

# ANDA Submissions — Content and Format Guidance for Industry

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

**September 2018  
Generics**

# ANDA Submissions — Content and Format Guidance for Industry

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# ANDA Submissions — Content and Format Guidance for Industry<sup>1</sup>

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

## I. INTRODUCTION

This guidance is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)). This guidance details the information that should be provided in each section of the common technical document (CTD) format for human pharmaceutical product applications<sup>2</sup> and identifies supporting guidance documents and recommendations issued by FDA to assist applicants in preparing their ANDA submission. This guidance identifies the information that an applicant should include to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance documents on the filing process, including the guidance for industry about refuse-to-receive standards,<sup>3</sup> and common, recurring deficiencies<sup>4</sup> which should be reviewed thoroughly prior to submission of an ANDA.

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.

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<sup>1</sup> This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), both at the Food and Drug Administration.

<sup>2</sup> As discussed in section III of this guidance, the CTD format streamlines the ANDA submission requirements for Japan, the European Union, and the United States.

<sup>3</sup> See the guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* (Rev. 2). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> See the draft guidance for industry *Good ANDA Submission Practices*. When final, this guidance will represent the FDA's current thinking on this topic.

## II. BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) created an abbreviated approval pathway for duplicates of a previously approved drug product in section 505(j) of the FD&C Act. An ANDA relies on the Agency's previous finding of safety and effectiveness for a reference listed drug (RLD)<sup>5</sup> and, as a result, may be approved without submission of the same type and extent of information that is requested for a stand-alone new drug application to establish the safety and effectiveness of the proposed product.<sup>6</sup> Section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA must contain information to demonstrate that the proposed drug product and the applicable RLD are the same with respect to active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and, with certain exceptions, labeling.<sup>7</sup> An ANDA must also include sufficient information (1) to demonstrate that the proposed product is bioequivalent to the RLD<sup>8</sup> and (2) to ensure the product's identity, strength, quality, and purity. Consistent with any statutory provisions related to the exclusivity of and patents listed for the RLD, FDA must approve an ANDA unless there is insufficient evidence that these criteria are met or there is inadequate information to ensure the identity, strength, quality, and purity of the drug product.<sup>9</sup>

GDUFA<sup>10</sup> was signed into law to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. As part of the commitments under the first iteration of GDUFA, FDA agreed to meet certain obligations, including performance review goals for the review of new ANDAs. To meet these and any future performance goals as provided for in subsequent reauthorizations of GDUFA, FDA is issuing this guidance to assist ANDA applicants in improving the quality of their submissions, to increase the number of original ANDAs acknowledged for receipt upon initial submission, and to decrease the number of ANDA review cycles. FDA is committed to providing comprehensive assistance in the early stages of the application process so that an ANDA will contain all information necessary for FDA to complete its review in one review cycle.

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<sup>5</sup> An *RLD* "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). A *listed drug* is a "new drug product that has been approved under section 505(c) or 505(j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or section 505(j)(6) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety and effectiveness." *Id.* "Listed drug status is evidenced by the drug product's identification in the current edition of FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* [(the Orange Book)] as an approved drug." *Id.*

<sup>6</sup> See section 505(j)(2)(A) of the FD&C Act. (Generally, clinical studies to demonstrate safety and effectiveness are outside the scope of information that can be required for ANDAs.)

<sup>7</sup> See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act, 21 CFR 314.94, and 21 CFR 314.127.

<sup>8</sup> See section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

<sup>9</sup> Section 314.127.

<sup>10</sup> *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.

### III. CTD FORMAT

The CTD format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in an attempt to streamline the submission requirements for Japan, the European Union, and the United States. The CTD collects quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. The electronic CTD (eCTD) is the standard format for electronic regulatory submissions for ANDAs. As of May 5, 2017, ANDAs and submissions to ANDAs (which includes amendments, supplements, and reports) must be submitted to FDA electronically in eCTD format.<sup>11, 12</sup>

FDA has issued several guidance documents specific to the CTD and eCTD submissions.<sup>13</sup> The information contained in these guidances focuses on the technical aspects of filing a CTD application and should be reviewed thoroughly prior to submitting an ANDA. This guidance, however, specifically addresses the content of the CTD for an ANDA.

The CTD is comprised of the following modules:

- Module 1:<sup>14</sup> Administrative Information and Prescribing Information
- Module 2: Summaries
- Module 3: Quality
- Module 4: Nonclinical
- Module 5: Clinical

The sections that follow in this guidance provide additional detail about the information that should be submitted in the applicable modules, sections, and subsections.

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<sup>11</sup> Guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Rev. 4). See also section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)) and guidance for industry *Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act*.

<sup>12</sup> Any record in electronic form submitted to FDA under requirements of the FD&C Act is subject to the provisions of part 11 (21 CFR part 11) unless exempted. Part 11 regulations were issued in 1997 to provide criteria to FDA for accepting electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures on paper. See the guidance for industry *Part 11, Electronic Records; Electronic Signatures — Scope and Application*.

<sup>13</sup> See the FDA guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and electronic submissions web page at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm>. See also the biologics web page at <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm163685.htm>.

<sup>14</sup> Module 1 contains administrative information and is not considered part of the *common* application. Each regulatory authority that accepts the CTD uses its own Module 1. The information described for Module 1 in this guidance applies only to ANDAs submitted to the U.S. FDA. Modules 2 through 5 of the CTD are common for all regions.

## A. Module 1 – Administrative Information

### 1. Forms and Cover Letter

Section 1.1 contains the following forms:<sup>15</sup>

- Form FDA 356h (Form 356h) – Application to Market a New or Abbreviated New Drug or Biologic for Human Use, which ANDA applicants must fully complete and sign for their submissions<sup>16</sup>
- Form FDA 3794 – Generic Drug User Fee Cover Sheet<sup>17</sup>
- Form 3674 – Certification of Compliance Under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

1.2 Contains a cover letter. A suggested cover letter template is included in this guidance in the appendix.<sup>18</sup> In addition, FDA recommends that a cover letter clearly state in its header whether it proposes any of the following:

- A new strength of a solid oral dosage-form drug product
- A change in concentration for a parenteral dosage-form drug product
- A change in vial size, fill volume, and/or package size to a parenteral dosage-form drug product (i.e., total drug content)
- A change in concentration of an oral liquid, ophthalmic, otic, transdermal, or topical drug product
- A change in the formulation for any dosage form<sup>19</sup>

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<sup>15</sup> FDA forms listed in this section and in other parts of this guidance are available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.

<sup>16</sup> Section 314.94(a)(1).

<sup>17</sup> All applicants submitting original ANDAs, except for original ANDAs for positron emission tomography drugs (see section 744B(1) of the FD&C Act (21 U.S.C. 379j-42(1)), are required to pay the generic drug user fee. See Generic Drug User Fee Cover Sheet and Payment Information, available at <http://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm322629.htm>.

<sup>18</sup> Applicants are not required to use this template. However, if applicants utilize the template, they should use judgment in adapting the template to their specific needs.

<sup>19</sup> Applicants who are requesting a change in the formulation for any dosage form should identify the level of the change in the header. Applicants should consult scale-up and post-approval changes (SUPAC) guidances for industry to determine the appropriate level of change. FDA has developed SUPAC guidances for immediate-release solid oral dosage forms, modified-release solid oral dosage forms, and nonsterile semisolid dosage forms, which are available CDER guidance web page for Pharmaceutical Quality/CMC guidances. The SUPAC guidances focus on

- A switch from a prescription drug product to an over-the-counter product (Rx-to-OTC switch)
- The reactivation of a product listed in the discontinued section of FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book)

**1.2** Contains (1) copies of any controlled correspondence from FDA related to meetings FDA holds with applicants to discuss their development of a generic drug product that is the subject of an ANDA and (2) any copies of the minutes from those meetings.

## 2. *Administrative Information*

**1.3.1.2** Contains a U.S. agent letter of appointment, if applicable. The U.S. agent letter of appointment is a separate document submitted in addition to the U.S. agent's signature on Form 356h, if applicable. If the applicant does not reside or have a place of business in the United States, an agent that resides or maintains a place of business in the United States must countersign the application.<sup>20</sup>

**1.3.2** Contains the field copy certification.<sup>21</sup> Applicants should notify the applicable Office of Regulatory Affairs district office by letter that their eCTD submission will be submitted to FDA. Because the district offices have access to the complete submission on the FDA network, an individual field copy is no longer required for the district office. The letter should include the drug name, application number, FDA center, and FDA division reviewing the application.<sup>22</sup> A separate letter certifying that the electronic quality section (i.e., Module 3) has been submitted to FDA should also be provided to the appropriate district office.<sup>23</sup>

**1.3.3** Contains the signed debarment certification required under the Generic Drug Enforcement Act of 1992.<sup>24</sup> The applicant must certify that it did not and will not use the services of any debarred persons in connection with the application.<sup>25</sup> The applicant must also list all convictions described in section 306(k) and 306(a) and (b) of the FD&C Act (21 U.S.C. 335a(k),

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post-approval changes; however, FDA recommends that applicants consult these guidances to determine the level of change for both amendments to original ANDAs and prior approval supplements.

<sup>20</sup> 21 CFR 314.50(a)(5).

<sup>21</sup> Section 314.94(d)(5).

<sup>22</sup> See the eCTD Technical Conformance Guide, available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>.

<sup>23</sup> Id.

<sup>24</sup> Section 306(k) and 306(a) and (b) of the FD&C Act (21 U.S.C. 335a(k), 335a(a), and 335a(b), respectively).

<sup>25</sup> See the draft guidance for industry *Submitting Debarment Certification Statements* for more information on debarment certifications, including a discussion on persons covered by those certifications. When final, this guidance will represent FDA's current thinking on this topic.



335a(a), and 335a(b), respectively). Under section 306(k)(1) of the FD&C Act, the applicant may use the following language:

*(Name of Applicant)* hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Qualifying phrases, such as “to the best of our knowledge,” should be avoided. Similarly, applicants with no convictions to list should submit a statement to that effect.<sup>26</sup>

**1.3.4** Contains a financial certification (FDA Form 3454) for any clinical investigator who has no disclosable financial interests in, or arrangements with, any applicant of the covered clinical study and a disclosure statement (FDA Form 3455) for each clinical investigator who, or whose spouse or dependent child, has or had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study.<sup>27</sup>

**1.3.5** Contains the patent and exclusivity information.

**1.3.5.1** Contains the patent information. Applicants are required to provide an appropriate patent certification or statement for each patent issued by the U.S. Patent and Trademark Office and subsequently listed in the Orange Book that claims (1) the drug substance, (2) the drug product, and/or (3) a use of the RLD that is cited by the ANDA.<sup>28</sup> FDA recommends that when providing patent information, applicants include the expiration date for each patent, whether the RLD is protected by any pediatric exclusivity, and when any such pediatric exclusivity will expire.

**1.3.5.2** Contains the patent certification(s). If the Orange Book does not list a patent for the RLD, the ANDA applicant must certify that such patent information has not been submitted by the NDA holder for listing in the Orange Book (Paragraph I Certification).<sup>29</sup>

For each patent issued by the U.S. Patent and Trademark Office and subsequently listed in the Orange Book, the applicant must certify to one of the following paragraphs:<sup>30</sup>

- That the patent information has expired (Paragraph II Certification)
- The date on which the patent will expire (Paragraph III Certification)

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<sup>26</sup> See the letter from Roger L. Williams to all ANDA and abbreviated antibiotic application applicants (January 15, 1993), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072885.pdf>.

<sup>27</sup> 21 CFR part 54.

<sup>28</sup> Section 314.94(a)(12).

<sup>29</sup> Section 314.94(a)(12)(i)(A)(I). If in the opinion of the ANDA applicant and to the best of its knowledge there are no patents claiming the drug product, drug substance, or method of use of the drug product, the applicant must submit to its ANDA a certification stating that opinion. Section 314.94(a)(12)(ii).

<sup>30</sup> Section 505(j)(2)(A)(vii) of the FD&C Act and § 314.94(a)(12)(i)(A)(2) through (4).

- That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted (Paragraph IV Certification)

If the RLD is covered by a patent claiming a method of using the listed drug and the labeling for the drug product for which the applicant is seeking approval does not include any indication or other condition of use that is covered by the method-of-use patent, the applicant must also submit a statement explaining that the method-of-use patent does not claim any of the proposed indications or other condition of use.<sup>31</sup>

Applicants submitting a Paragraph IV Certification must provide the following language:<sup>32</sup>

I, *(name of applicant)*, certify that Patent No. \_\_\_\_\_ *(is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product)* for which this application is submitted.

Applicants submitting a Paragraph IV Certification must also certify that they will provide notice to the owner of the patent(s) and to the holder of the approved application that lists the patent(s) that is/are being challenged.<sup>33, 34</sup>

Applicants should also submit an exclusivity statement regarding their marketing intentions when the applicant intends to remove or *carve out* any protected indication or other condition of use from the labeling to gain market entry for other uses prior to expiry of exclusivity for that protected indication or other condition of use.

### 3. *References*

**1.4.2** Contains the statement of a right of reference for each and every drug master file (DMF) referenced in the application and identified on Form 356h. Applicants should submit the letter of authorization provided to the applicant by the DMF holder which gives authorization to rely on the information in the DMF.<sup>35</sup>

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<sup>31</sup> Section 314.94(a)(12)(iii).

<sup>32</sup> Section 314.94(a)(12)(i)(A)(4).

<sup>33</sup> Section 314.94(a)(12)(i)(A)(4).

<sup>34</sup> The process for this notice is provided in section 505(j)(2)(B) of the FD&C Act and in 21 CFR 314.95. An ANDA applicant must send notice of a paragraph IV certification on or after the date on which it receives a paragraph IV acknowledgment letter from FDA but not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter stating that the application is sufficiently complete to permit a substantive review. See § 314.95(a) and (b).

<sup>35</sup> 21 CFR 314.420(d). More information on DMFs, as well as the list of DMFs that FDA has received, is available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>.

#### 4. *Other Correspondence*

**1.12.4** Contains a statement, if applicable, that a request for a proprietary name has been made. An ANDA applicant requesting a proprietary name should submit that request when the ANDA is submitted to help ensure that an acceptable name is available at the time of approval. When requesting a proprietary name, a separate electronic submission should be made and identified as a **“REQUEST FOR PROPRIETARY NAME REVIEW.”**<sup>36</sup>

**1.12.11** Contains the basis for submission.<sup>37, 38</sup> The applicant should provide: (1) the name of the RLD, (2) the application number of the RLD, and (3) the holder of the application for the RLD.

If the generic drug differs from the RLD in strength, route of administration, dosage form, or in that one active ingredient is substituted for one of the active ingredients in a listed combination drug product, applicants must first submit a suitability petition to FDA’s Division of Dockets Management to obtain permission to file their ANDA.<sup>39</sup> FDA will review the suitability petition to determine whether the requested change from the listed drug will impact the safety and effectiveness of the generic product and if any applicable requirements of the Pediatric Research Equity Act may be waived. The suitability petition must be approved by FDA before the ANDA is submitted.<sup>40</sup> For an ANDA based on an approved petition under 21 CFR 10.30 or 314.93, the name of the RLD in section 1.12.11 must be the same as the listed drug in the petition, and section 1.12.11 must contain the FDA docket number for the petition and a copy of FDA’s correspondence approving the suitability petition.<sup>41</sup> When an applicant submits a petitioned ANDA, the basis for submission is the RLD and the approved suitability petition. Section 1.12.11 should contain (1) the name of the RLD, which must be the same as the listed drug identified in the approved suitability petition, (2) a reference to the suitability petition’s FDA-assigned document number, and (3) a copy of FDA’s correspondence approving the suitability petition.<sup>42, 43</sup> When an ANDA applicant seeks approval of a generic drug that is a duplicate of a

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<sup>36</sup> See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names* (Rev.1).

<sup>37</sup> Section 314.94(a)(3). See also the draft guidance for industry *Referencing Approved Drug Products in ANDA Submissions*. When final, this guidance will represent the FDA’s current thinking on this topic.

<sup>38</sup> Applicants should review the guidance for industry *Variations in Drug Products That May Be Included in a Single ANDA* to determine whether one or more ANDAs should be submitted for variations of a specific drug product dosage form.

<sup>39</sup> 21 CFR 314.93(b). To request such a change from the RLD, the suitability petition must be submitted in accordance with 21 CFR 10.20 and in the format specified in 21 CFR 10.30.

<sup>40</sup> Section 314.93(b).

<sup>41</sup> Section 314.94(a)(3)(i) and (iii).

<sup>42</sup> Section 314.94(a)(3)(i) and (iii). See also the draft guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

<sup>43</sup> If after approval of a suitability petition and before approval of an ANDA submitted pursuant to the approved petition, a drug product is approved in an NDA for the change described in the petition, the suitability petition and the listed drug identified in the petition can no longer be the basis for submission. The applicant must submit a new

drug product in an approved petitioned ANDA (and for which the same drug has not been approved under section 505(c) of the FD&C Act), the basis for submission is the RLD and the approved suitability petition. Section 1.12.11 should contain: (1) the RLD, which must be the same as the listed drug identified in the approved suitability petition, and RLD application number; (2) a reference to the suitability petition's FDA-assigned docket number; and (3) a copy of FDA's correspondence approving the suitability petition. The first petitioned ANDA approved should be used for and identified in the appropriate sections of a subsequent ANDA as the reference standard. However, the RLD for that subsequent ANDA remains the listed drug referenced in the approved suitability petition.<sup>44</sup>

**1.12.12** Contains information demonstrating that the generic product is the *same as* the RLD.<sup>45</sup> *Same as* means that the generic product is identical to the RLD in "active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted."<sup>46</sup> To demonstrate that the proposed generic drug product meets this standard, applicants should provide:

- (1) A statement that the conditions of use for the generic product have been previously approved for the RLD<sup>47</sup>
- (2) Information to show that the active ingredient(s) in the generic drug product is/are the same as the active ingredient(s) in the RLD<sup>48</sup>
- (3) Information to show that the route of administration, dosage form, and strength of the generic drug product are the same as those of the RLD<sup>49</sup>
- (4) As applicable, information to indicate the strength of the generic drug product used in the in vivo bioequivalence (BE) studies (fasting and fed) to demonstrate BE of the generic drug product to the RLD

FDA recommends that applicants submit, within their original application, all strengths that they intend to market. Applicants generally should not submit a new pharmacy bulk package strength or fill volume in an amendment.<sup>50</sup>

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ANDA that identifies the drug product with the same active ingredient, dosage form, route of administration, and strength that has been approved under an NDA as the RLD and as its basis for submission. See §314.93(f)(2).

<sup>44</sup> See the draft guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.

<sup>45</sup> See section 505(j)(2)(A) of the FD&C Act and § 314.94.

<sup>46</sup> 21 CFR 314.92(a)(1).

<sup>47</sup> Section 314.94(a)(4).

<sup>48</sup> Section 314.94(a)(5).

<sup>49</sup> Section 314.94(a)(6).

<sup>50</sup> See the guidance for industry *Variations in Drug Products That May Be Included in a Single ANDA* for exceptions.

**1.12.14** Contains the environmental assessment,<sup>51</sup> the environmental impact statement,<sup>52</sup> or the claim of categorical exclusion<sup>53</sup> and the justification for the exclusion. A claim of categorical exclusion must (1) “include a statement of compliance with the categorical exclusion criteria” and (2) “state that to the applicant's knowledge, no extraordinary circumstances exist.”<sup>54</sup>

**1.12.15** Contains a request, if applicable, to waive the requirement that applicants submit evidence either measuring in vivo bioavailability (BA) or demonstrating in vivo BE of the generic product (known as a *biowaiver*).<sup>55</sup> The data necessary to support a waiver request can vary by product. For this reason, applicants should submit a controlled correspondence to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov), consult both the Product-Specific Guidances for Generic Drug Development website<sup>56</sup> for current product-specific guidances and the Biopharmaceutics guidances website,<sup>57</sup> or contact the appropriate Center for Biologics Evaluation and Research review division prior to submission of the application, as appropriate.

## 5. Labeling

**1.14.1** Contains labeling for the generic drug product.<sup>58</sup> If the application is for a sterile pharmacy bulk package product, applicants should complete and submit a Pharmacy Bulk Package Sterility Assurance table<sup>59</sup> to address sterility assurance aspects of the drug product associated with the labeling and the microbiological study data that may be submitted in the application.

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<sup>51</sup> See 21 CFR 25.20.

<sup>52</sup> 21 CFR 25.22.

<sup>53</sup> 21 CFR 25.30 or 21 CFR 25.31.

<sup>54</sup> 21 CFR 25.15(a).

<sup>55</sup> 21 CFR 320.22.

<sup>56</sup> The Product-Specific Guidances for Generic Drug Development website is available at <https://www.fda.gov/drugs/guidancecomplianceinformation/guidances/ucm075207.htm>.

<sup>57</sup> The Biopharmaceutics guidances website is available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm>.

<sup>58</sup> See section 314.94(a)(8)(ii). See also the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design To Minimize Medication Errors*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>59</sup> This table is available on the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm>.

**1.14.1.1** Contains the draft label and labeling<sup>60</sup> for each strength and container including the package size in a text-based PDF file.<sup>61</sup> Applicants should ensure that the label and labeling design<sup>62</sup> do not contribute to medication error<sup>63</sup> and confirm whether the container closure is child resistant.

**1.14.1.2** Contains the annotated draft labeling text, including side-by-side labeling comparison of the generic drug product's container(s) and carton(s) to the RLD's container(s) and carton(s) for each strength (or total drug content and concentration for injections) and for each container closure system. All differences should be highlighted and annotated. Applicants should indicate the RLD version (e.g., strength, package size, of carton) used for the side-by-side comparison.<sup>64</sup>

**1.14.1.3** Contains the prescribing and patient information in text-based PDF, Microsoft Word, and structured product labeling files.

**1.14.1.4** Contains the Pharmacy Bulk Package Sterility Assurance table,<sup>65</sup> if applicable.

**1.14.1.5** Contains the labeling history.

Applicants are encouraged to review and use the Labeling Question-Based Review (QbR) model when developing labels and labeling.<sup>66</sup> Responses to the QbR should be provided in section 1.14.1.5, as applicable.

**1.14.3** Contains the RLD labeling and a comparison of that labeling to the draft labeling for the generic product. Applicants must submit side-by-side labeling comparison(s) with all differences annotated and explained.<sup>67</sup> Applicants should also submit the RLD package insert,

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<sup>60</sup> FDA has determined that, in general, an ANDA may be approved based on a draft labeling provided that the only deficiencies in the draft labeling are of an editorial or similarly minor nature. See the guidance for industry *Acceptability of Draft Labeling To Support ANDA Approval*.

<sup>61</sup> For all PDF submissions, FDA recommends that applicants submit text-based PDF files, not image-based PDF files.

<sup>62</sup> For FDA to assess whether there are any significant deficiencies in the draft carton and container labeling, the design should not only reflect the content of the carton and/or container but also provide an accurate representation of the layout, text size, style, color, and other formatting factors that will be used for the final printed labeling.

<sup>63</sup> See the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design To Minimize Medication Errors*.

<sup>64</sup> For example, if the proposed product is to be packaged in a bottle as 30-, 60-, and 100-count along with a 10-count blister packaging, side-by-side comparisons should be provided for the bottle count and the blister packaging for each strength. Also for example, if the proposed product comes in a 5 milligram (mg)/milliliter (mL), 5 mL, and 10 mL vial, and a 10 mg/mL, 5 mL, and 10 mL vial, a side-by-side comparison should be provided for all four size and concentration combinations.

<sup>65</sup> This table is available on the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>66</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>67</sup> Section 314.94(a)(8)(iv).

Medication Guide, one container label, and one outer carton, if applicable, for each strength and package size listed in the application.<sup>68</sup> Applicants are reminded to use the most recent RLD labeling available at the Drugs@FDA website.

**1.14.3.1** Contains a side-by-side labeling comparison, with any differences annotated and explained, and the Medication Guide, if applicable. In addition, applicants should do the following:

- (1) State that a sufficient number of Medication Guides will be included in each package size (i.e., an amount to ensure that the authorized dispenser is able to provide a Medication Guide to each patient receiving a prescription for the drug product)<sup>69</sup>
- (2) Confirm that the Medication Guides will be distributed in accordance with 21 CFR 208.24

**1.14.3.3** Contains the RLD labeling, the Medication Guide, one RLD container label, and one RLD outer carton label for each strength and package size, if applicable.

**1.16.1** Contains a risk management plan (non-REMS)<sup>70</sup> for products that require tools to minimize risks while preserving benefits.

**1.16.2** Contains, for applicants relying on an RLD with a risk evaluation and mitigation strategy (REMS), a REMS for the generic drug product and any REMS supporting documents.<sup>71</sup> A REMS for an ANDA must have the same Medication Guide and patient package insert as the RLD.<sup>72</sup> In addition, if applicable, a REMS for an ANDA must use a single, shared system of elements to assure safe use unless FDA waives the requirement under section 505-1(i)(1)(B) of the FD&C Act (21 U.S.C. 355-1(i)(1)(B)). However, an ANDA REMS does not include a timetable for submission of assessments of the REMS and does not include a communication plan.<sup>73</sup>

## **B. Module 2 – CTD Summaries**

### *1. Quality Overall Summary*

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<sup>68</sup> See section 314.94(a)(8)(i).

<sup>69</sup> 21 CFR 208.24(b)(1).

<sup>70</sup> See section 505-1 of the FD&C Act (21 U.S.C. 355-1).

<sup>71</sup> See the draft guidance for industry *Format and Content of a REMS Document*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>72</sup> Section 505-1(i)(1)(A) of the FD&C Act.

<sup>73</sup> Id.

**2.3** Contains the Quality Overall Summary (QOS), which provides an overview of the chemistry, manufacturing, and controls (CMC) section of the application.<sup>74</sup> The QOS summarizes information from both section **2.3.S** about the drug substance (i.e., the active pharmaceutical ingredient (API)) and section **2.3.P** about the drug product. In section **2.3.S**, applicants should provide separate information on each drug substance contained in the product. All information provided in the QOS should be accurate and supported by information, data, or a justification that should also be included in Module 3 or other parts of the application.<sup>75</sup>

Applicants should use the QbR model when writing their QOSs. FDA introduced the QbR initiative in 2005 as a tool for the review of the CMC (i.e., the drug substance and drug product quality sections of the ANDA)<sup>76</sup> and updated the QbR model in 2011 to include additional CMC questions from microbiology. The QbR model assists applicants in developing their QOS by providing specific questions that, when answered, ensure that applicants submit adequate information for FDA review. FDA has posted the QbR-QOS outlines designed for simple dosage form products (solution or immediate-release solid oral dosage forms)<sup>77</sup> and for sterility assurance of products terminally sterilized by moist heat.<sup>78, 79</sup> FDA has also developed example QOS summaries for controlled-release capsules<sup>80</sup> and immediate-release tablets.<sup>81</sup> Additionally, FDA recommends that applicants refer to the QbR Frequently Asked Questions and the QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions for further guidance on completing the QOS, including page limits.<sup>82</sup>

Failure to submit the QOS in text-based PDF and Microsoft Word files will result in a deficiency during the filing review conducted by FDA upon submission of the ANDA. FDA recommends against submitting a scanned PDF copy of the QOS.

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<sup>74</sup> Section 314.50(c)(2)(iv).

<sup>75</sup> See the ICH guidance for industry *M4Q: The CTD — Quality*. ICH guidances for industry can be found on the FDA guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>76</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>77</sup> See the Question-Based Review for CMC Evaluations of ANDAs web page, available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm>.

<sup>78</sup> Id.

<sup>79</sup> Portions of the QbR for terminally sterilized products may also directly apply to sterile drug products that are aseptically filled. Specifically, the P.1, P.2, P.5, P.8, Appendices A.2, and Regional Information components of section 2.3.P would also apply to sterile products that are aseptically filled.

<sup>80</sup> See the Question-Based Review for CMC Evaluations of ANDAs web page, note 77.

<sup>81</sup> Id.

<sup>82</sup> Id.



## 2. *Clinical Summary*

**2.7** Contains summary data critical to the determination of BE.<sup>83</sup> FDA has developed model summary tables to assist applicants in summarizing the BE data.<sup>84, 85</sup> The 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. These model tables are available on the FDA Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page.<sup>86</sup> In addition, applicants should submit summary tables for all studies conducted, regardless of whether they are passing or failed studies,<sup>87</sup> in text-based PDF and Microsoft Word files.

**2.7.1** Contains a summary of biopharmaceutical studies and associated analytical methods, as well as summary tables<sup>88</sup> in a standardized format for data to be submitted, including, but not necessarily limited to: BE summary tables for in vitro feeding tube testing, clinical endpoint summary tables, topical dermatologic corticosteroid in vivo BE study summary tables, in vitro binding BE study summary tables, and BE summary tables for aqueous nasal spray solutions. This section also contains the identity and complete addresses of all sites used to generate data submitted in support of the determination of BE (e.g., data submitted either under 21 CFR 320.21(b) or 320.24(b) or in support of a Biopharmaceutics Classification System waiver request).<sup>89</sup> Additionally, certificates of analysis (COAs) of all RLDs used in the biopharmaceutical studies should be provided in this section.

Section 2.7 also contains dissolution data testing for the whole tablet and the half tablet (if applicable), comparing the test product to the RLD. Additionally, comparative individual unit data should be provided along with COAs for all RLDs used in the testing. Dissolution should be conducted in all medias recommended by the Agency or the United States Pharmacopeia (USP).<sup>90</sup>

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<sup>83</sup> 21 CFR 320.21(b) and 21 CFR 320.24(b).

<sup>84</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59, for the Model Bioequivalence Data Summary Tables.

<sup>85</sup> FDA has developed various BE summary tables to assist applicants including, for example, clinical endpoint BE study tables, BE summary tables for in vitro feeding tubes, and summary tables for the listing and characterization of impurities and a justification for the limits in drug substance and drug products. See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 66.

<sup>86</sup> Applicants should periodically refer to the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59, because the Agency may update existing tables or expand the number of tables to address additional study types as well as waiver requests.

<sup>87</sup> See the guidance for industry *Submission of Summary Bioequivalence Data for ANDAs*.

<sup>88</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>89</sup> See the guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*.

<sup>90</sup> See, for example, FDA's Dissolution Methods Database, available at <https://www.fda.gov/Drugs/InformationOnDrugs/ucm135742.htm>.

## C. Module 3 – Quality

Module 3 contains all of the CMC information necessary to support the application,<sup>91</sup> including the information supporting and verifying what was summarized in section 2.3. The specific placement of product quality microbiology information in Module 3 is listed in CDER’s Manual of Policies and Procedures (MAPP) 5040.1 *Product Quality Microbiology Information in the Common Technical Document – Quality (CTD-Q)*.<sup>92, 93</sup> Any analytical procedure submitted in the summaries of Module 2 should be described in sufficient detail to allow an analyst to reproduce the conditions and obtain results comparable to what is stated in the application.<sup>94</sup> It is recommended that applicants review the following three guidances for industry to assist in the preparation of Module 3: (1) *ANDAs: Impurities in Drug Products*, (2) *ANDAs: Impurities in Drug Substances*, and (3) *ANDAs: Stability Testing of Drug Substances and Products*.<sup>95</sup>

### 1. Drug Substance

**3.2.S** contains the CMC information specific to the drug substance(s).<sup>96</sup> For a drug product containing more than one drug substance, the information requested for part “S” should be provided in its entirety for each drug substance as a separate Module 3.2.S.

**3.2.S.1** Contains general information about the drug substance, including: (1) the nomenclature, (2) the structure, and (3) general properties. Section 3.2.S.1 should not include any references to the DMF.

**3.2.S.2** Contains information related to the manufacture of the drug substance. This section should include all intermediate and final drug substance manufacturing facilities listed on the Form 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). All testing labs that perform functions integral to the control strategy — including, but not limited to,

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<sup>91</sup> Section 314.94(a)(9)(i).

<sup>92</sup> For this and other MAPPs, see the Manual of Policies and Procedures (CDER) web page at <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/default.htm>.

<sup>93</sup> See also the guidances for industry *Submission 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*.

<sup>94</sup> See the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics*.

<sup>95</sup> FDA further recommends that applicants review, as applicable, the ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk* and the draft guidances for industry *Elemental Impurities in Drug Products* and *Quality Attribute Considerations for Chewable Tablets*. When final, these guidances will represent the FDA’s current thinking on these topics. In addition, FDA recommends that applicants review, as applicable, the following guidances for industry: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*; *Size of Beads in Drug Products Labeled for Sprinkle* (Rev. 1); *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*; *ANDAs: Stability Testing of Drug Substances and Products: Questions and Answers*; and *ANDA Submissions – Refuse-to-Receive Standards* (Rev. 2).

<sup>96</sup> Section 314.50(d)(1)(i).

a characterization and comparison of molecules and comparability testing — should be listed. This section should include any testing sites that generate stability testing, and release data to support the application as well as the testing sites for planned commercial testing.

**3.2.S.2.1** Contains information about each drug substance manufacturer, including the:

- (1) Name and full address of the facility(ies) of each manufacturer, including the contractors, and each proposed production site or facility involved in the manufacturing and testing
- (2) Contact information for an agent at the facility (including phone and fax numbers and email addresses)
- (3) U.S. agent's name, if applicable
- (4) Function or responsibility of the manufacturer
- (5) Type II DMF number for the API or any critical or final intermediates, if applicable
- (6) Central File Number, Facility Establishment Identifier, and Data Universal Numbering System numbers, if known

Subsections **3.2.S.2.2** through **3.2.S.2.6** may refer to the DMF. If there is no DMF referenced in the application, detailed information should be provided in these subsections.

**3.2.S.2.2** Contains a complete description of the manufacturing process and process controls, including the manufacturing and sterilization processes for the sterile substance(s) used in the sterile drug product.<sup>97</sup>

**3.2.S.2.3** Contains the control of materials used in the manufacture of the drug substance.

**3.2.S.2.4** Contains controls of critical steps and intermediates.

**3.2.S.2.5** Contains process validation and/or evaluation, including the manufacturing and sterilization processes for the sterile drug substance(s) used in the sterile drug product.

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<sup>97</sup> See MAPP 5040.1 *Product Quality Microbiology Information in the Common Technical Document — Quality (CTD-Q)* and the Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances web page, available at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm149499.htm>. See also QbR for Sterility Assurance of Terminally Sterilized Products: Quality Overall Summary Outline; QbR for Sterility Assurance of Terminally Sterilized Products: Frequently Asked Questions; and QbR for Sterility Assurance of Aseptically Processed Products, which are all available on the Question-Based Review for CMC Evaluations of ANDAs web page, note 77.

**3.2.S.2.6** Contains the manufacturing process development.

**3.2.S.3** Contains characterization information for the API.

**3.2.S.3.1** Contains an elucidation of the API structure and other characteristics.

**3.2.S.3.2** Contains all potential impurities.<sup>98</sup> FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance and Drug Products.<sup>99</sup>

**3.2.S.4** Contains information about the control of the drug substance, including the validation procedures and the results of the microbiological analytical tests, as applicable.

**3.2.S.4.1** Contains the drug substance specification. The specification includes the tests, acceptance criteria, and references to methods in tabular form, including any microbiological attributes for the drug substance (e.g., sterility for a sterile product or microbial limits for a non-sterile product), as appropriate.

**3.2.S.4.2** Contains the analytical procedures (compendial and/or in-house), including, if appropriate, the analytical procedures used to perform microbiological tests of the drug substance.

**3.2.S.4.3** Contains a validation of the analytical procedures, including:

- (1) The full validation reports for the in-house methods and their equivalence to USP procedures, if available for the drug substance
- (2) A verification of USP General Chapter <1226> or DMF procedures, if referenced
- (3) Legible spectra and chromatograms for reference standards and test samples
- (4) The Sample Statement(s) of Availability and identification of the drug substance<sup>100</sup>

**3.2.S.4.4** Contains the batch analysis, including the COAs from both the drug substance manufacturer(s) and the drug product manufacturer(s) for the batches used to produce the

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<sup>98</sup> FDA may refuse to receive an ANDA for: (1) failing to provide justification for proposed limits in drug substances and drug products for specified identified impurities that are above qualification thresholds, (2) failing to provide justification for proposed limits for specified unidentified impurities that are above identification thresholds, and (3) proposing limits for unspecified impurities (e.g., any unknown impurity) that are above identification thresholds. See the guidance for industry *ANDA Submissions — Refuse to Receive for Lack of Justification of Impurity Limits*.

<sup>99</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>100</sup> See section 314.50(e)(1).

exhibit batch(es) of the drug product. Applicants should clearly identify the drug substance lot(s) used in any BE studies.

**3.2.S.4.5** Contains a justification of the specification, including, but not limited to, references to compendia (e.g., the USP, the European Pharmacopeia, and the Japanese Pharmacopeia), the ICH, and/or the RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance and Drug Products.<sup>101</sup>

**3.2.S.5** Contains information about the reference standards or materials. Appropriate certification, characterization, and qualification information should be provided for the reference standards of the drug substance and impurities.

**3.2.S.6** Contains information about the container closure systems.<sup>102</sup> If the application contains a sterile substance for use in a sterile drug product, this section will also contain both a description of the container closure system used for the drug substance and a validation of the container closure integrity. The applicant may refer to the DMF.

**3.2.S.7** Contains stability information.

**3.2.S.7.1** Contains stability summary and conclusions. The applicant may refer to the DMF for complete stability data. However, the retest date or expiration date of the API should, at a minimum, be provided at both the drug product manufacturing site and the drug substance manufacturing site.<sup>103</sup>

**3.2.S.7.2** Contains the postapproval stability protocol. The applicant may refer to the DMF.

**3.2.S.7.3** Contains stability data. The applicant may refer to the DMF.

## 2. *Drug Product*

**3.2.P** contains detailed information known about the drug product.<sup>104</sup> During the development of the application, applicants should review the ICH guidance for industry *Q8(R2) Pharmaceutical Development* (Rev. 2), the guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, and the product-specific CMC guidances for industry (e.g., metered dose inhalers and nasal sprays), as applicable. A drug product supplied with a reconstitution diluent should include a separate section 3.2.P with the diluent information. Additionally, a drug product supplied with multiple

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<sup>101</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>102</sup> See the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics*.

<sup>103</sup> See the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* and *ANDAs: Stability Testing of Drug Substances and Products: Questions and Answers*.

<sup>104</sup> Section 314.50(d)(1)(ii).

active tablets and inert tablets should include a separate section 3.2.P for each strength of active tablets along with a separate section 3.2.P for the inert tablets.

**3.2.P.1** Contains the description and composition of the drug product. For each drug strength,<sup>105</sup> applicants should provide:

- (1) The quantitative composition and function of each component in their generic drug product, include any solvents and processing aids that are used during the manufacture of the drug product
- (2) Information related to the physical description of the product (tablet size, scoring) and comparison to the RLD<sup>106</sup>
- (3) The quality standards (e.g., the USP or the National Formulary) of components; the composition of colors, flavors,<sup>107</sup> and imprinting ink, if applicable
- (4) The amounts of their inactive ingredients that are appropriate per the Inactive Ingredient Database<sup>108</sup> (per dose or unit dose) and a justification, preferably in a tabular format, for those amounts
- (5) A conversion from percentage to milligram (mg)/dose values for all components, as applicable
- (6) A conversion from percentage to mg/milliliter (mL) and/or mg/vial for injectable and injection products, indicating the unit of percentage (weight/weight or weight/volume) for liquid dosage forms
- (7) A conversion from percentage to mg/mL for oral solution products
- (8) A conversion from percentage to mg/dose for dry powder to oral solution or oral suspension
- (9) An identification and justification of any formulation overages or overfills that appear in the final product

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<sup>105</sup> ICH guidance documents indicate that the information for all strengths should be combined and presented together in one drug product section. If the quality information is the same between all strengths, the data should appear only once. See, e.g., the guidances for industry *M4: The CTD — Quality Questions and Answers/Location Issues* and *M2 eCTD: Electronic Common Technical Document Specification*

<sup>106</sup> See the guidances for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation and Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*.

<sup>107</sup> Flavor manufacturers can provide the composition information directly to the reviewer if the information is not available to ANDA applicants because of proprietary reasons.

<sup>108</sup> The Inactive Ingredient Database is available at <https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>.

- (10) A daily elemental iron calculation or statement of adherence to 21 CFR 73.1200<sup>109</sup>
- (11) If the proposed product is packaged with a specific diluent, a demonstration that the diluent is qualitatively and quantitatively the same as the diluent packaged with the RLD
- (12) For products that contain aspartame, a calculation of the amount of phenylalanine (mg per dosage unit)<sup>110</sup>
- (13) For nonprescription products that contain potassium, calcium, magnesium, and/or sodium, a calculation for the potassium, calcium, magnesium, and/or sodium content of a single maximum recommended dose<sup>111</sup>
- (14) For products that contain alcohol, a calculation of the absolute alcohol in terms of percent volume (volume/volume)<sup>112</sup>
- (15) For antibiotics that contain sodium, a calculation for the sodium content (per tablet/capsule or per unit dose)

For sterile products, applicants should include a brief description of the primary container closure system, as well as any secondary packaging, for each configuration in section 3.2.P.1, and detailed information on the primary container closure system and secondary packaging should be included in section 3.2.P.7.

For generic drug products containing inactive ingredient changes permitted in accordance with § 314.94(a)(9)(iii)-(v), applicants must also identify and characterize the changes and provide information that demonstrates that these changes do not affect the safety or efficacy of the drug product.<sup>113</sup> (In other words, applicants must identify and demonstrate that any differences in the identity or amount of an inactive ingredient between the proposed product and the RLD product will have no effect on the safety or efficacy of the proposed product.) Given that the nature of the data and information necessary to demonstrate safety and efficacy can vary by product, applicants should submit a controlled correspondence to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov) or consult the Product-Specific Guidances for Generic Drug Development website<sup>114</sup> for current product-specific data recommendations prior to their submission of the application.

**3.2.P.2** Contains the pharmaceutical development report (for the product and the manufacturing process) and the microbial attributes (container closure integrity testing report for sterile product

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<sup>109</sup> FDA recommends that applicants provide a calculation of elemental iron intake based on the maximum daily dose of the drug product.

<sup>110</sup> 21 CFR 201.21.

<sup>111</sup> 21 CFR 201.72, 201.70, 201.71 and 201.64, respectively.

<sup>112</sup> 21 CFR 201.10(d)(2).

<sup>113</sup> Section 314.94(a)(9)(iii)-(v).

<sup>114</sup> Product-Specific Guidances for Generic Drug Development web page, note 56.

and the antimicrobial effectiveness testing for multi-dose sterile products, and if the sterile drug product is packaged, single-use/dose/multi-dose and/or pharmacy bulk.)

If the applicant has moved toward a Quality by Design approach,<sup>115</sup> applicants may demonstrate this approach in section 3.2.P.2. Applicants are encouraged to review FDA's Quality by Design for ANDAs: An Example for Modified Release Dosage Forms and An Example for Immediate-Release Dosage Forms.<sup>116</sup> For sterile products that are reconstituted (or further diluted) and stored prior to administration, the applicant should provide microbiological studies to support the worst-case postconstitution or postdilution storage times, diluents, and conditions that are stated in the product package insert labeling. The study should be a risk assessment that shows that adventitious microbial contamination does not grow (generally accepted as no more than 0.5log<sub>10</sub> growth) under the specified storage conditions.<sup>117</sup>

The applicant should include:

- (1) A table comparing the equipment, process parameters, and in-process controls for all exhibit and commercial batches
- (2) The procedures for reprocessing/reworking, if applicable
- (3) The batch reconciliation data

The applicant should clearly indicate which manufacturing process:

- (1) Was used in the preparation of the BE batch(es)
- (2) Is proposed for commercial production

**3.2.P.3** Contains information about the manufacture of the generic drug product.

**3.2.P.3.1** Contains information about the drug product manufacturer(s), including the:

- (1) Name and full address of the facility(ies) of each manufacturer, including the contractors, and each proposed production site or facility involved in the manufacturing and testing
- (2) Contact information for an agent at the facility (including phone and fax numbers and email addresses)
- (3) U.S. agent's name, if applicable

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<sup>115</sup> *Quality by Design* is defined as systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. See the ICH guidance for industry *Q8(R2) Pharmaceutical Development*.

<sup>116</sup> See the Question-Based Review for CMC Evaluations of ANDAs web page, note 77.

<sup>117</sup> See MAPP 5016.1 *Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review*.



- (4) Function or responsibility of the manufacturer<sup>118</sup>
- (5) Current good manufacturing practice certifications for both the applicant and the drug product manufacturer (if they are different entities)
- (6) Central File Number, Facility Establishment Identifier, and Data Universal Numbering System numbers, if known

This section should also contain all facilities listed on Form 356h as well as all research and development manufacturing and testing sites that generated data to support the application in accordance with § 314.50(d)(1)(ii)(b). All testing labs that perform functions integral to the control strategy, including but not limited to characterization and comparison of molecules, comparative analytical testing, and comparability testing labs, should be listed. For testing sites, applicants should include any testing sites that (1) generate stability testing/release data and BE data to support the application and (2) are used for commercial testing.

**3.2.P.3.2** Contains the batch formula for the generic drug product, including: (1) the amounts of the components including processing aids, if any, that come into contact with the drug substance or product during any stage of the manufacture (quantitative comparison, including the total numbers of dosage units, between the pilot scale and commercial scale in a tabular form recommended) and (2) an indication and justification of any overage(s) or weight adjustment(s) used. The applicant should clearly identify the formulation used in any BE studies, including the study identification number.

**3.2.P.3.3** Contains a complete description of the manufacturing process and controls, including:

- (1) A description of the manufacturing process and facility. (For a sterile drug product, this section should contain a description of the manufacturing and sterilization processes (e.g., the sterilization and/or depyrogenation of the primary packaging, the product contact manufacturing equipment, and the bulk drug product) and the associated manufacturing in-process controls.)
- (2) A manufacturing process flowchart showing the process flow, applicable process parameters, and in-process controls. If process analytical technology methods are used, applicants should indicate those methods in the manufacturing flowchart.
- (3) The master production batch record(s) for the largest intended production runs (i.e., commercial batch records) that is/are no more than 10 times the exhibit batch(es).

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<sup>118</sup> Applicants are encouraged to provide the complete testing description if the facility performs testing on the drug substance, the drug product, or both.

- (4) The master packaging record(s) for the intended marketing container(s). (If commercial scale batch records are not written in English, applicants must submit an English translation for them.<sup>119</sup>)
- (5) An indication whether the drug product is a sterile product.
- (6) A reprocessing statement in accordance with 21 CFR 211.115.

**3.2.P.3.4** Contains the controls of the critical steps and intermediates, including: (1) the acceptance criteria and test results for the exhibit batch(es), (2) a comparison of the controls and equipment between the exhibit and commercial batch manufacture, and (3) information about the holding periods.

**3.2.P.3.5** Contains information to demonstrate that the manufacturing process produces a dosage form that meets the product specifications, including an evaluation of the data generated for the critical material attributes and the critical process parameters that were found to meet the established scale-up guideline and/or acceptance criteria. (For a sterile product, this section should contain a validation of the sterilization processes (such as validation (bacterial retention studies) of the sterilizing grade filters) and/or the depyrogenation processes (such as the processes for the sterilization and/or depyrogenation of the primary packaging, the product contact manufacturing equipment, and the bulk drug product) and the manufacturing processes that impact the sterility assurance of the drug product.)<sup>120</sup>

**3.2.P.4** Contains information on the control of the excipients, including the identity of the source of inactive ingredients (including the supplier and the supplier's address) and the grades (e.g., compendial or noncompendial).

**3.2.P.4.1** Contains the testing specifications, including the retest schedule and the excipient manufacturer's or supplier's COA(s).

**3.2.P.4.2** Contains the analytical procedures for the noncompendial methods used for testing the excipients. For compendial excipients, applicants should reference the USP or the National Formulary but need not mention the analytical procedure.

**3.2.P.4.3** Contains the validation data of the noncompendial or in-house analytical procedures.

**3.2.P.4.4** Contains a justification of the specifications and includes: (1) the applicant's or the drug product manufacturer's COA(s), (2) the residual solvents statement(s) from the

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<sup>119</sup> Section 314.50(g)(2).

<sup>120</sup> See the guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* and MAPP 5040.1 *Product Quality Microbiology Information in the Common Technical Document — Quality (CTD)*.

manufacturer(s), and (3) the bovine spongiform encephalopathy, transmissible spongiform encephalopathy, and melamine certifications, as applicable.<sup>121</sup>

**3.2.P.5** Contains information on the control of the drug product.

**3.2.P.5.1** Contains the specifications for the drug product, including the microbiological specifications (e.g., the microbial limits, sterility, and bacterial endotoxins), as applicable. These specifications should include the tests, acceptance criteria, and references to methods in a tabular format.<sup>122</sup>

**3.2.P.5.2** Contains a description of the analytical procedures (compendial and/or in-house) used for testing the drug product, including any microbiological tests, as applicable. For sterile drug products, this section should contain the methods for the product release tests (e.g., sterility tests or bacterial endotoxins tests (if applicable)).

**3.2.P.5.3** Contains the validation of the analytical procedure, including:

- (1) The full validation reports for the in-house methods and their equivalence to USP procedures, if available for the drug product
- (2) A verification of USP General Chapter <1226> procedures, if referenced
- (3) The legible spectra and chromatograms for reference standards and test samples
- (4) The Sample Statement(s) of Availability and identification of the finished dosage form of the drug products<sup>123, 124</sup>

For sterile drug products, this section should contain the validation procedures and results for the microbiological analytical tests (e.g., sterility tests or bacterial endotoxins tests (if applicable)).

**3.2.P.5.4** Contains the batch analysis, including the executed COAs for all presentations and/or strengths of the finished dosage form. The applicant should clearly identify the drug product batch(es) used in any BE studies, including the study identification number.

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<sup>121</sup> See the guidance for industry *Pharmaceutical Components at Risk for Melamine Contamination*.

<sup>122</sup> For products requiring a bacterial endotoxin specification (i.e., when a USP monograph reports an endotoxins specification for a parenteral or intrathecal drug product), the applicant should alternatively propose a bacterial endotoxins specification based on the maximum patient dosage prescribed in the package insert labeling, not based on the USP monograph. The acceptance criteria for the maximum endotoxins dose to a patient are established in USP General Chapter <85>.

<sup>123</sup> Section 314.50(e)(1).

<sup>124</sup> Applicants are to provide method validation or verification reports for all analytical methods in section 3.2.P.5.3.

**3.2.P.5.5** Contains the characterization of impurities.<sup>125</sup> FDA recommends that applicants control all degradation products and process solvents if they are used during the manufacture of the finished dosage form. FDA also recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance and Drug Products.<sup>126</sup>

**3.2.P.5.6** Contains the justification of the specifications, including but not limited to references to compendia (e.g., the USP or the Japanese Pharmacopeia), the ICH, and/or the RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance and Drug Products.<sup>127</sup>

**3.2.P.6** Contains information about the reference standards or reference materials used for testing the drug product.

**3.2.P.7** Contains information on the container closure system, including:

- (1) A summary of the primary and/or secondary container closure system (including data for any resin used and technical diagrams/drawings of the container closure components, a statement whether the closure for each proposed packaging configuration is child resistant or non-child resistant, and a description of markings on the cap/ferrule overseals<sup>128</sup>)
- (2) The component specifications, including dimensional (drawing) and test data for each packaging component received by the applicant<sup>129</sup>
- (3) The packaging configuration(s) and size(s)
- (4) The container closure testing data in accordance with USP General Chapters <660>, <661>, and <671> (for solid oral, dosage forms, test for water permeation and light transmission; for liquids, test for leachable, extractables, and light transmission)
- (5) The source of the container closure system supply and the supplier's address<sup>130</sup>

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<sup>125</sup> See the guidance for industry *ANDA Submissions — Refuse to Receive for Lack of Justification of Impurity Limits*.

<sup>126</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>127</sup> Id.

<sup>128</sup> See USP General Chapter <7>.

<sup>129</sup> See the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics*.

<sup>130</sup> See the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics*. See also the draft guidance for industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use*. When final, this guidance will represent the FDA's current thinking on this topic.

For controlled substances, the applicant should provide a description of the tamper-evident properties of the container closure system as described in 21 CFR 1302.06. For OTC products, the applicant should confirm that the container closure system meets the requirements of 21 CFR 211.132.

**3.2.P.8** Contains the stability data<sup>131, 132</sup>

**3.2.P.8.1** Contains the stability summary and conclusions for the finished dosage form, including:

- (1) The preapproval stability protocol
- (2) The proposed expiration dating period for marketing packaging
- (3) The proposed expiration dating period for bulk packaging, if applicable
- (4) A storage temperature statement

**3.2.P.8.2** Contains the post-approval stability protocol. If the applicant and drug product manufacturer are different entities, stability protocols should be provided by the applicant. This section should also contain analytical procedures and testing schedules for maintenance of the microbial product quality (e.g., the container closure integrity/sterility, bacterial endotoxins, and microbial limits), as appropriate.<sup>133</sup>

**3.2.P.8.3** Contains stability data, including:

- (1) Accelerated and long-term data
- (2) Intermediate stability data, if applicable<sup>134</sup>
- (3) The batch numbers on the stability records that are the same as the test batch
- (4) The date the stability studies were initiated

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<sup>131</sup> See the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* and *ANDAs: Stability Testing of Drug Substances and Products: Questions and Answers*.

<sup>132</sup> FDA recommends that applicants use either three pilot-scale batches or two pilot-scale batches plus one small-scale batch with both accelerated and long-term data provided for each batch covering a period of no less than 6 months (180 days).

<sup>133</sup> See the guidance for industry *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products*.

<sup>134</sup> The applicant should provide either three pilot-scale batches or two pilot-scale batches and one small-scale batch with both accelerated and long-term data provided for each batch covering a period of no less than 6 months (180 days) and with data from three time points (e.g., 0, 3, and 6 months). However, if 6 months of accelerated data show a significant change or failure of any attribute in one or more batches, the applicant should also include 6 months of intermediate stability studies at the time of submission. See the guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* (Rev. 2).

- (5) The date that each stability sample was removed from the stability chamber for each testing time point<sup>135</sup>
- (6) Data on all presentations of the container-closure system

For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into worst-case and non-worst-case scenarios. For post-approval stability studies, the applicant should pick the worst-case orientation for the study.

The following information and data can also be included in this section:

- (1) One-time special stability studies conducted to confirm the quality of the constituted drug products (for example, parenterals and/or powders reconstituted with diluents and/or drug admixtures) per the labeling's instructions
- (2) One-time thermal cycling studies (freeze-thaw/heat-cool), as applicable
- (3) One-time in-use stability studies for oral liquids and other dosage forms (e.g., a solution to be used within a certain period of opening the container per labeling instructions, compatibility with a dropper when provided as part of the container closure system), as applicable

### 3. *Appendices*

**3.2.A.2** Contains an appendix for the Adventitious Agents Safety Evaluation for sterile products. This section will contain a description of the processes used to control for potential contamination with adventitious agents (e.g., transmissible spongiform encephalopathy and viruses). These processes may include assays to detect adventitious agents and actions taken to avoid them, as well as procedures to eliminate or inactivate them.

### 4. *Regional Information*

**3.2.R** Contains regional information for the drug substance and the drug product.<sup>136</sup>

**3.2.R.1.S** Contains the executed batch records for the drug substance. Applicants may refer to the DMF(s) for this information. If no DMF is referenced in the application, applicants should provide the executed and blank master batch records. The executed records should clearly identify the drug substance lot(s) used in any BE studies.

**3.2.R.2.S** Contains any comparability protocols proposed for the drug substance.<sup>137</sup>

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<sup>135</sup> See the guidance for industry *ANDAs: Stability Testing of Drug Substances and Products*.

<sup>136</sup> Section 314.50(d)(1)(ii)(b).

<sup>137</sup> See the draft guidance for industry *Comparability Protocols — Chemistry, Manufacturing, and Controls Information*. When final, this guidance will represent the FDA's current thinking on this topic.

**3.2.R.3.S** Contains the methods validation package for non-USP drugs. This information may also be placed in section 3.2.S.4.3.

**3.2.R.1.P.1** Contains the executed batch records<sup>138</sup> that include: (1) a copy of the executed batch record(s) with equipment specified and the packaging records (the packaging and labeling procedures); (2) the batch reconciliation and label reconciliation for the theoretical yield, the actual yield, and the packaged yield, all in a tabular format; and (3) the bulk package reconciliation for any bulk packaging that is considered a commercial container. The bulk package reconciliation is recommended if the bulk packaging is used to achieve the minimum package requirement. As part of the bulk package reconciliation recommendation, the applicant should submit bulk package stability data in section 3.2.P.8.3.<sup>139</sup>

**3.2.R.1.P.2** Contains information on components including but not limited to the applicants' and suppliers' COAs for the drug substance lots, inactive ingredients lots, and packaging components lots that are contained in the exhibit batches of the drug product, as well as the supplier's address.

**3.2.R.2.P** Contains the comparability protocols for the drug product, if applicable.<sup>140</sup>

**3.2.R.3.P** Contains the methods validation package. This package may also be contained in section 3.2.P.5.3.

## 5. *Literature References*

**3.3** Contains copies of any documents referred to in the application. The documents may include published articles, official meeting minutes, or other regulatory guidance or advice provided to the applicant. FDA recommends that these documents be provided in text-based PDF files.

## D. **Module 4 – Nonclinical Study Reports**

ANDAs generally do not contain data that are typically included in Module 4. If nonclinical study reports or safety assessments are submitted in support of a proposed specification (i.e., toxicology studies to qualify (1) impurities per the ICH guidances for industry *Q3A*<sup>141</sup> and

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<sup>138</sup> If the batch records are not written in English, applicants must submit an English translation for them. Section 314.50(g)(2).

<sup>139</sup> If the bulk package is to be shipped, the applicant should submit accelerated stability data at 0, 3, and 6 months; if the bulk package is warehoused only for repackaging, the applicant may provide real-time stability data at 0, 3, and 6 months. The applicant should provide bulk package labeling in section 1.14.1 and bulk package container and closure information in section 3.2.P.7.

<sup>140</sup> See the draft guidance for industry *Comparability Protocols — Chemistry, Manufacturing, and Controls Information*.

<sup>141</sup> See the ICH guidance for industry *Q3A Impurities in New Drug Substances* (Rev. 2).

*Q3B(R2)*,<sup>142</sup> (2) residual solvents, (3) leachables, or (4) excipients), these reports or assessments should be included in Module 4.

## **E. Module 5 – Clinical Study Reports**

Module 5 contains all of the clinical study report data needed to support the application and to demonstrate that the generic drug product is bioequivalent to the RLD.<sup>143</sup> To facilitate the submission of complete data, FDA develops product-specific guidances,<sup>144</sup> summary data tables (as referenced in section III.B.2 of this guidance),<sup>145</sup> and multiple guidances on biopharmaceutics.<sup>146</sup> Applicants should use an eCTD Study Tagging File for each study submitted.<sup>147</sup>

### *1. Complete Study Data*

**5.2** Contains the tabular listing of all clinical studies (e.g., pivotal, pilot, and failed studies) conducted.

**5.3** Contains the clinical study reports and related information.

**5.3.1** Contains the complete study data for the biopharmaceutic studies<sup>148</sup> and the lot numbers and strength of the products used in the BE study(ies). Applicants should document the study type.

**5.3.1.2** Contains reports of the comparative BA and BE studies (e.g., fasting or fed studies). This section should also contain information of in vivo BE studies including, but not limited to:<sup>149</sup>

- A synopsis of the study
- A study report
- The study's protocol and amendments

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<sup>142</sup> See the ICH guidance for industry *Q3B(R2) Impurities in New Drug Products* (Rev. 2).

<sup>143</sup> Section 314.94(a)(7).

<sup>144</sup> See the Product-Specific Guidances for Generic Drug Development web page, note 56.

<sup>145</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>146</sup> See the Biopharmaceutics guidances website, note 57.

<sup>147</sup> See ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files, available at <http://estri.ich.org/STF/STFV2-6-1.pdf>.

<sup>148</sup> See the ICH guidance for industry *M4E(R2): The CTD — Efficacy* (Rev. 1).

<sup>149</sup> See the FDA Study Data Standards Resources web page at <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm> to access the current FDA Data Standards Catalog.



- All case report forms
- A list of the independent ethics committees or institutional review boards and consent and/or assent forms
- The institutional review boards' approval letters for the protocol, amendments, and consent/assent forms
- A list and description of the investigators
- The number of subjects enrolled in each study site
- The signatures of the principal or coordinating investigator(s) or the sponsor's responsible medical officer
- A listing of the subjects receiving the test drug(s) from a specified batch
- The randomizations scheme
- The audit certificates and reports
- A statistical analysis plan and amendments
- Documentation of interlaboratory standardization methods of quality assurance procedures, if used<sup>150</sup>
- The publications based on the study<sup>151</sup>
- The important publications referenced in the report<sup>152</sup>
- A list of the discontinued patients, including the specific reason for each discontinuation<sup>153</sup>
- A list of subjects included in the per protocol (PP), modified/intent-to treat ((M)ITT), and safety populations<sup>154</sup>
- A list of subjects excluded from the PP, (M)ITT, and safety populations<sup>155</sup>

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<sup>150</sup> See the Abbreviated New Drug Application (ANDA) Forms and Submission Requirements web page, note 59.

<sup>151</sup> Id.

<sup>152</sup> Id.

<sup>153</sup> Id.

<sup>154</sup> Id.

<sup>155</sup> Id.

- A reason for excluding the PP, (M)ITT, and safety populations for each subject<sup>156</sup>
- Any protocol deviations, including the specific reason for each deviation
- Demographic data
- Drug concentration data
- Treatment compliance rate data
- The individual subject's response scores/data per visit
- The adverse event listings
- The concomitant medication listings
- A listing of the individual laboratory measurements by subject
- The site (identifier)
- The individual subject data listings
- The in vivo and/or in vitro BE study datasets
- A summary dataset containing a separate line listing for each subject<sup>157</sup>
- An analysis dataset containing a separate line listing for each visit per subject<sup>158</sup>
- The individual analysis datasets (e.g., adverse events or concomitant medications)<sup>159</sup>
- The analysis programs
- The annotated case report form
- The annotated electrocardiogram waveform datasets
- The image files
- The narrative safety reports for serious adverse events
- Source data

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<sup>156</sup> Id.

<sup>157</sup> Id.

<sup>158</sup> Id.

<sup>159</sup> Id.

- In vitro BE study information<sup>160</sup>

**5.3.1.3** Contains in vitro-in vivo correlation study reports.

**5.3.1.4** Contains reports of bioanalytical and analytical methods. If a method is used in multiple studies, the method and its validation should be included only once in section 5.3.1.4 and then referenced again in the individual study reports. Additionally, 100% raw numerical data and 20% chromatograms should be provided for each study.<sup>161</sup>

Case report forms should be placed under the study to which they pertain and appropriately tagged.<sup>162</sup>

The data provided in all of these sections should support the summary tables submitted in section 2.7. All comparative dissolution data from the in vitro-in vivo correlation study reports should be placed in section 2.7 with the dissolution summary tables.

## 2. *Literature References*

**5.4** Contains copies of any documents referred to in the application. The documents may include published articles, official meeting minutes, or other regulatory guidance or advice provided to the applicant. Applicants should submit one copy of all important references cited in the QOS or the individual technical reports contained in section 5.3.<sup>163</sup> FDA recommends that these documents be provided in text-based PDF files.

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<sup>160</sup> This information may also be included in section 5.3.1.

<sup>161</sup> See the draft guidance for industry *Bioanalytical Method Validation* (Rev. 1). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>162</sup> See the ICH guidance for industry *M4E(R2): The CTD — Efficacy* (Rev. 1).

<sup>163</sup> Id.

## APPENDIX: SUGGESTED COVER LETTER TEMPLATE<sup>1</sup>

*Date*

Heading: Provide the pre-assigned abbreviated new drug application (ANDA) number, if applicable  
Indicate, if applicable, that the submission is an original application  
Indicate that expedited review is being requested by providing the statement, “Expedited Review Request”

Reference: Provide the name of generic product name and strengths

*Dear Sir or Madam:*

Paragraph 1: Provide the name of the applicant  
Provide the name of the generic drug product and strengths  
Provide the drug product packaging description as single patient-use or single dose, multiple dose, and/or pharmacy bulk

Paragraph 2: Provide the reference listed drug (RLD) application number  
Provide the proprietary name, nonproprietary name, and drug product strengths as it appears on the RLD labeling  
Provide the name of the RLD holder

Paragraph 3: Indicate whether the GDUFA<sup>2</sup> fee has been paid  
Provide the amount of any GDUFA fees that were paid  
Provide the User Fee Payment ID Number  
Indicate that a copy of the Generic Drug User Fee Cover Sheet is contained in section 1.1

Paragraph 4: Indicate whether a Pre-Submission Facility Correspondence (PFC) was submitted  
Provide the date of any PFC submission

Paragraph 5: Indicate whether the application is for a combination product or a complex product (as defined in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter))  
Indicate whether Controlled Correspondence was used to develop the application  
Provide the numbers of any Controlled Correspondence that were used to develop the application  
Indicate that copies of any Controlled Correspondence are contained in section 1.2

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<sup>1</sup> Applicants are not required to use this template. However, if applicants utilize the template, they should use judgment in adapting the template to their specific needs.

<sup>2</sup> 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.

Indicate whether meeting minutes are contained in the application  
 Indicate that copies of any meeting minutes are contained in section 1.2  
 Indicate whether the Food and Drug Administration (FDA) reviewed any protocols or conducted telephone conferences with the applicant during development of the application  
 Indicate whether a suitability petition was approved in relation to this application  
 Indicate that the docket number of the suitability petition and a copy of FDA's approval letter are contained in section 1.12.11  
 Indicate whether a citizen petition was filed that relates to this application  
 Indicate that the docket number of the citizen petition, a copy of the petition, and FDA's response (if applicable) are contained in section 1.12.11

Paragraph 6: Indicate that Letters of Authorization for DMFs are contained in section 1.4.1  
 List all drug master files (DMFs) referenced in the application

Product name	DMF number	DMF holder and address	FEI/DUNS	Fee status

Indicate whether any approved ANDAs are referenced in the application  
 List all ANDAs referenced in the application

Product name	ANDA number	ANDA holder and address	FEI/DUNS	Fee status

Paragraph 7: Indicate whether any information or data in the application should be highlighted for a specific discipline's review  
 Indicate whether any method of sterilization (e.g., aseptic processing or terminal sterilization) was used for the drug product  
 Indicate that any pharmacological/toxicological data for review is contained in section 3.2.P.1

Paragraph 8: Identify the sites where the ANDA batches were manufactured (including each site's FEI or DUNS number)  
 Identify the sites where the marketed product will be manufactured for marketing (including each site's FEI or DUNS number)

Paragraph 9: Indicate the proposed drug product expiration date and the basis for the request is contained in section 3.2.P.8.1

Paragraph 10: Provide the basis for the expedited review request (if applicable)

Paragraph 11: Indicate whether a letter of Non-Repudiation Agreement for digital signatures was submitted to FDA

Provide the date of any letter of Non-Repudiation Agreement for digital signatures

Paragraph 12: Indicate the file structure (e.g., Microsoft Word, structured product labeling, or PDF) of the labeling

Paragraph 13: Indicate whether the RLD has a risk evaluation and mitigation strategy  
Indicate that information on any proposed risk evaluation and mitigation strategy is contained in section 1.16

Paragraph 14: Indicate that information related to the physical description of the product (e.g., the tablet size or scoring) and a comparison of the physical properties of the generic product to the physical properties of the RLD are contained in section 3.2.P.1  
Provide information about the tamper-resistant properties of the drug product

Paragraph 15: Provide a summary table of subsections applicable to the ANDA

Paragraph 16: Provide a summary of any comparability protocol that is contained in the application

Paragraph 17: Provide the name and contact information for a technical point of contact

Paragraph 18: Provide the signatory's contact information

*Signature*