Beilke, and J Bercu, et al., 2016, Principles and Procedures for Implementation of ICH M7 Recommended (Q)SAR Analyses, Regul Toxicol Pharmacol, 77:13–24; Barber, C, A Amberg, and L Custer, et al., 2015, Establishing Best Practise in the Application of Expert Review of Mutagenicity Under ICH M7, Regul Toxicol Pharmacol, 73:367–377.

[71] ICH M7; ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*; and *OECD Guidelines for Testing of Chemicals, Section 4: Health Effects*, available at http://www.oecd-ilibrary.org/environment/test-no-471-bacterial-reverse-mutation-test_9789264071247-en.

how the impurity specifications for the intermediates were chosen, particularly if that was the only point in the process where a particular impurity was controlled. If the DMF holder did not isolate an intermediate, it should explain why that was a reasonable choice. FDA also recommends that DMF holders review the FDA guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*, which makes recommendations about the information on intermediates that should be included in a DMF.

5. Tests for Certain Critical Quality Attributes

Tests for Critical Quality Attributes (CQAs) should be included in the drug substance specifications, but DMF holders have failed to demonstrate a clear rationale that includes CQAs when establishing drug substance specifications. DMF holders should follow the ICH limits or justify their proposed limits for the existing tests (i.e., the limits for impurities, including the residual solvents).

FDA recommends that DMF holders set appropriate limits based on ICH guidances for industry[72] and include a complete justification and the necessary information for qualification of the limits when they exceed ICH recommendations, as explained in the FDA guidance for industry *ANDAs: Impurities in Drug Substances*.

B. Drug Product

1. Establishing Critical Quality Attributes

CQAs describe product characteristics that are chosen to demonstrate that any given drug product is of sufficient quality to ensure that drug product's safety and effectiveness. Failure to establish appropriate CQAs of the proposed generic drug product (including meaningful ranges or limits) may lead to a determination that the ANDA cannot be approved.

FDA recommends that applicants evaluate their drug products using (1) the general and dosage form-specific recommendations for the relevant characteristics and testing described in the ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and (2) the recommendations on quality target product profiles and CQAs in the ICH guidance for industry *Q8(R2) Pharmaceutical Development*. In their ANDAs, applicants should include information developed from their use of these two ICH guidances for industry to support their selection of and rationale for CQAs.

2. Impurities: Identification, Control, and Qualification

a. Identifying and controlling impurities

[72] ICH guidances for industry *Q3A Impurities in New Drug Substances, Q3C Impurities: Residual Solvents, Q3D Elemental Impurities*, and ICH M7.

Applicants' identification and control of impurities are important aspects in ensuring the safety of the drug product. When applicants have used inadequate protocols for generating and identifying impurities and have failed to provide an appropriate rationale for their acceptance criteria for impurities, FDA has refused to approve their ANDAs.

To develop acceptance criteria for impurities in generic drug products, FDA recommends that applicants refer to the FDA guidance for industry *ANDAs: Impurities in Drug Products*; the FDA draft guidance for industry *Elemental Impurities in Drug Products*;[73] the ICH guidances for industry *Q3B(R2) Impurities in New Drug Products, Q3C Impurities: Residual Solvents, Q3D Elemental Impurities;* and ICH M7.

b. Safety qualification of impurities in drug substances or drug products that exceed relevant qualification thresholds

Generic drug formulations are expected to have the same safety profile as the RLD.[74] Applicants may qualify drug substance degradants or drug product impurities either by using a comparative impurity analysis with the RLD[75] or by submitting a safety justification for these impurities if they exceed the relevant qualification thresholds.[76] A safety justification for impurities that exceeds the relevant qualification thresholds should include an assessment of both genetic toxicology and general toxicity (14- to 90-day) in a single species. Below is information that applicants should include in their application but have commonly failed to include:

- Applicants should provide general toxicity information to qualify their impurity. Applicants have submitted (Q)SAR evaluations to predict general toxicity, but their *in silico* predictions have not been validated for the endpoints of a general toxicity study. To address this, applicants should submit either safety information such as a repeat-dose general toxicology study or published literature to characterize the safety of the impurity for the intended route of administration.

- When providing a justification that an impurity is a metabolite, applicants should provide qualitative and quantitative information to support this justification. Applicants have submitted qualitative information that an impurity is a metabolite but failed to provide quantitative data to demonstrate the relevant systemic exposure to the proposed impurity level. Applicants should provide quantitative information (e.g., plasma levels of the metabolite in animals and humans at the maximum daily dose or the exposure levels in animals that equals or exceeds the proposed clinical exposure levels) to demonstrate that the systemic exposure is at such a level to qualify the proposed level of the impurity.

[73] When final, this guidance will represent FDA's current thinking on this topic.

[74] 21 CFR 314.3(a).

[75] FDA guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

[76] ICH guidances for industry *Q3A Impurities in New Drug Substances* and *Q3B(R2) Impurities in New Drug Products*.

- Applicants should provide full articles of the publications that are cited in their justification to facilitate a complete review of their ANDA.

Applicants should submit nonclinical information to Module 4 of their submission. Applicants that submit a justification for the safety of their impurities should also include references and hyperlinks between related topics in the quality module (Module 3) and the nonclinical safety module (Module 4).

3. Inactive Ingredients

a. Justification by reference to the Inactive Ingredient Database

Unless otherwise specified in 21 CFR 314.94(a)(9)(ii), applicants must identify and characterize the inactive ingredients in their proposed drug product and provide information demonstrating that these inactive ingredients do not affect the safety or efficacy of that product. The quantity of an inactive ingredient in a given formulation should be based on a prior determination by FDA of the safety of that inactive ingredient in an FDA-approved product. However, applicants have sought approval for formulations that contain amounts of inactive ingredients at levels higher than the maximums listed in the Agency's Inactive Ingredient Database (IID)[77] without providing a justification for exceeding those maximum levels.

FDA recommends that applicants (1) refer to the IID to determine the previously approved level of an inactive ingredient in a given drug product and not exceed that level or (2) submit controlled correspondence to the Agency requesting information on whether the use of a particular inactive ingredient is acceptable in an ANDA if it is higher than the maximum listed in the IID.[78] Applicants should provide an adequate justification to the Agency regarding the safety of that inactive ingredient if the amount exceeds the maximum level indicated in the IID for the proposed route of administration (see subsection (b) immediately below).

b. Justification of the safety of inactive ingredients in generic drug products that exceed the maximum level in the IID

A generic drug formulation should include inactive ingredients that have a well-defined safety profile for the proposed context of use (i.e., dose, route of administration, duration of use, and patient population) and maintain a similar safety profile as the RLD. Applicants, however, should provide a safety justification for inactive ingredients that exceed FDA-approved levels for the route of administration. Below is information that applicants should include in a safety justification for inactive ingredients that exceed FDA-approved levels:

- Applicants should provide a justification to demonstrate that an inactive ingredient is safe for the proposed context of use (i.e., dose, route of administration, duration of use, and

[77] FDA's IID is available at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

[78] See FDA's draft guidance for industry *Controlled Correspondence Related to Generic Drug Development*. When final, this guidance will represent FDA's current thinking on this topic.

patient population). Applicants have submitted justifications that fail to address context-specific information that is necessary to evaluate the safety of a proposed dose, route of administration, or duration of use for an inactive ingredient in a specific patient population. Additionally, applicants have proposed inactive ingredients without a well-established safety profile, which has led to FDA's refusal to approve the ANDA. Generic drug formulations do not undergo clinical safety studies during ANDA development, so inactive ingredients without an established safety profile should not be included in a generic drug formulation.

- Applicants should provide a complete account of the composition of complex mixtures of inactive ingredients (e.g., flavors and fragrances) — including the mixtures' individual components and quantities — in either the ANDA or by referencing a DMF. Applicants should identify each component of a complex mixture, including its synonyms, the Chemical Abstracts Service Number, and any applicable citations to the Code of Federal Regulations that are relevant to its proposed use. In addition, applicants should include safety information for each component, including a history of the component's prior use and safety profile (i.e., the component's general safety and genetic toxicity).

- Applicants should provide a justification supporting the safety of a proposed inactive ingredient grade when relying on the established safety information from a similar grade of inactive ingredient.[79] The grades of an inactive ingredient may have different manufacturing processes, impurity profiles, and chemical or physical characteristics. Because these factors may result in different safety profiles for each grade of inactive ingredient, FDA needs sufficient details to identify the proposed inactive ingredient grade and to determine whether similarities or differences between grades may affect safety.

4. Validating Analytical Methods

Analytical methods that applicants use for the characterization or analysis of drug products should be validated by the applicant to determine if these methods are suitable for such use. However, applicants have failed to appropriately validate their analytical methods, which has led to incorrect results and incorrect conclusions about the drug product quality because the analytical methods were not specific, accurate, or precise. This failure has contributed to FDA's refusal to approve the ANDAs.

FDA recommends that applicants (1) refer to the ICH guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* to identify the appropriate validation of the analytical methods used in their drug product analysis and (2) provide method validation reports in their application.

C. In Vitro Dissolution (Biopharmaceutics)

[79] FDA guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

1. Development and Validation of an In-House Dissolution Testing Method When Dissolution Testing Cannot Be Standardized

It is critical that applicants submit a complete method development and validation report when an in-house dissolution testing method is used. Below is information that should be included in the dissolution method development and validation report but applicants have commonly omitted:

- Solubility data for the drug substance over the physiologic pH range
- A detailed description of both the dissolution test being proposed for the evaluation of the product and the developmental parameters used to select the proposed dissolution method
- Data (with appropriate statistics) to support the discriminating ability of the selected dissolution method related to the critical material attributes and critical process parameters
- Complete dissolution data (i.e., individual (n=12), mean, range, and percent relative standard deviation at each time point and mean profiles) and detailed information for all strengths of the test product and the reference product (e.g., the batch/lot number, manufacturing date, manufacturing site, testing date, and batch size) in Module 2.7.1
- Supportive validation data for the dissolution method (e.g., method robustness and method transfer) and analytical method (e.g., specificity, precision, accuracy, linearity, and stability)

FDA recommends that applicants include a summary of the in vitro dissolution development in Module 3.2.P.2.2.3 with a cross-reference to studies in Module 5, as appropriate. A justification for the dissolution specification should be included in Module 3.2.P.5.6. FDA also recommends that applicants refer to the U.S. Pharmacopeia (USP) General Chapter <1092> and certain FDA guidances for industry[80] that provide general guidelines on the development and validation of dissolution procedures.

2. Dissolution Acceptance Criteria

The specification for solid oral dosage forms normally includes a test to measure the in vitro release of a drug substance from the drug product. Applicants should provide a justification for the in vitro release specification (i.e., the dissolution method and acceptance criteria) that is reflective of the dissolution data from the representative batch that underwent in vivo BE testing

[80] See FDA guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* and FDA draft guidance for industry *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs*. When final, the draft guidance will represent FDA's current thinking on this topic.

(bio-batch) and supported by exhibit and registration batches that were included for stability.[81] Below is information that should be included in the selection of dissolution acceptance criteria:

Immediate-release solid oral dosage forms:

- A single-point acceptance criterion where Q=80%[82] dissolution occurs
- The setting of the dissolution acceptance criterion, which is drug product specific and based on USP Level 2 testing (n=12) (understanding that Level 2 testing and Level 3[83] testing may be needed)
- Support for a wider (i.e., more permissive) dissolution specification with an approved in vitro/in vivo correlation model, a physiologically based absorption and pharmacokinetic model, or a clinically relevant justification

Modified-release solid oral dosage forms:

- Acceptance criteria time points that cover the early, middle, and late stages of the release profile
- Dissolution acceptance criteria ranges that are based on (1) a mean target value ±10% at any given time point and (2) >80% for the last specification time point
- Support for a wider (i.e., more permissive) dissolution specification with an approved in vitro/in vivo correlation model, a physiologically based absorption and pharmacokinetic model, or a clinically relevant justification
- A two-stage testing approach for delayed-release dosage forms

Applicants should provide a justification for the in vitro release specification in Module 3.2.P.5.6. Applicants should also refer to certain FDA guidances for industry[84] and ICH guidance for industry[85] that provide general guidelines for dissolution specification settings. In addition, the applicant's dissolution specification should not only confirm adequate formulation and process control but also ensure consistent in vivo performance to the bio-batch.

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[81] FDA guidance for industry *ANDAs: Stability Testing of Drug Substances and Products.*

[82] USP General Chapter <711> defines the quantity, *Q*, as "the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content of the dosage unit."

[83] USP General Chapter <711>.

[84] See FDA guidances for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* and *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.

[85] ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.*

D. Facilities

1. Identification of Manufacturing Facilities

Applicants should provide information on their manufacturing facilities both in their Form FDA 356h and in the appropriate module within the application. However, applicants have not consistently provided (1) complete manufacturing facility information in their Form FDA 356h and (2) manufacturing facility information in the correct modules within their application, both of which have made this information not readily accessible to Agency reviewers and led to FDA's refusal to approve the ANDAs.

For "original (initial) applications . . . CMC supplements, and resubmissions to these submission types," applicants should include "complete information on the locations of all manufacturing, packaging, and control sites for both [the] drug substance and [the] drug product" in Form FDA 356h (i.e., the facility information that is listed in Modules 3.2.S.2 and 3.2.P.3.1).[86] Form FDA 356h should include information on:[87]

- All drug product (in process material and final) manufacturing and testing sites — including the stability testing, primary packaging, and labeling sites — that are proposed to be involved in the commercial manufacture of the drug product[88]

- All intermediate (i.e., performing operations governed by the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*) and final drug substance manufacturing and testing sites, including the sterilization and micronization sites, that are proposed to be involved in the commercial manufacture of the drug substance

- For combination products,[89] all manufacturing sites[90] for the non-lead constituent part of the combination product, including any separate sites responsible for design activities, that are proposed to be involved in the commercial manufacture of the finished product

- All current good manufacturing practice (CGMP) storage and warehousing facilities involved in the manufacture of the drug product

[86] Instructions for Filling out Form 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use, available at https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

[87] See 21 CFR 314.50.

[88] FDA does not recommend listing facilities (1) that have not performed any functions or (2) for which a technology transfer of data has not occurred.

[89] See 21 CFR 3.2(e).

[90] See 21 CFR 4.

Applicants do not need to list "bioequivalence testing sites, excipient testing sites, and container/closure manufacturing and testing establishments" on their Form FDA 356h.[91]

Module 3.2.S.2 should include all manufacturing facilities that are listed on Form FDA 356h as well as all research and development manufacturing and testing sites that generated data to support the application in accordance with 21 CFR 314.50(d)(1)(ii)(b). Applicants should list all laboratories that perform testing, including drug substance characterization and method comparisons, and functions integral to the control strategy. This module should also include any testing sites that generate stability testing or release data to support the application as well as the testing sites for the planned commercial testing.

2. Readiness for Inspection

All manufacturing facilities should be ready for inspection at the time of the ANDA submission, and applicants should indicate whether each site is ready for inspection on their Form FDA 356h. In the past, applicants have specified on Form FDA 356h that a manufacturing facility was ready for inspection, but once FDA was ready to commence inspection, the manufacturing facility indicated it was not ready for this inspection, which has led to FDA's refusal to approve the ANDAs.

If there are extenuating circumstances that prevent a facility from being ready for inspection, applicants should indicate this on Form FDA 356h. FDA considers it a good business practice for applicants to regularly communicate with manufacturing facilities, including contract manufacturing facilities, about changes in their inspection status to prevent any problems that may delay approval of their application.

3. Selection of Contract Manufacturing Facilities and CGMPs

Applicants should consider several factors in selecting suitable contract manufacturing facilities, including their manufacturing capability for the product and compliance with CGMPs. In the application, applicants should certify that contract manufacturing facilities are compliant with CGMPs.[92] FDA has observed that applicants have certified that contract manufacturing facilities are CGMP compliant, but upon assessment or inspection, FDA determined that they were not compliant at the time of the ANDA submission, which caused the ANDA to not be approved.

FDA recommends that applicants and contract manufacturing facilities clearly define the CGMP-related roles and manufacturing operations and activities of each of the parties in a quality agreement.[93] A quality agreement should clearly describe the materials or services to be

[91] Instructions for Filling out Form 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use.

[92] Section 505(j)(4) of the FD&C Act states that FDA shall approve an ANDA unless "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity." See also FDA's draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*.

[93] FDA guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*.

provided, quality specifications, and communication mechanisms between the applicant and the contract manufacturing facility.

E. Commercial Manufacturing Process

Applicants should provide — in Modules 3.2.P.2, 3.2.P.3, and 3.2.R — both details of the commercial manufacturing process and information to support the use of that particular process. These details and information help FDA determine whether applicants are ready to commercially manufacture a drug product. However, applicants often provide inconsistent, inaccurate, or incomplete information in these modules, leading to refusals to approve. Below is information that should be included in these modules:

- Applicants should provide, in Module 3.2.P.2, a justification for their process selection that relies on established scientific principles to identify potential risks to their manufacturing process. This justification should include batch data (from the exhibit and/or development batches) that demonstrate that any risks to the manufacturing process are adequately mitigated. Applicants should also include a discussion of their risk mitigation approaches and explain any differences between the exhibit and commercial batches regarding their manufacturing processes and in-process controls.

- Applicants should demonstrate that their proposed control strategy will ensure that the quality of the intermediate critical material attributes will remain unchanged across the exhibit and commercial batches. Applicants should clearly identify and justify, in Module 3.2.P.3.4, the in-process controls utilized in the exhibit and commercial batch manufacturing processes.

- The commercial batch formula identified in Module 3.2.P.3.2 should (1) reflect the unit dose composition identified in Module 3.2.P.1 and (2) clearly identify and justify any overage and overfill used. Applicants should provide a table comparing the quantity and the quality standard of each ingredient, including any solvents removed during the process, used in the exhibit and commercial batches.[94]

- Applicants should demonstrate a readiness for the commercial scale manufacture of the drug product by providing the set points and ranges of the commercial scale process parameters in the commercial equipment. Applicants should also clearly identify and justify, in Module 3.2.P.3, any differences in the equipment used for the exhibit and commercial batches, as well as provide process parameters that are (1) scaled-up using established principles, (2) supported by process development data, and (3) specified (i.e., "To Be Determined" should not be used) and not open-ended (e.g., no more than 200 revolutions per minute).

[94] Please note that FDA may request the manufacture of a new batch if there are inappropriate overages, overfills, or composition differences in the exhibit and commercial batches.

- Applicants should use a table, in Module 3.2.P.3.3, to submit the hold times and hold conditions of the intermediates and bulk drug products used in the commercial process.

- Executed batch records provided in Module 3.2.R should clearly specify the batch usage (e.g., development and stability) for each submitted executed batch record. In particular, the batch used for BE testing should be noted along with the BE study identifier.

F. Microbiology Considerations

1. In-Process Bioburden Testing and Acceptance Criteria

An ANDA for an aseptically processed generic drug product should contain in-process acceptance criteria for the total number of microorganisms associated with the unfiltered bulk drug solution prior to its sterilization (bioburden) because the "bioburden can contribute impurities (e.g., endotoxin) to, and lead to degradation of, the drug product."[95] Applicants have commonly submitted ANDAs for drug products without providing bioburden testing and in-process bioburden acceptance criteria for the bulk drug solution prior to any filtration, which has led to FDA's refusal to approve the ANDAs.

As described in the guidances for industry *For the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* and *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, FDA recommends that applicants both establish a prefiltration bioburden acceptance criteria and design manufacturing process controls to minimize the bioburden in the bulk drug solution prior to sterilization.

2. Description and Validation of Bacterial Endotoxins Test Method

An application for a parenteral generic drug product with a product endotoxin specification should contain both a description and validation of the bacterial endotoxins test method used. However, applicants have submitted ANDAs for parenteral generic drug products with a product endotoxin specification that have not described the bacterial endotoxins test method used, including the sample preparation and routine test dilution. Without this test method description, the Agency has been unable to determine whether the bacterial endotoxins method was adequately validated, which has led to FDA's refusal to approve the ANDAs. For the bacterial endotoxins method validation, applicants have not always accounted for the additional dilution that resulted from sample pooling in maximum valid dilution (MVD) calculations, which has again led to FDA's refusal to approve the ANDAs.

[95] FDA guidance for industry *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice,* at 36.

Applications for parenteral generic drug products with a product endotoxin specification should contain a description and validation of the endotoxins test method used,[96] including any test sample pooling and dilution performed routinely for method validation. In validating the chosen test method, applicants should understand that FDA generally accepts sample pooling for

> small-volume parenterals (those with volumes of 100 mL or less) as long as the MVD is adjusted to a proportional, lower value because of the potential for diluting a unit containing harmful levels of endotoxins with other units containing lower, less harmful, levels of endotoxins. This "adjusted MVD" is obtained by dividing the MVD computed for an individual sample by the total number of samples to be pooled . . . . If this reduction in MVD results in an inability to overcome product-related assay interference because of an insufficient dilution, then the samples should be tested individually.[97]

3. Microbiological Data To Support Extended Storage Times

If the proposed generic drug product is sterile, then the extended post-constitution and/or post-dilution storage times in the draft labeling should be supported by microbiological data. This data should demonstrate that the drug product does not support microbial growth from inadvertent contamination over the storage periods/conditions described in the labeling.

FDA recommends that applications contain a summary of the microbiological study, including the challenge organisms and challenge titers, the product sample concentrations and storage conditions, the diluents tested, and a summary of the study results. In addition, applicants should refer to FDA's *Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Quality Overall Summary Outline*,[98] *Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions*,[99] and *Question-based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall Summary Outline*.[100]

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[96] FDA guidances for industry *Pyrogen and Endotoxins Testing: Questions and Answers*, at 4, and *For the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, at 8.

[97] FDA guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers*, at 4.

[98] This document is available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM276168.pdf.

[99] This document is available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM276170.pdf.

[100] This document is available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM401339.pdf.

VI. BIOEQUIVALENCE DEFICIENCIES

A. Bioanalytical Study Data

It is critical for applicants to submit complete bioanalytical study reports and to validate bioanalytical methods used in their BE studies. Below is information that should be included in an application's bioanalytical study report:

- Complete dilution integrity data, stock stability data, and recovery data
- Analytical raw data from the study runs (accepted and rejected) of all subjects
- Serially selected chromatograms for 20% of the study subjects
- Bioanalytical standard operating procedures used in the application

FDA recommends that applicants submit complete bioanalytical reports and review the FDA draft guidance for industry *Bioanalytical Method Validation*[101] to help ensure that applicants provide the bioanalytical method validation data needed for FDA's review of the ANDA. Providing complete bioanalytical study reports and bioanalytical methodology validation data will help ensure that FDA has the information required to determine whether the method used was suitable and reliable.

B. Clinical Summary

Applicants should submit clinical summary data from in vivo BE studies that are critical to FDA's determination of BE. To help applicants summarize this data,

> FDA has developed model summary tables . . . . The[se] tables provide a format for applicants to summarize various aspects of the BE submission such as the design and outcome of in vivo and in vitro BE studies as well as the results of in vitro dissolution testing.[102]

Applicants can find these model tables on the FDA ANDA Forms and Submission Requirements website.[103]

Applicants, however, have submitted summary tables that are neither filled out completely nor prepared properly. For example, applicants have failed to list, in formulation tables, all of the strengths of the products for which they are seeking approval. Applicants have also submitted

[101] When final, this guidance will represent FDA's current thinking on this topic.

[102] FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*, at 10-11.

[103] These tables are available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm. Applicants should periodically refer to that website because the Agency may update the existing tables or add new tables to address both additional study types and waiver requests.

summary tables to FDA in a scanned document rather than in a text-based PDF file and Microsoft Word document. These actions have led to FDA's refusal to approve the ANDAs.

FDA recommends that applicants provide accurate and complete information in their model summary tables. Applicants should submit summary tables for all studies conducted, whether they were passing or failing studies,[104] in a text-based PDF file and Microsoft Word document.[105]

C. Deviations from Product-Specific Guidances

Applicants that deviate from a relevant product-specific guidance[106] should provide a detailed justification for this deviation, as well as data to support this deviation, in their original ANDA submission. Below is information that should be included, as applicable:

- A detailed justification for and data (such as their inclusion/exclusion criteria or demographic information) to support why their use of a particular study population does not affect their BE determination

- A detailed explanation of how any deviation in their primary endpoint from the product-specific guidance is as sensitive as the product-specific guidance's endpoint for detecting differences between the RLD and the generic product

- A detailed justification, in their protocol and Statistical Analysis Plan, for why their proposed prespecified statistical method is different from the product-specific guidance's recommendation

D. Information on BE and Safety Related to In Vivo BE Studies

In original ANDA submissions, applicants should include all of the BE and safety information related to the conduct of in vivo BE studies that is listed in the FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*. However, applicants have not always included in their original ANDAs the information that is necessary for FDA to fully evaluate the BE of the test product in a timely manner, resulting in FDA's refusal to approve the ANDAs. Below is information that applicants should provide:

- To ensure the welfare of human subjects involved in comparative clinical BE studies, applicants should provide, with dates, their protocol, Institutional Review Board approval forms, and consent forms. If their protocol was amended after the study was initiated, applicants should highlight the changes, compare the original protocol with the amended

[104] FDA guidance for industry *Submission of Summary Bioequivalence Data for ANDAs*.

[105] FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*, at 11.

[106] FDA regularly publishes product-specific guidances that describe the Agency's current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to the RLD.

protocol, and provide an explanation for why the change did not affect the safety or efficacy of the study product.

- For subjects with serious adverse events, who died, or became pregnant, applicants should provide a written narrative that provides complete follow-up details on the condition of the subjects so that the Agency can complete a comprehensive review of safety reports for the generic drug product. In particular, if a pregnancy follow-up is not complete at the time of the original ANDA submission, applicants should provide updates (such as whether the pregnancy resulted in a live birth) as soon as the information becomes available.

E. Differences in Formulations and Inactive Ingredients

For drug products for parenteral use, applicants should provide a clear justification and documentation for any differences permissible under FDA regulations between the formulation of the proposed generic drug product and the formulation of the RLD.[107] In addition, if applicants used inactive ingredients or amounts of inactive ingredients in their placebo test formulation used for BE testing that were different than the inactive ingredients or amounts of inactive ingredients in the proposed generic drug product formulation, they should provide a rationale and documentation in their original ANDA submission that explains why these differences did not affect their demonstration of BE of the proposed generic drug product to the RLD. Applicants, however, have commonly failed to provide necessary justifications and documentation for these differences, which has led to FDA's refusal to approve the ANDAs.

F. Waiver Requests Under 21 CFR 314.99(b)

Applicants have submitted ANDAs for formulations for products for ophthalmic or otic use that are not qualitatively and quantitatively (Q1/Q2) the same as the approved RLD's formulation but for which Q1/Q2 sameness is required under FDA's regulations.[108] When an applicant has sought approval for a formulation that is Q1/Q2 the same as the formulation previously marketed by the innovator, FDA has determined that, in appropriate circumstances, under 21 CFR 314.99(b), it may waive the requirement in the regulation that the inactive ingredients approved in the drug product under an ANDA be the same as those in the current formulation of the RLD if the statutory requirement regarding safety of inactive ingredients has been met.

FDA recommends that ANDA applicants:

[107] See, e.g., 21 CFR 314.94(a)(9)(iii).

[108] 21 CFR 314.94(a)(9)(iii) and 21 CFR 314.94(a)(9)(iv). Generally, a generic drug product is considered qualitatively and quantitatively the same as the RLD if the concentration or amount of each inactive ingredient in the test product differs by no more than +/- 5% of the concentration or amount for the same ingredient in the RLD.

- Determine whether they are seeking approval of a drug product where Q1/Q2 sameness to the RLD is required but the proposed generic product duplicates a previously approved (and not current) formulation of the RLD[109]

- Consider submitting a request for waiver of the above-identified regulatory requirements under 21 CFR 314.99(b)

FDA will determine whether to grant a waiver under 21 CFR 314.99(b) during its substantive review of the ANDA.

[109] 21 CFR 314.127(a)(8).