Guidance for Industry

ANDA Submissions — Content and Format of Abbreviated New Drug Applications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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For questions regarding this draft document contact (CDER) Elizabeth Giaquinto 240-402-7930 or (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-7800.

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)

June 2014
Generics

Guidance for Industry

ANDA Submissions — Content and Format of Abbreviated New Drug Applications

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Guidance for Industry[1]
ANDA Submissions — Content and Format of Abbreviated New Drug Applications

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

I. INTRODUCTION

This guidance is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to the Food and Drug Administration (FDA) under section 505(j) of the Federal Food, Drug and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)). This guidance details the information to be provided in each section of the Common Technical Document (CTD) format for human pharmaceutical product applications and identifies supporting guidance documents and recommendations issued by FDA to assist in preparing the submission. This guidance does not address the fee structure or payment of obligations under the Generic Drug User Fee Amendments (GDUFA)[2] and does not address the submission and assessment of drug master files (DMFs), amendments to original ANDAs, and changes being effected or prior approval supplements.

This guidance identifies the information an applicant should include to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance on the filing process, including the refuse-to-receive standards, which should be reviewed thoroughly to avoid common deficiencies found in ANDA submissions (Ref. 1).

FDA's guidance documents, including this guidance, 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.

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration in cooperation with the Center for Biologics Evaluation and Research.
[2] Information on fees and industry obligations is available at http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm.

II. BACKGROUND

Procedures for ANDAs submissions are set forth in FDA's regulations in part 314 (21 CFR part 314). An ANDA is usually[3] submitted for a drug product that is the same as an already approved drug or listed drug. A *listed drug* is defined in § 314.3(b) as a new drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the FD&C Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness (§ 314.161). An applicant submits an ANDA based on a listed drug, and the previously approved drug product on which the ANDA relies is officially known as the *reference listed drug* (RLD). A reference listed drug (RLD) is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application (§ 314.3(b)). FDA lists approved drugs that may be referenced in an ANDA in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).[4] The Orange Book is updated by a monthly cumulative supplement.

On July 9, 2012, GDUFA was signed into law by the President to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. Under GDUFA, FDA agreed to meet certain obligations as laid out in the GDUFA Commitment Letter.[5] Among these obligations is FDA's commitment to performance metrics for the review of new ANDAs that are submitted electronically following the electronic CTD (eCTD) format. For example, FDA has committed to review and act[6] on 90 percent of original ANDA submissions within 10 months from the date of submission in Year 5 of the program, which begins on October 1, 2016.

To meet these performance goals, FDA is issuing this guidance to assist ANDA applicants in improving the quality of submissions, to increase the number of original ANDAs acknowledged for receipt upon initial submission, and to decrease the number of review cycles. FDA is committed to providing comprehensive assistance in the early stages of the application process so that an original ANDA will contain all information necessary for FDA to complete its review in one review cycle.

III. CTD FORMAT

The CTD format was developed by the International Conference on Harmonisation (ICH) in an attempt to streamline the variability of submission requirements among 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. As previously stated, only

[3] An ANDA may be submitted for certain changes in drug product that differ from the RLD in accordance with section 505(j)(2)(C) of the FD&C Act and § 314.93.

[4] Available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[5] See GDUFA Program Performance Goals and Procedures available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[6] As defined in the Commitment Letter, an action on a submission includes issuance of a complete response, an approval letter, a tentative approval letter, or a refuse-to-receive action.

ANDA submissions made electronically following the eCTD format on the date of submission will be subject to the review metric goals described in the GDUFA Commitment Letter.[7]

Section 745A(a) of the FD&C Act, added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), requires that submissions under section 505(b), (i), or (j) of the FD&C Act and section 351(a) or (k) of the Public Health Service Act (42 U.S.C. 262(a) or (k)) be submitted in electronic format specified by FDA, beginning no earlier than 24 months after FDA issues a final guidance specifying an electronic submission format. When finalized, the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Ref. 2) will implement the electronic submission requirements of section 745A(a) of the FD&C Act by requiring the eCTD format for ANDA submissions, among other submission types.

Applicants are reminded that any record in electronic form submitted to FDA under requirements of the FD&C Act are subject to the provisions of 21 CFR part 11 (part 11) unless exempted. Part 11 regulations were issued in 1997 to provide criteria for acceptance of electronic records, electronic signature and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures on paper (Ref. 3).

FDA has issued several guidance documents specific to the CTD and eCTD submissions.[8] 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 addresses the content of the CTD for an original ANDA.

The CTD is comprised of the following modules:

- Module 1:[9] Administrative information;
- Module 2: CTD Summaries;
- Module 3: Quality;
- Module 4: Nonclinical study reports; and
- Module 5: Clinical study reports.

The sections that follow in this guidance detail the information to be submitted in the applicable Modules, sections, and subsections.

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[7] See Commitment Letter at 7.

[8] See the Drugs 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 the Biologics Web page at http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm163685.htm.

[9] 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 of the ANDA submission contains several forms.[10]

1.1.2 Contains the completed, signed Application Form FDA 356h (§ 314.94(a)(1)).[11] Applicants should provide complete contact information, including phone and fax numbers, for the agent stationed at each facility listed in the 356h form, along with detailed descriptions of the type of testing performed at each, where applicable. Applicants will be notified of failure to complete facility and testing information. Failure to provide the requested information in a timely fashion will result in the application being refused for receipt (Ref. 1). Applicants may use continuation pages, as necessary.

1.1.2 Also contains copy of the GDUFA user fee cover sheet (FDA Form 3794).[12]

1.2 Contains a cover letter. A suggested cover letter template is attached to this guidance at Appendix B.

1.2.1 Contains the completed, signed Form FDA 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)).

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

[10] FDA Forms listed in this section and other parts of this guidance are available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm.

[11] For original (initial) applications, Field 29 should include complete information on the locations of all manufacturing, packaging, and control sites for both drug substance and drug product. For each site, include the establishment name, address, registration (FEI) number, Master File (MF); Drug Master File (DMF) or Biologic Master File (BMF) number (for facilities used under a MF), and establishment DUNS number. Indicate whether the establishment is new to the application (new establishments will have, by default, a "pending" status). If the establishment is not new, indicate its current status (e.g., active, inactive, or withdrawn) in the appropriate box. Also provide the name, address, phone number, fax number and email address for the contact at the site. In the section "Manufacturing Steps, and/ or Type of Testing," provide a brief description of the specific manufacturing steps and/or type of testing (e.g., final dosage form, stability testing) conducted at the site (i.e., describe the type(s) of assays or testing completed). Also, indicate whether the site is ready for inspection so that FDA can evaluate whether the site is able to reliably perform intended operation(s) at a commercial scale. Regarding readiness for commercial manufacturing, refer to Compliance Program Guidance Manual 7346.832. If the establishment is not ready for inspection at the time of submission of Form 356h, indicate when it will be ready. Instructions for completing FDA Form 356h are available at http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm321897.pdf.

[12] All applicants submitting original ANDAs, with the exception of positron emission tomography drugs (section 744B(l) of the FD&C Act), 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.

States, an agent that resides or maintains a place of business in the United States must countersign the application (§ 314.50(a)(5)).

1.3.2 Contains the field copy certification (§ 314.94(d)(5)). The applicant will certify that the field copy submitted to the appropriate district office is a true copy of the technical section contained in the archival and review copies of the ANDA.

1.3.3 Contains the debarment certification required under the Generic Drug Enforcement Act of 1992 (section 306(k) and 306(a) and (b) of the FD&C Act (21 U.S.C. 335a(k) and 335(a) and (b))). The applicant must certify that it did not and will not use the services of any debarred persons in connection with the application. The applicant must also list all convictions described in the FD&C Act (section 306(k) and 306(a) and (b)). The applicant may use the following language from section 306(k)(1) for the certification required for section 1.3.3:[13]

> *(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.

(See also Ref. 4.)

1.3.4 Contains financial certification for any clinical investigator who has no disclosable financial interests in, or arrangements with, any applicant of the covered clinical study (FDA Form 3454) or disclosure statement for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study (FDA Form 3455) (21 CFR part 54 and § 54.2(e)).

1.3.5 Contains patent information and certification. Applicants are required to list each patent issued by the U.S. Patent and Trademark Office that claims the drug substance, drug product, or that claims a use of the RLD that is cited by the ANDA (§ 314.94(a)(12)). 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 that pediatric exclusivity will expire. For each patent listed, the applicant must certify to one of the following paragraphs (§ 314.94(a)(12)(i)(A)(1) through (4)):

- That the patent information has not been submitted to FDA (Paragraph I certification)
- That the patent information has expired (Paragraph II certification)
- The date on which the patent will expire (Paragraph III certification)
- 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 indications that

[13] Qualifying phrases, such as "to the best of our knowledge," should be avoided.

are covered by the use patent, the applicant must also submit a statement explaining that the method of use patent does not claim any of the proposed indications (§ 314.94(a)(12)(iii)).

Applicants submitting a Paragraph IV certification will provide the following language from § 314.94(a)(12)(i)(A)(4):

> 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 the holder of the approved application that lists the patent(s) that is/are being challenged (§ 314.94(a)(12)(i)(A)(4)). The process for notice is provided in section 505(j)(2)(B) of the FD&C Act and § 314.95.[14]

Applicants should also submit an exclusivity statement regarding their marketing intentions. This statement is relevant when the generic applicant intends to remove or *carve out* any protected indication(s) from the labeling in order to gain market entry prior to a use's expiry.

3. References

1.4.2 Contains the statement of right of reference for each and every DMF referenced in the application. Applicants should submit the letter of authorization (LOA) provided to the applicant by the DMF holder which gives authorization to rely on the information in the DMF (§ 314.420(d)).[15]

4. Other Correspondence

1.12.4 Contains a statement that a request for a proprietary name has been made, if applicable. An ANDA applicant requesting a proprietary name should submit that request when the ANDA is submitted to ensure 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**" (Ref. 5).

1.12.11 Must contain the basis for submission, which is the reference to the RLD (§ 314.94(a)(3)). Applicants should review the guidance for industry *Variations in Drug Products that May Be Included in a Single ANDA* (Ref. 6) to determine whether one or more ANDAs should be submitted for variations of a specific drug product dosage form. The applicant should provide: (1) the name of the RLD; (2) the NDA or ANDA number of the RLD; and (3) the holder of the application for the RLD.

[14] Notice is to be provided only **after** the applicant has received a formal correspondence from FDA stating that the ANDA has been acknowledged for receipt.

[15] More information on DMFs and the list of received DMFs is available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm.

For an ANDA based on an approved petition under § 10.30 (21 CFR 10.30) or § 314.93, this section must contain the FDA docket number and a copy of FDA's correspondence approving the suitability petition (§ 314.94(a)(3)(iii)). If the generic drug differs from the RLD in strength, route of administration, dosage form, or single active ingredient in a combination drug product, applicants must first submit a suitability petition to FDA's Division of Dockets Management to obtain permission to file their ANDA (§ 314.93; § 10.20 (21 CFR 10.20), § 10.30). The applicant must submit the suitability petition in accordance with the requirements of §§ 10.20 and 10.30 (§ 314.93(c)). The suitability petition must be approved before the ANDA is submitted (§ 314.93(b)). The information to be included in the suitability petition is listed at § 314.93(d). FDA will review the suitability petition to determine whether the requested change from the listed drug will have an impact on the safety and effectiveness of the generic product and if any applicable requirements of the Pediatric Research Equity Act (PREA) may be waived (Ref. 7). After a suitability petition is approved for a change to a drug product, any applicant may refer to that petition as the basis of submission for an ANDA. Once an application based on a suitability petition is approved, the suitability petition may no longer be relied upon as a basis of submission. The approved drug product will become the RLD for the basis of submission.

When an applicant wants FDA to designate a second RLD, the request is made through a citizen petition submitted to FDA's Division of Dockets Management in accordance with §§ 10.20 and 10.30. An applicant may submit the application only after the citizen petition has been granted.

If an applicant refers to a listed drug that has been voluntarily withdrawn from sale in the United States, the applicant must submit a citizen petition under § 10.25(a) (21 CFR 10.25(a)) and § 10.30 to FDA's Division of Dockets Management requesting FDA to determine whether the listed drug was withdrawn for reasons of safety or effectiveness (§ 314.122) (often referred to as a relisting petition). A relisting petition may be submitted concurrently with the ANDA. However, approval of the ANDA will be dependent on FDA's response to the petition.

1.12.12 Contains information demonstrating that the generic product is the *same* as the RLD (section 505(j)(2)(A) of the FD&C Act and § 314.94). *Same* means that the generic product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as the RLD (§ 314.92(a)(1)). To demonstrate the comparison to the RLD, applicants provide:

(1) a statement that the conditions of use for the generic product have been previously approved for the RLD (§ 314.94(a)(4));

(2) information to show that the active ingredient(s) is the same as the RLD (§ 314.94(a)(5));

(3) information to show that the route of administration, dosage form and strength are the same as those of the RLD (§ 314.94(a) (6)); and

(4) as applicable, information to indicate the strength of the generic drug product used in the in vivo bioequivalence studies (fasting and fed) to demonstrate bioequivalence of the generic drug product to the RLD.

Applicants must also identify and characterize the inactive ingredients and demonstrate that the inactive ingredients do not affect the safety or efficacy of the proposed drug product

(§ 314.94(a)(9)(ii)). This means that any differences in the identity or amount of an inactive ingredient between the proposed product and the RLD product must be identified and demonstrated as having no effect on safety or efficacy. 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, consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product-specific data recommendations and the Biopharmaceutics guidances Web site, or contact the appropriate CBER review division prior to submission of the application.

FDA recommends that an applicant submit within the original application all strengths that the applicant intends to market. However, note that applicants are not able to submit a new pharmacy bulk strength in an amendment (see Ref. 6 for more exceptions).

1.12.14 Contains the environmental assessment (EA) (21 CFR 25.20), environmental impact statement (EIS) (21 CFR 25.22), or claim of categorical exclusion under 21 CFR 25.30 or 21 CFR 25.31 and the justification for the exclusion. Failure to provide the EA or statement for categorical exclusion is sufficient grounds to refuse to receive the application (§ 314.101(d)(4)) (Ref. 8).

1.12.15 Contains a request to waive the requirement to submit evidence measuring in vivo bioavailability (BA) or demonstrating in vivo bioequivalence (BE) of the generic product (known as a biowaiver), if applicable (21 CFR 320.22). The data necessary to support a waiver request vary by product. For this reason, applicants should submit a controlled correspondence to GenericDrugs@fda.hhs.gov, consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product-specific data recommendations and the Biopharmaceutics guidances Web site, or contact the appropriate CBER review division prior to submission of the application.

5. Labeling

1.14.1 Contains labeling for the generic product submitted in text-based Portable Document Format (PDF),[16] Microsoft Word, and Structured Product Labeling (SPL) formats (§ 314.94(a)(8)(ii) and Ref. 9). If the application is for a pharmacy bulk package product, applicants should complete and submit the Pharmacy Bulk Package Sterility Assurance Table to address sterility assurance of the drug product associated with the labeling and microbiological study data that may be submitted in the application.[17]

1.14.1.1 Contains the draft label and labeling for each strength and container including package size. Applicants should ensure that label and labeling design do not contribute to medication error (Ref. 9). Confirm if the container closure is child resistant (CRC).

[16] For all PDF submissions, FDA requests that applicants submit text-based PDF files, not image-based PDF files

[17] See the ANDA Forms and Submission Requirements page on the FDA Web site available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm.

1.14.1.2 Contains side-by-side labeling comparison of container(s) and carton(s) with the RLD for each strength and package size. All differences should be highlighted and annotated. Applicants should indicate the RLD version used for the side-by-side comparison.

1.14.1.3 Contains the prescribing and patient information in text-based PDF, Microsoft WORD and SPL formats. Applicants should identify the RLD version used for the side by side comparison.

1.14.1.4 Contains Pharmacy Bulk Package Sterility Assurance Table, if applicable.

1.14.1.5 Contains labeling history.

Applicants are encouraged to review and use the Labeling Question-Based Review (QbR) model when developing labels and labeling.[18] 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 highlighted and annotated (§ 314.94(a)(8)(iv)). Applicants should also submit the RLD package insert, Medication Guide, one container label, and one outer carton, if applicable, for each strength and package size listed in the application (§ 314.94(a)(8)(i)). Applicants are reminded to use the most recent RLD labeling available at the Drugs@FDA Web site.

1.14.3.1 Contains side-by-side labeling (professional insert, patient insert and Medication Guide) comparison. All differences are highlighted and annotated. In addition, applicants should state that a sufficient number of patient inserts will be included in each package size. Applicants should confirm that Medication Guides will be distributed in accordance with 21 CFR 208.24.

1.14.3.3 Contains the RLD professional and patient inserts, Medication Guide, one (1) RLD container label, and one (1) RLD outer carton label for each strength and package size, if applicable.

1.16.1 Contains the risk management plan (section 505-1 of the FD&C Act (21 U.S.C. 355-1)) for products that require tools to minimize risks while preserving benefits.

1.16.2 Contains the risk evaluation and mitigation strategy (REMS) and all supporting documents, if the RLD has a REMS (Ref. 10). A REMS for an ANDA must have the same Medication Guide and patient package insert as does the RLD (section 505-1(i)(1)(A) of the FD&C Act). 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 505-1(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 (Ref. 10).

[18] Id.

B. Module 2 – CTD Summaries

1. Quality Overall Summary

2.3 Contains the Quality Overall Summary (QOS), which provides an overview of the chemistry, manufacturing, and controls (CMC) section of the application (§ 314.50(c)(2)(iv)). The QOS summarizes what is known about the drug substance (the active pharmaceutical ingredient (API)) in section **2.3.S** and the drug product in section **2.3.P.** Applicants should provide separate information on each drug substance contained in the product in section 2.3.S. All information provided in the summary needs to be accurate and supported by information, data, or justification included in Module 3 or other parts of the application (Ref. 11).

Applicants should use the Question-Based Review (QbR) model when writing their summaries. FDA introduced the QbR initiative in 2005 as a tool for the review of the CMC — Drug Substance and Drug Product Quality — sections of the ANDA[19] and updated the QbR model to include additional CMC questions from microbiology in 2011. The QbR model assists applicants in developing their QOS by providing specific questions that, when answered, ensure adequate information is submitted for FDA review. FDA has posted the QbR-QOS outlines designed for simple dosage form products (solution or immediate-release solid oral dosage forms)[20] and for sterility assurance of products terminally sterilized by moist heat.[21, 22] FDA has also developed example QOS summaries for controlled-release capsules[23] and immediate-release tablets.[24] 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.[25]

FDA recommends that the QOS be submitted in MS Word and text-based PDF file. If the applicant provides a scanned PDF copy of the QOS, FDA requests that the applicant also submit the QOS in Microsoft Word.

2. Clinical Summary

2.7 Contains the submission of summary data critical to the determination of bioequivalence (21 CFR 320.21(b) and 21 CFR 320.24(b)). FDA has developed model summary tables to assist applicants in summarizing these data.[26, 27] The tables provide a format for applicants to

[19] Id.
[20] Id.
[21] Id.
[22] 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 Module 2.3.P would also apply to sterile products that are aseptically filled.
[23] Supra note 17.
[24] Id.
[25] Id.
[26] See id. for the Model Bioequivalence Summary Data Tables.
[27] FDA has also developed summary tables for clinical endpoint bioequivalence studies. Id.

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 ANDA Forms and Submission Requirements Web site.[28] In addition, applicants should submit summary tables for all studies conducted, whether they are passing or failed studies (Ref. 12).

2.7 Contains the completed tables in Microsoft Word and text-based PDF file.

2.7.1.1 Contains summary reports and/or data for in vivo BE studies with clinical endpoints or skin irritation/sensitization/adhesion studies.[29]

C. Module 3 – Quality

Module 3 contains all of the CMC information necessary to support the application (§ 314.94(a)(9)(i)), including the information supporting and verifying what was summarized in Module 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*[30] (see also Ref. 13 and Ref. 14). 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 (Ref. 15). FDA recommends that applicants submit a table of contents for Module 3.

It is recommended that applicants review the following guidances for industry to assist in the preparation of Module 3: *ANDAs: Impurities in Drug Products* (Ref. 16), *ANDAs: Impurities in Drug Substances* (Ref. 17), and *ANDAs: Stability Testing of Drug Substances and Products* (Ref. 18).[31]

1. Drug Substance

Section 3.2.S contains the CMC information specific to the drug substance(s) (§ 314.50(d)(1)(i)). 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. To assist in preparing data for the drug substance section, applicants should review the guidance for industry *Guideline for*

[28] Applicants should periodically refer to the Web site as the Agency may update existing tables or expand the number of tables to address additional study types as well as waiver requests.

[29] See the FDA Data Standards Resources Web Site for current FDA data standards catalog available at http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

[30] See the CDER Manual of Policies and Procedures page of the FDA Web site available at http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/default.htm.

[31] FDA further recommends that applicants review the following guidances for industry, as applicable: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Ref. 19); *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (Ref. 20); *Size of Beads in Drug Products Labeled for Sprinkle* (Ref. 21); *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (Ref. 22); *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (Ref. 23) and *ANDA Submissions — Refuse-to-Receive Standards* (Ref. 1).

Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (Ref. 24).

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 each drug substance manufacturer including:

(1) the name and full address of the facility(ies);

(2) contact information for an agent at the facility (phone, fax numbers and email address);

(3) function or responsibility;

(4) the Type II DMF number for the API; and

(5) the Central File Number (CFN), Facility Establishment Identifier (FEI) or Data Universal Numbering System (DUNS) numbers, if known.

The applicant should also provide current good manufacturing practice (cGMP) and/or Debarment Certification of the facility that matches the information provided in FDA Form 356h. 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 (Ref. 24). For a sterile substance for use in a sterile drug product, section 3.2.S.2.2 will include the sterilization process and any in-process controls and section 3.2.S.2.5 will contain the validation of sterilization processes for the drug substance.

3.2.S.3 Contains characterization information for the API. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance.[32]

3.2.S.4 Contains all information about the control of the drug substance.

3.2.S.4.1 Contains the drug substance specifications. These specifications include the tests, acceptance criteria, and references to methods in tabular form. If the application contains a sterile substance for use in a sterile drug product, this section will also contain the microbiological specification for the drug substance.

3.2.S.4.2 Contains the description of analytical procedures (compendial and/or in-house). If the application contains a sterile substance for use in a sterile drug product, this section will also contain the microbiological analytical procedures used to test the drug substance.

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

(1) full validation reports for in-house methods and their equivalence to United States Pharmacopeia (USP) procedures if available for the drug substance;

(2) verification of USP <1226> or DMF procedures, when referenced;

[32] Supra note 17.

(3) legible spectra and chromatograms for reference standards and test samples; and

(4) Sample Statement(s) of Availability and identification of the drug substance, along with associated lot numbers (Ref. 15).[33]

If the application contains sterile substance for use in a sterile drug product, this section will also contain the validation of the microbiological analytical procedures used to test the drug substance.

3.2.S.4.4 Contains the batch analysis including the Certificates of Analysis (COAs) from both the drug substance manufacturer (s) and drug product manufacturer for the batches used to produce the exhibit batch(es) of the drug product.

3.2.S.4.5 Contains the justification of the specifications including, but not limited to, references to compendia (e.g., USP, European Pharmacopeia (EP), and the Japanese Pharmacopeia (JP)), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance.[34]

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. Reference to the DMF alone is inadequate.

3.2.S.6 Contains information about the container closure systems (Ref. 25). If the application contains a sterile substance for use in a sterile drug product, this section will also contain a description of the container closure system used for the drug substance and the validation of the container closure integrity.

3.2.S.7 Contains stability data including the retest date or expiration date of the API. Information provided should include the retest date or expiration date of the API at both the drug product manufacturing site and the drug substance manufacturing site (Refs. 18 and 23).

2. Drug Product

Section 3.2.P contains detailed information known about the drug product (§ 314.50(d)(1)(ii)). During the development of the application, applicants should review the guidances for industry *Q8(R2) Pharmaceutical Development* (Ref. 26) and *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (Ref. 13) and the product-specific CMC guidances for industry (e.g., metered dose inhalers, nasal spray) as applicable. A drug product supplied with a reconstitution diluent should include a separate Module 3.2.P with the diluent information.

[33] Method validation/verification reports for all analytical methods are to be provided in section 3.2.S.4.3.

[34] Supra note 17.

3.2.P.1 Contains the description and composition of the drug product. For each strength,[35] provide:

(1) the quantitative composition and function of each component in the drug product; include solvents and processing aids that are used during manufacture, as applicable;

(2) information related to the physical description of the product (tablet size, scoring) and comparison to the RLD (Refs. 20 and 22);

(3) the quality standards (e.g., USP, National Formulary (NF)) of components; composition of colors, flavors,[36] and imprinting ink, if applicable;

(4) amounts of inactive ingredients that are appropriate per the Inactive Ingredient Database[37] (per dose or unit dose) and justification (FDA recommends that applicants provide the justification in a tabular format);

(5) conversion from percentage to milligram (mg)/dose values for all components, as applicable;

(6) identification and justification of any formulation overages or overfills that appear in the final product;

(7) daily elemental iron calculation or statement of adherence to 21 CFR 73.1200;[38]

(8) if the RLD is packaged with a specific diluent, demonstration that the diluent is qualitatively and quantitatively the same (Q/Q same) as that packaged with the RLD;

(9) a calculation of the amount of phenylalanine (mg per dosage unit) for products that contain aspartame (21 CFR 201.21);

(10) for OTC products that contain potassium calcium, magnesium, and/or sodium: the calculation for potassium, calcium, magnesium and/or sodium content of a single maximum recommended dose;

(11) a calculation of absolute alcohol in terms of percent volume (v/v) for products that contain alcohol (21 CFR 201.10(d)(2)); and

(12) for antibiotics that contain sodium: the calculation for sodium content (per tablet/capsule, per unit dose).

For sterile products, this section will contain a description of the primary container closure system information for each configuration.

For drug products containing inactive ingredient changes permitted in accordance with § 314.94(a)(9)(iii)-(v), applicants must also identify and characterize the differences and provide information that demonstrates the change(s) does/do not affect the safety or efficacy of the drug product. This means that any differences in the identity or amount of an inactive ingredient between the proposed product and the RLD product must be identified and demonstrated as

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[35] One 3.2.P section should encompass all strengths. 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 only appear once.

[36] Flavor manufacturers can provide the composition information directly to the reviewer if the information is not available to ANDA applicants due to proprietary reasons.

[37] The Inactive Ingredient database is available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm.

[38] FDA recommends that applicants provide a calculation of elemental iron intake based on the maximum daily dose of the drug product.

having no effect on safety or efficacy. 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 or consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product-specific data recommendations prior to submission of the application.

3.2.P.2 Contains information on the pharmaceutical development of the drug product including the pharmaceutical development report and the microbial attributes — the container closure integrity testing report for sterile product, antimicrobial effectiveness testing for multi-dose sterile products, and if the sterile drug product is packaged, as single-use/dose/multi-dose and/or pharmacy bulk. If the applicant has moved toward a Quality by Design (QbD) approach,[39] applicants may demonstrate their methods in section 3.2.P.2. Applicants are encouraged to review FDA's information on Quality by Design for ANDAs: An Example for Modified Release Dosage Forms and An Example for Immediate-Release Dosage Forms.[40] 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 stated in the product package insert labeling. The study should be a risk assessment that shows adventitious microbial contamination does not grow (generally accepted as not more than (NMT) $0.5\log_{10}$ growth) under the specified storage conditions. [41]

3.2.P.3 Contains information about the manufacture of the drug product including:

(1) the name and full address of the facility(ies);

(2) contact information for an agent at the facility (phone and fax numbers, email address);

(3) function or responsibility;[42]

(4) cGMP certification for both the applicant and the drug product manufacturer if different entities; and

(5) the CFN, FEI, or DUNS numbers, if known.

The information provided in this section should match the information provided in Form FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories.

3.2.P.3.2 Contains the batch formula for the drug product including: (1) amounts of components including processing aids, if any, that come into contact with the drug substance or product during any stage of manufacture (quantitative comparison between the pilot scale and commercial scale in a tabular form recommended) and (2) indication and justification of any overage(s) or weight adjustment(s) used.

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

[39] Pharmaceutical Quality by Design (QbD) is defined as systematic approach to development that beings with predefined objectives and emphasizes product and process understanding and process control, based on sounds science and quality risk management (Ref. 26).

[40] Supra note 17.

[41] See MAPP 5016.1 *Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review*, Supra note 33.

[42] Applicants are encouraged to provide the complete testing description if the facility performs testing on either the drug substance, the drug product, or both.

(1) a description of the manufacturing process and facility;
(2) manufacturing process flow chart showing controls;
(3) master production batch record(s) for the largest intended production runs (i.e., commercial batch records);
(4) master packaging records for intended marketing container(s);
(5) indication whether the drug product is a sterile product; and
(6) reprocessing statement pursuant to 21 CFR 211.115 submitted by the applicant, at a minimum.

3.2.P.3.3.1 For sterile products, this section contains: (1) a description of the manufacturing process for the drug product, including sterilization processes and any in-process controls, and (2) the sterilization information including the sterilization and depyrogenation of packaging components and equipment.

For products sterilized by terminal moist heat, this section will include a description of the:
(1) autoclave process and performance specifications; autoclave loading patterns;
(2) methods and controls to monitor production cycles;
(3) requalification of production autoclaves;
(4) reprocessing; and
(5) environmental monitoring, including a bulk drug solution bioburden action level prior to sterilization.

For products sterilized by aseptic processing, this section will include a description of the:
(1) building and facilities;
(2) overall manufacturing operation;
(3) sterilization and depyrogenation of containers, closures, equipment, and components; and
(4) environmental monitoring, including a bulk drug solution bioburden action level prior to sterilization. (Ref. 14 and MAPP 5040.1)

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

3.2.P.3.5 Contains process validation information to demonstrate that the manufacturing process produces a dosage form that meets product specifications including evaluation of data generated for the critical material attributes and critical process parameters that were found to meet the established scale-up guideline and/or acceptance criteria (Ref. 27).

For a terminally sterilized product, this information includes: (1) validation of the production terminal sterilization process; (2) validation of depyrogenation of all product container and closures; and (3) holding periods.

For an aseptically filled product, this information includes:

(1) validation (bacterial retention studies) of sterilizing grade filters;
(2) validation of the sterilization of sterile bulk drug or product contact equipment;
(3) validation of sterilization and depyrogenation of product containers and closures;
(4) validation of aseptic filling process/line/room (media fills/process simulations);
(5) holding periods; and
(6) actions taken after a media fill failure. (Ref. 14 and MAPP 5040.1)

3.2.P.4 Contains information on the controls of excipients including the identity of the source of inactive ingredients and the grades (e.g., compendial or noncompendial).

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

3.2.P.4.2 Contains the analytical procedures for the testing.

3.2.P.4.3 Contains the validation data of the analytical procedures.

3.2.P.4.4 Contains the justification of the specifications and includes: (1) the applicant's or drug product manufacturer's COA(s); (2) residual solvents statement(s) from manufacturer(s); and (3) bovine spongiform encephalopathy (BSE), transmissible spongiform encephalopathy (TSE), and melamine certifications, as applicable (Ref. 28).

3.2.P.5 Contains information supporting the controls of the drug product.

3.2.P.5.1 Contains the specifications for the drug product. These specifications include the tests, acceptance criteria, and references to methods in a tabular form. For sterile products, this section will contain the release specifications for the drug product (sterility, bacterial endotoxins, etc.). In cases where 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 the USP monograph. The acceptance criteria for the maximum endotoxins dose to a patient are established in USP <85>.

3.2.P.5.2 Contains the description of analytical procedures (compendial and/or in-house). For sterile products, this section will contain methods for product release tests (sterility, bacterial endotoxins (if applicable), etc.)

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

(1) full validation reports for in-house methods and their equivalence to USP procedures if available for the drug product;
(2) verification of USP <1226> procedures, when referenced;
(3) legible spectra and chromatograms for reference standards and test samples; and

(4) the Sample Statement(s) of Availability and Identification of (a) the finished dosage form and (b) the lot numbers and strength of the drug products.[43]

For sterile products, this section will contain a summary of validation procedures and results for analytical procedures (sterility, bacterial endotoxins (if applicable), etc.).

3.2.P.5.4 Contains the batch analysis including the executed COAs for all presentations and/or strengths of the finished dosage form.

3.2.P.5.5 Contains the characterization of impurities. FDA recommends controlling all potential degradation products (Ref. 16) and processing solvents if used during manufacture in the finished dosage form. 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.[44]

3.2.P.5.6 Contains the justification of the specifications including but not limited to references to compendia (e.g., USP, JP), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Products.[45]

3.2.P.6 Contains information about the reference standards or materials.

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

(1) a summary of the container closure system (including data for any new 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 (USP General Chapters <1> Injections));

(2) components specification and test data;

(3) packaging configuration and size;

(4) container closure testing pursuant to USP <661> and <671> (testing should be conducted; for liquid drug products contained in plastic containers, applicants should also provide test data for leachables and/or extractables); and

(5) the source of supply and the supplier's address (Ref. 25).

For controlled substances, 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 if the container closure system meets the requirements of 21 CFR 211.132.

[43] Method validation/verification reports for all analytical methods are to be provided in section 3.2.P.5.3

[44] Supra note 17.

[45] Id.

3.2.P.8 Contains the stability data (Refs. 18 and 23).[46]

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

(1) preapproval stability protocol;
(2) proposed expiration dating period for marketing packaging;
(3) proposed expiration dating period for bulk packaging, if applicable; and
(4) storage temperature statement.

3.2.P.8.2 Contains the postapproval stability protocol and stability commitment. If the applicant and drug product manufacturer are different entities, both will provide stability commitments. For sterile products, this section contains analytical procedures and testing schedule for maintenance of microbial product quality (e.g., container closure integrity/sterility, bacterial endotoxins, and microbial limits) (Ref. 29).

3.2.P.8.3 Contains stability data including:

(1) accelerated, long-term, and intermediate stability data, if applicable;
(2) batch numbers on stability records that are the same as the test batch;
(3) the date the stability studies were initiated; and
(4) the date the stability sample(s) were removed from the stability chamber for each testing time point (Ref. 18).

For liquid or semisolid products, applicants should submit accelerated stability data reflecting the worst-case storage conditions (related to orientation), at minimum. The following information and data can also be included in this section:

(1) one-time special stability studies conducted to confirm quality of constituted drug products (for example parenterals and/or powders reconstituted with diluents and/or drug admixtures) per labeling instructions;
(2) one-time thermal cycling studies (freeze-thaw/heat-cool), as applicable; and
(3) one-time in-use stability studies for oral liquids as applicable (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).

3. Appendices

3.2.A.2 Contains an appendix for 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., TSEs, viruses). These processes may include assays to detect adventitious agents, actions taken to avoid them, as well as procedures to eliminate or inactivate them.

[46] FDA recommends 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.

4. Regional Information

Section 3.2.R contains regional information for the drug substance and the drug product (§ 314.50(d)(1)(ii)(b)).

3.2.R.1.S Contains the executed batch records and blank master batch records. Applicants can 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.

3.2.R.2.S Contains the comparability protocols (Ref. 30).

3.2.R.3.S Contains the methods validation package. This information may also be placed in section 3.2.S.4.3.

3.2.R.1.P.1 Contains the executed batch records including: (1) a copy of the executed batch record(s) with equipment specified and 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; and (3) the bulk package reconciliation for all bulk packaging considered a commercial container. The bulk package reconciliation is recommended if 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. If bulk is to be shipped, the applicant should submit accelerated stability data at 0, 3, and 6 months; if the bulk is only warehoused for repackaging, the applicant may provide real time stability data at 0, 3, and 6 months. Provide bulk package container and closure information in section 3.2.P.7.

3.2.R.1.P.2 Contains information on components including and not limited to applicants' and suppliers' COAs for drug substance lots, inactive ingredients lots, and packaging components lots contained in the exhibit batches of the drug product

3.2.R.2.P Contains comparability protocols, if applicable (Ref. 30).

3.2.R.3.P Contains the methods validation package. This information may also be placed 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 the documents be provided in text-based PDF.

D. Module 4 – Nonclinical Study Reports

ANDAs generally do not contain data that are required for Module 4.

E. Module 5 – Clinical Study Reports

Module 5 contains all of the clinical study report data needed to support the application and demonstrate that the generic is bioequivalent to the RLD (§ 314.94(a)(7)). To facilitate the submission of complete data, FDA develops product-specific guidances,[47] summary data tables (as referenced in section III.B.2 of this guidance),[48] and multiple guidances on biopharmaceutics.[49] Applicants should use an eCTD Study Tagging File for each study submitted.[50]

1. Complete Study Data

5.2 Contains the tabular listing of the clinical studies submitted in the module.

5.3 Contains the clinical study reports and related information.

5.3.1 Contains the complete study data for the biopharmaceutic studies (Ref. 31) and the lot numbers and strength of products used in the BE study(ies); and documents the study type. The section will also contain information of in vivo and in vitro studies including, but not limited to:[51]

- Synopsis
- Study report
- Protocol and amendments
- All case report forms
- List of independent ethics committees (IECs) or institutional review boards (IRBs) and consent and/or assent forms
- IRB approval letters for protocol, amendments, and consent/assent forms
- List and description of investigators and sites
- Number of subjects enrolled in each site
- Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer
- Listing of subjects receiving test drug(s) from specified batch
- Randomizations scheme
- Audit certificates and reports
- Documentation of statistical methods and interim analysis plans
- Documentation of interlaboratory standardization methods of quality assurance procedures if used[52]
- Publications based on the study[53]

[47] See the Bioequivalence Recommendations for Specific Products guidances on the FDA Drugs guidance Web page.
[48] Supra note 17.
[49] See the Biopharmaceutics guidances on the CDER Guidances Web page.
[50] See ICH M2 EWG: The eCTD Backbone File Specification for Study Tagging Files (June 2008).
[51] See the FDA Data Standards Resources Web Site for current FDA data standards catalog. Supra note 29.
[52] Supra note 17.

- Important publications referenced in the report[54]
- Discontinued patients including specific reason for discontinuation[55]
- List of subjects included in the PP (per protocol), (M)ITT (modified/intent-to treat), and safety populations[56]
- List of subjects excluded from the PP, (M)ITT, and safety populations[57]
- Reason for exclusion from the PP, (M)ITT, and safety populations for each subject[58]
- Protocol deviations including specific reason for deviation
- Demographic data
- Drug concentration data
- Treatment compliance rate data
- Individual subject's response scores/data per visit
- Adverse event listings
- Concomitant medication listings
- Listing of individual laboratory measurements by subject
- Site (identifier)
- Individual subject data listings
- In vivo and/or in vitro BE study datasets
- Summary dataset containing a separate line listing for each subject[59]
- Analysis dataset containing a separate line listing for each visit per subject[60]
- Individual Analysis datasets (e.g., adverse events, concomitant medications etc.)[61]
- Analysis programs
- Annotated case report form (CRF)
- Annotated ECG waveform datasets
- Image files
- Narrative safety reports for serious adverse events
- Source documents
- Clinical raw data/medical records

5.3.1.2 Contains the comparative BA and BE study reports (e.g., fasting studies, fed studies).

5.3.1.3 Contains in vitro-in vivo correlation study reports (e.g., comparative dissolution data).

5.3.1.4 Contains reports of bioanalytical and analytical methods provided in individual study reports. If a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and then referenced in individual study reports.

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[53] Id.
[54] Id.
[55] Id.
[56] Id.
[57] Id.
[58] Id.
[59] Id.
[60] Id.
[61] Id.

The data provided in all of these sections 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 5.3.1.3, while the dissolution summary tables should be placed in section 2.7.

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. One copy of all important references cited in the QOS or individual technical reports provided in section 5.3 will also be submitted in this section (Ref. 31). FDA recommends that the documents be provided in text-based PDF.

APPENDIX A: REFERENCED GUIDANCES

The following documents have been referenced in this guidance document and may be relevant to applicants developing or considering development of an ANDA. This is not a comprehensive list of available information from CDER. All guidances documents listed here are available on the Drugs guidance Web page (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

1. Draft Guidance for Industry *ANDA Submissions — Refuse-to-Receive Standards* (Issued by CDER, October 2013).

2. Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Issued jointly by CDER and CBER, January 2013 Rev. 3).

3. Guidance for Industry *Part 11, Electronic Records; Electronic Signatures — Scope and Application* (Issued by CDER, CBER, CDRH, CFSAN, CVM, ORA, August 2003).

4. Draft Guidance for Industry *Submitting Debarment Certification Statements* (Issued by CDER, CBER, and CVM, September 1998).

5. Guidance for Industry *Contents of a Complete Submission for the Evaluation of Proprietary Names* (Issued jointly by CDER and CBER, February 2010).

6. Guidance for Industry *Variations in Drug Products that May Be Included in a Single ANDA* (Issued by CDER, December 1998).

7. Draft Guidance for Industry *How to Comply with the Pediatric Research Equity Act* (Issued jointly by CDER and CBER, September 2005).

8. *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (Issued jointly by CDER and CBER, July 1998).

9. Draft Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (Issued by CDER, April 2013).

10. Guidance for Industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (Issued by CDER, September 2009)

11. Guidance for Industry *ICH M4Q: The CTD — Quality* (Issued by CDER, August 2001).

12. Guidance for Industry *Submission of Summary Bioequivalence Data for ANDAs* (Issued by CDER, May 2011).

13. Guidance for Industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (Issued jointly by CDER and CVM, November 1994).

14. Guidance for Industry *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice* (Issued jointly by CDER and CBER, September 2004).

15. Draft Guidance for Industry *Analytical Procedures and Methods Validation for Drugs and Biologics* (Issued jointly by CDER and CBER, February 2014).

16. Guidance for Industry *ANDAs: Impurities in Drug Products* (Issued by CDER, November 2010).

17. Guidance for Industry *ANDAs: Impurities in Drug Substances* (Issued by CDER, June 2009).

18. Guidance for Industry *Abbreviated New Drug Applications: Stability Testing of Drug Substances and Products* (Issued by CDER, June 2013).

19. Draft Guidance for Industry *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches* (Issued by CDER, December 2008).

20. Guidance for Industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (Issued by CDER, March 2013).

21. Guidance for Industry *Size of Beads in Drug Products Labeled for Sprinkle* (Issued by CDER, May 2012 Rev. 1).

22. Draft Guidance for Industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (Issued by CDER, December 2013).

23. Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products Questions and Answers* (Issued by CDER, May 2014).

24. Guidance for Industry *Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (Issued by CDER, February 1987).

25. Guidance for Industry *Container Closure Systems for Packaging Human Drugs and Biologics* (Issued jointly by CDER and CBER, May 1999).

26. Guidance for Industry *ICH Q8(R2) Pharmaceutical Development* (Issued jointly by CDER and CBER, November 2009).

27. Guidance for Industry *Process Validation: General Principles and Practices* (Issued jointly by CDER, CBER and CVM, January 2011 Rev. 1).

28. Guidance for Industry *Pharmaceutical Components at Risk for Melamine Contamination* (Issued jointly by CDER and CVM, August 2009).

29. Guidance for Industry *Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products* (Issued by CBER, CDER, CDRH, and CVM, February 2008).

30. Draft Guidance for Industry *Comparability Protocols -- Chemistry, Manufacturing, and Controls Information* (Issued by CDER, CBER and CVM, February 2003).

31. Guidance for Industry *ICH M4E: The CTD — Efficacy* (Issued by CDER, August 2001).

See also:

Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (Issued by CDER and CBER, February 2014).

Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (Issued by CDER and CBER, February 2014 Rev. 1).

APPENDIX B: COVER LETTER TEMPLATE

Date

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII,
7620 Standish Place
Rockville, MD 20855

Heading:	Provide pre-assigned ANDA number, if applicable Indicate 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-use or single dose, multi dose and/or pharmacy bulk.
Paragraph 2:	Provide the RLD NDA or ANDA number Provide brand and generic drug product name and strengths Provide the name of the RLD holder
Paragraph 3:	Indicate whether the GDUFA fee has been paid and provide the amount paid Provide User Fee Payment ID Number Indicate that a copy of the Generic Drug User Fee Cover Sheet is contained in the application at Module 1.2
Paragraph 4:	Indicate whether Controlled Correspondence were used to develop this application Provide the Controlled Correspondence numbers and indicate that copies are provided in Module 1.2 Indicate whether Meeting Minutes are contained in this application Indicate that the Meeting Minutes are provided in Module 1.2 Indicate whether 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
Provide the docket number and a copy of FDA's approval letter in Module 1.12.11
Indicate whether a Citizen Petition was filed and/or granted in relation to this application
Provide the docket number, a copy of the petition, FDA's response (if applicable) in Module 1.12.11

Paragraph 5: Indicate that Letters of Authorization for DMFs enclosed in section 1.4.1
List all DMFs referenced in the application

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

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

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

Paragraph 6: Indicate whether any information or data in the application should be highlighted for a specific discipline's review
Indicate the method of sterilization for the drug product (e.g., aseptic processing or terminal sterilization) if applicable
Indicate whether the application contains pharm/tox data for review in Module 3.2.P.1.

Paragraph 7: Identify the sites where the ANDA batches were manufactured (including FEI or DUNS number)
Identify the sites where the marketed product will be manufactured for marketing (including FEI or DUNS number)

Paragraph 8: Indicate the proposed drug product expiration date and the basis for the request in Module 3.2.P.8.1

Paragraph 9: Provide the basis for the expedited review request (if applicable)

Paragraph 10: Indicate whether the ANDA was compiled and submitted pursuant to FDA's guidance on electronic submissions

Paragraph 11: Indicate whether a letter of Non-Repudiation Agreement for digital signatures has been submitted to the FDA and provide the date of that submission

Paragraph 12: Indicate the file structure of the labeling

Paragraph 13: Indicate whether the RLD has a REMS
Indicate whether information on the proposed REMS has been submitted in Module 1.16

Paragraph 14: Provide information related to the physical description of the product (tablet size, scoring) and comparison to the RLD in Module 3.2.P.1

Provide information about the tamper-resistant properties of a controlled substance in Module 3.2.P.7 if applicable.

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

Paragraph 16: Provide the name and contact information for a technical point of contact (for electronic submissions)

Paragraph 17: Provide the signatory's contact information

Signature