POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Filing Review of Abbreviated New Drug Applications

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PURPOSE

This MAPP outlines the policies and procedures for the conduct of a filing review of an abbreviated new drug application (ANDA) by the Division of Filing Review (DFR), Office of Regulatory Operations (ORO) in the Office of Generic Drugs (OGD).

BACKGROUND

FDA evaluates each submitted ANDA[1] individually to determine whether the ANDA can be received. The receipt of an ANDA means that FDA made a threshold determination that the ANDA is a substantially complete application, that is, an ANDA that on its face

[1] For purposes of this MAPP, "ANDA" means ANDAs and prior approval supplements (PASs) to approved ANDAs. For further information on supplements reviewed by the Division of Filing Review, refer to MAPP 5200.7 ANDA Amendments and Supplements Reviewed by the Division of Filing Review (Rev. 1, April 2020).

is sufficiently complete to permit a substantive review.[2] Sufficiently complete means that the ANDA contains all the information required under section 505(j)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and does not contain a deficiency described in 21 CFR 314.101(d) and (e).[3] Our regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in others, refuse to receive (RTR) an ANDA.[4]

POLICY

- DFR Reviewers will use the attached ANDA Filing Checklist (the checklist)[5] to identify the required and recommended content in an ANDA.

    - There are items included in this MAPP and on the checklist that are statutory or regulatory requirements for approval but are not considered as a threshold matter for the substantial completeness determination of an ANDA. These items are denoted with an asterisk in this document.

    - We also have included items in this MAPP and on the checklist that, while recommended in a guidance or elsewhere to assist applicants in preparing a high quality ANDA, are not considered as a threshold matter for the substantial completeness determination of an ANDA. These items are italicized in this document. The checklist is a general tool designed to assist the DFR Reviewer in assessing the information and data contained in the submission and does not reflect all the bases upon which a submission may be refused for receipt.

- The DFR Reviewer will not review an applicant's completed checklist during the filing review. (Some applicants submit a completed checklist with the submission.)

- The attached checklist follows the Common Technical Document (CTD) format and backbone and specifies the content of each module of the submission.

- DFR will update the checklist as necessary. The updates may reflect, for example, revised recommendations and/or guidances pertaining to the technical reviews that are conducted for an ANDA.

- At the conclusion of the filing review, the DFR Reviewer will determine whether to receive the ANDA, issue an Information Request (IR) to the applicant providing an opportunity to remedy identified deficiencies, or refuse-to-receive

[2] See 21 CFR 314.101(b)(1) and 314.3(b).
[3] 21 CFR 314.3(b).
[4] See 21 CFR 314.101(d)-(e).
[5] See attachment 1 for the checklist and additional attachments 2-9.

the ANDA.

RESPONSIBILITIES AND PROCEDURES

The DFR Reviewer will:

1. Commence review of an ANDA to determine whether the submission is substantially complete and may be received for review by checking for the following:

    - Module 1 (administrative information)

        - Completed and signed Form FDA 356h

            - U.S. agent signature or countersignature by the same if the form has been signed by a person who does not reside or have a place of business within the U.S.

            - Name and U.S. address of the authorized official for the ANDA

        - Completed and signed Form FDA 3674*

        - *Cover letter for a summary of the submission, special requests, and application-specific references*[6]

        - Certifications

            - Debarment Certification and List of Convictions[7]

            - Completed and signed Form FDA 3454 and/or 3455 (as applicable)

        - Patent and exclusivity certifications. The DFR reviewer will:

            - Assess whether an appropriate patent certification or statement for every patent listed in the electronic version of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for the reference listed drug (RLD) is submitted

[6] Further information can be found in the draft guidance for industry on *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions* (December 2021), located at, https://www.fda.gov/media/154762/download. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] No list is required if there are no convictions to report.

- Assess whether an exclusivity statement is submitted

- Right of reference letter for Type II, Type III, and Type IV Drug Master Files (DMFs) referenced in the ANDA

- *Proprietary name request*

  - *Proprietary name requests should be submitted as a separate amendment to the ANDA submission and identified as a "Proprietary Name Request"*

- Basis of submission. The DFR reviewer will:

  - Assess whether the appropriate RLD is referenced in accordance with the Orange Book at the time of submission

  - If a suitability petition is required, confirm that the petition docket number has been provided along with copies of FDA's correspondence approving the petition

  - If a citizen petition is required requesting a determination whether the RLD was withdrawn for safety or effectiveness reasons, assess whether a copy of the petition has been provided in the ANDA*

- Comparison demonstrating "sameness" to or differences from the RLD (i.e., conditions of use, active ingredient, route of administration, dosage form, and strength)

- Environmental impact analysis or request for categorical exclusion

- Request for waiver of in vivo bioequivalence studies (as applicable)

- Draft ANDA and RLD labeling

  - *The DFR reviewer will assess whether the proposed labeling appears congruent with the applicant's patent certification(s) or statement(s)*

- Module 2 (data summaries)

  - The DFR reviewer will review Module 2 for summaries of the data contained in the ANDA including but not limited to (see attachments 2-9, as applicable):

- Comparative in vitro dissolution data with the Certificate of Analysis (COA) for the test and RLD for each proposed strength

- Complete bioequivalence summary tables, pilot and pivotal data (as applicable) in PDF and Word files

- Module 3.2.S (drug substance)

  - The DFR reviewer will review Module 3.2.S of the ANDA for information on the quality of the drug substance including the following documents and information:

    - General information (e.g., nomenclature, structure, and general properties)

    - Drug substance manufacturer information

  - The DFR reviewer will assess whether all required information has been submitted for all facilities involved with the manufacture and testing of commercial drug substance (active pharmaceutical ingredient (API)) batches

    - Drug substance characterization information

    - Complete information in all subsections of Module 3.2.S.4 (specifications, analytical procedures, validation/verification of analytical procedures, batch analysis, and justification of specifications)

    - Complete information on reference standards or materials

    - Container closure systems and stability data (reference to DMF is acceptable)

- Module 3.2.P (drug product)

  - The DFR reviewer will review Module 3.2.P of the ANDA for information on the quality of the drug product including the following documents and information:

    - Description and composition of drug product

    - Unit composition for each proposed strength in the appropriate units

- Justification for all inactive ingredients in the proposed drug product[8]
- Pharmaceutical development report
- Drug product manufacturer information

- The DFR reviewer will assess whether all required information has been submitted for all facilities involved with the manufacture and testing of the commercial drug product batches
  - Batch formula for each strength of the drug product
    - As part of the stability data requirements, the DFR reviewer will assess theoretical yield for the commercial batch (21 CFR 314.50(d)(1)(ii) and 21 CFR 314.94(a)(9)(i)). These requirements may be fulfilled by assessing whether the proposed maximum theoretical yield for the commercial batch is no more than 10X scale-up compared to the theoretical yield for the exhibit batch as recommended in FDA's guidance for industry *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014) or using an alternative approach.
  - Description of the manufacturing process and controls
    - Complete description of manufacturing process including flow charts, master production batch records, master packaging records (as applicable), and product sterilization process (as applicable)
    - Submission of critical steps and intermediates information
    - Process validation or evaluation (for sterile products only)
  - Complete information on the control of excipients including information on the source of inactive ingredients, specifications, analytical procedures, validation of analytical procedures, and justification of specifications
  - Complete information on controls of the drug product including information on specification, analytical procedures, validation/verification of analytical procedures, batch analysis, characterization of impurities, justification of specifications

[8] Reference to controlled correspondence(s) response(s) pertaining to qualitative and quantitative formulation evaluations and inactive ingredient queries should be included in the original ANDA submission in module 3.2.P.1.

- Complete information on container closure system including summary of container closure system, components specification and test data, packaging configuration and sizes, container closure testing, and source of supply and suppliers' address

- Stability data for the finished dosage form including the stability protocol and expiration dating period, post-approval stability protocol and commitment, and stability data and batch numbers

- Module 3.2.R (regional)

  - The DFR reviewer will review Module 3.2.R for regional information related to the ANDA including:

    - Executed batch records with manufacturing and packaging reconciliation

    - Methods validation package (as applicable)

- Module 5 (clinical)

  - The DFR reviewer will review Module 5 (see attachments 2-9) of the ANDA for clinical study(ies) including:

    - Data supporting the information contained in the summary tables included in Module 2.7

    - Literature references, as applicable

2. Identify and list all deficiencies noted in review of Modules 1 – 5, including:

   - English translation

   - eCTD standards compliance

3. Determine whether to receive the ANDA, issue an IR to the applicant providing an opportunity to remedy identified deficiencies, or refuse-to-receive the ANDA.

4. Ensure that the appropriate communication based on the result of the Filing Review (i.e., acknowledgment of receipt, IR, or RTR letter) is drafted and issued to the applicant.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/1/2017	Initial	N/A
10/3/2023	1	Updated to streamline process and revise the checklist to meet the most current recommendations

ATTACHMENT 1: Abbreviated New Drug Application (ANDA) Filing Checklist Modules 1-5

ANDA:	
APPLICANT:	
RELATED APPLICATION(S):	
DRUG PRODUCT NAME AND STRENGTH(S):	
LETTER (356h) DATE:	
RECEIVED DATE:	
GDUFA GOAL DATE:	
Type II DRUG MASTER FILE (DMF) #:	

BASIS OF SUBMISSION:

(If reference standard is an ANDA, complete right column)

Reference listed drug (RLD):	Reference Standard (RS):
Application Number:	Application Number:
Application Holder:	Application Holder:
Drug Product:	Drug Product:

MODULE 1: ADMINISTRATIVE

1.1	**1.1.2**	**Signed and completed application Form FDA 356h** (Prescription (Rx) / Over-the-Counter (OTC) Status) 21 CFR 314.94(a)(1) • original signature – countersignature by U.S. Agent, if ANDA is signed by a person who does not have a place of business within the U.S. 21 CFR 314.50(a)(5). • Name and address of the designated U.S. Agent, if applicable **Electronic, fillable copy** (if a signed, scanned copy is provided) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **Are one or more facilities NOT ready for inspection?**
		Comments
1.2	*	***Cover letter*** ***Is the drug product subject to REMS requirements?*** *http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm*
		Comments
	1.2.1	**Form FDA 3674* (PDF)** 42 U.S.C. 282(j)(5)(B) **Electronic, fillable copy** (if a signed, scanned copy is provided)
		Comments
1.3	**1.3.3**	**Debarment certification from applicant** Generic Drug Enforcement Act (GDEA)/

<table>
<tr><td></td><td></td><td>Other: FD&C Act 306(k), 306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b))
(no qualifying statement)
1. Debarment certification (original signature)
2. List of convictions statement (original signature) (if applicable)
Comments</td></tr>
<tr><td></td><td>1.3.4</td><td>Financial certifications 21 CFR 54 | 21 CFR 54.2(e) | 21 CFR 314.94(a)(13)
Bioavailability (BA)/bioequivalence (BE) financial certification (Form FDA 3454)
Disclosure statement (Form FDA 3455)
Comments</td></tr>
<tr><td></td><td>1.3.5</td><td><u>Patent and exclusivity</u>
1.3.5.1 Patent information 21 CFR 314.94(a)(12) | FD&C Act 505(j)(2)(A)(vii)
Patents listed for the RLD in the electronic Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book)
1.3.5.2 Patent certification or statement 21 CFR 314.94(a)(12)(i)(A)(1) through (4) or 314.94(a)(12)(iii)
1. Patent number(s)
(Check all situations that apply)
<table>
<tr><td></td><td>Certification</td><td>Patents</td></tr>
<tr><td>☐</td><td>No Relevant Patents</td><td></td></tr>
<tr><td>☐</td><td>MOU/section (viii) statement</td><td></td></tr>
<tr><td>☐</td><td>PI</td><td></td></tr>
<tr><td>☐</td><td>PII</td><td></td></tr>
<tr><td>☐</td><td>PIII</td><td></td></tr>
<tr><td>☐</td><td>PIV</td><td></td></tr>
</table>
Statement of notification (21 CFR 314.95 | 505(j)(2)(B))
2. Pediatric extension
a. Expiration of pediatric extension?
1.3.5.3 Exclusivity claim
Exclusivity statement: Is an exclusivity statement in accordance with 21 CFR 314.94(a)(3)(ii) provided?
Pediatric exclusivity (new patient population (NPP), pediatric exclusivity (PED))
PEPFAR NCE-1 Waiver of Exclusivity
Comments</td></tr>
<tr><td>1.4</td><td>1.4.2</td><td><u>Statement of right of references</u> 21 CFR 314.50(g)(1)
DMF written statement of authorization for reference (copy of letter of authorization (LoA) received from DMF holders)
1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient (API)
2. Type II DMF#
3. Type III DMF authorization letter(s) for container closure
4. Type IV DMF authorization letter(s) for inactive ingredients
5. Type V DMF authorization letter(s) for FDA accepted information
Comments</td></tr>
</table>

1.12	**1.12.4**	***Request for comments and advice*** *– proprietary name requested* *If yes, did the applicant provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing* 1. *Yes* 2. *No – contact the applicant to submit the request as a separate electronic amendment*
		Comments
	1.12.11	**Basis for submission** 21 CFR 314.94(a)(3) Applicant identifies the following: 1. RLD application # 2. RLD drug product 3. RLD Holder 4. RS (if different from RLD) 5. RS application # (if applicable) **ANDA suitability petition required?** 21 CFR 10.20 | 21 CFR 10.30 | 21 CFR 314.93 | 21 CFR 314.94(a)(3)(iii) If yes, assigned docket number Copy of FDA's correspondence approving the petition **Citizen petition required?*** 21 CFR 10.25(a) | 21 CFR 10.30 | 21 CFR 314.122 If yes, petition number Copy of petition
		Comments
	1.12.12	**Comparison between generic drug and RLD** 505(j)(2)(A) | 21 CFR 314.94(a)(4) - (6) |21 CFR 314.94(a)(9)(ii) 1. Condition(s) of use 2. Active ingredient(s) 3. Route of administration(s) 4. Dosage form 5. Strength(s)
		Comments
	1.12.14	**Environmental analysis from applicant** 21 CFR 25.15(d)| 21 CFR 25.20 | 21 CFR 25.22 | 21 CFR 25.30 or 25.31 Environmental assessment (EA) If applicable, environmental impact statement (EIS) Claim of categorical exclusion statement**:** "to the applicant's best of knowledge no extraordinary circumstances exist"
		Comments
	1.12.15	**Request for waiver** 21 CFR 320.22 | 21 CFR 320.24(b)(6) Request for waiver of in vivo BA/BE Study(ies)
		Comments
1.14	**1.14.1**	**Draft labeling** 21 CFR 314.94(a)(8)(ii) and (iv) *(if applicant provides "Final Labeling," the labeling information should be provided in Module 1.14.2.)* **1.14.1.1 Draft carton and container labels** Electronic copy (each strength and container) **1.14.1.2 Annotated draft labeling text**

		Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated **1.14.1.3 Draft labeling text (does not apply to OTC products)** Package insert (content of labeling) in PDF *and WORD format*, and SPL submitted electronically
		Comments
	1.14.3	**Listed drug labeling** 21 CFR 314.94(a)(8)(i) and (iv) **1.14.3.1 Annotated comparison with listed drug** Side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated **1.14.3.3 Labeling text for reference listed drug** RLD package insert, RLD container label, and if applicable, RLD outer container label
		Comments

MODULE 2: CTD SUMMARIES

2.7	**Clinical summary (BE)** model BE data summary tables 21 CFR 320.21(b) and § 320.24(b) See Attachments 2-9 for data-specific summary tables

MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (API)

21 CFR 314.94(a)(9)(i) | 21 CFR 314.50(d)(1)(i)

3.2.S.1	**General information** (May not refer to DMF) **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General properties**
	Comments
3.2.S.2.1	**Manufacturer** **Drug substance (API)** Must correlate to the establishment information submitted in annex to Form FDA 356h 1. Name and full address(es) of the facility(ies) 2. Contact name, phone and fax numbers, email address 3. Specify function or responsibility 4. *Type II DMF number(s) for API(s)* 5. Additional sources of API and information (1 through 4, if applicable)
	Comments
3.2.S.3	**Characterization** *All potential impurities should be listed in tabular format* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

		Comments
		Control of drug substance (API)
3.2.S.4	3.2.S.4.1	**Specification** Testing specifications and data from drug substance manufacturer(s)
		Comments
	3.2.S.4.2	**Analytical procedures**
		Comments
	3.2.S.4.3	**Validation of analytical procedures** (API that meets United States Pharmacopeia (USP) standards or reference made to DMF, provide verification of USP or DMF procedures) 1. Spectra and chromatograms for **reference standards** and **test samples** *(ref. std. can be located in 3.2.S.5)*
		Comments
	3.2.S.4.4	**Batch analysis** 1. Certificate of analysis (COA) specifications and test results from drug substance (API) manufacturer(s) 2. Drug product manufacturer's certificate of analysis
		Comments
	3.2.S.4.5	**Justification of specifications** *All potential impurities should be listed in tabular format* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf
		Comments
3.2.S.5		**Reference standards or materials** (Do NOT refer to DMF)
		Comments
3.2.S.6		**Container closure systems**
		Comments
3.2.S.7		**Stability** 1. Retest date or expiration date of API(s)
		Comments

3.2.P DRUG PRODUCT

21 CFR 314.94(a)(9) | 21 CFR 314.50(d)(1)(ii)

3.2.P.1		**Description and composition of the drug product** 1. Unit composition with indication of the function of the inactive ingredient(s) 2. Inactive ingredient(s) and amount(s) are appropriate per the Inactive Ingredient Database (IID) (per/dose, unit, or maximum daily dose (MDD) justification) (*provide justification in a tabular format*) 3. Parenteral, Ophthalmics, and Otics: Qualitatively and quantitatively the same as the RLD? 4. Formulation Oral tablet and oral capsules: % to mg/dosage unit Oral suspensions and oral solutions: % to mg/dose (dry powder) Parenterals/Ophthalmics/Otics: same unit of measure as RLD 5. Injections: If the RLD includes a diluent, then the diluent must be qualitatively and quantitatively the same (Q1/Q2 same) and must be provided in the application.
		Comments
3.2.P.2		**Pharmaceutical development report**
		Comments
3.2.P.3		**Manufacture**
	3.2.P.3.1	**Drug product manufacturer(s)** Correlate with the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories 1. Name and full address(es) of the facility(ies) 2. Contact name, phone and fax numbers, email address 3. Specify function or responsibility
		Comments
	3.2.P.3.2	**Batch formula** Largest intended commercial batch size
		Comments
	3.2.P.3.3	**Description of manufacturing process and process controls** 1. Description of the manufacturing process and (for aseptic fill products) facility 2. Master production batch record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified 3. Master packaging records for intended marketing container(s)
		Comments
	3.2.P.3.4	**Controls of critical steps and intermediates**
		Comments
	3.2.P.3.5	**Process validation and/or evaluation** 1. If sterile product, terminally sterilized product? 2. Aseptically filled product? • If yes, Validation (bacterial retention studies) of sterilizing grade filter(s)

		Comments
		Controls of excipients (inactive ingredients)
3.2.P.4		Source of inactive ingredients identified
		Comments
	3.2.P.4.1	**Specifications** 1. Testing specifications (including identification and characterization) 2. Supplier's COA (specifications and test results)
		Comments
	3.2.P.4.2	**Analytical procedures**
		Comments
	3.2.P.4.3	**Validation of analytical procedures**
		Comments
	3.2.P.4.4	**Justification of specifications** (as applicable) Applicant COA
		Comments
		Controls of drug product
3.2.P.5	3.2.P.5.1	**Specification(s)**
		Comments
	3.2.P.5.2	**Analytical procedures**
		Comments
	3.2.P.5.3	**Validation of analytical procedures** (if using USP procedure, provide verification of USP procedure)
		Comments
	3.2.P.5.4	**Batch analysis** Certificates of Analysis for finished dosage form Lot number(s) and strength of drug product(s)
		Comments
	3.2.P.5.5	**Characterization of impurities** *All potential degradation products should be listed in a tabular format* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf
		Comments
	3.2.P.5.6	**Justification of specifications** *All potential degradation products should be listed in a tabular format* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf
		Comments
3.2.P.7		**Container closure system** (21 CFR 314.50(d)(1)(ii)(*a*) and 21 CFR 314.94(a)(9)(i)) These requirements may be fulfilled by submission of the container closure system information recommended in the guidance for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999), set forth below, or by an alternative approach: 1. Summary of container closure system (data should be provided for each resin)

		2. Component specifications and test data 3. Packaging configuration(s) and size(s) 4. Container/Closure Testing (recommended additional testing for **all plastic**) a. Solid orals: water permeation, light transmission b. Liquids: leachables, extractables, light transmission i. Injectables with rubber stoppers: extractables 5. Source of supply and supplier's address Comments
		Stability
3.2.P.8	3.2.P.8.1	**Stability summary and conclusion (Finished Dosage Form)** 1. Stability protocol submitted 2. Expiration dating period for marketed packaging 3. Expiration dating period for bulk packaging (if applicable) Comments
	3.2.P.8.2	**Post-approval stability protocol and stability commitment** 1. Post-Approval Protocol and Commitment from applicant http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120979.pdf Comments
	3.2.P.8.3	**Stability data** (21 CFR 314.50(d)(1)(ii) and 21 CFR 314.94(a)(9)(i)) These requirements may be fulfilled by submission of the stability information recommended in the guidance for Industry *ANDAs: Stability Testing Drug Substances and Products* (June 2013), set forth below, or by an alternative approach: 1. Data (Generated using the exhibit batches manufactured to support the ANDA) A. Accelerated i. Minimum 6-month (180 days hold-time) a. Date stability study initiated b. Date stability sample removed from stability chamber at the purported 6-month time point ii. Three (3) time points a. *Date stability sample removed from stability chamber for each testing time point* B. Long Term i. Minimum 6-month (180 days hold-time) a. Date stability study initiated b. Date stability sample removed from stability chamber at the purported 6-month time point ii. Three (3) time points a. *Date stability sample removed from stability chamber for each testing time point* C. Intermediate (needed only if significant change is observed with accelerated data) i. Minimum 6-month (180 days hold time) a. Date stability study initiated b. Date stability sample removed from stability chamber at the

		purported 6-month time point ii. 2 time points, at minimum 2. Batch numbers on stability records the same as the test batch 3. Additional stability data to support additional API sources (if applicable) 4. For liquid and semi-solid products, all of the data described in (1) above generated from worst-case and non-worst-case orientations 5. Explanation of alternative approach, if applicable
		Comments

3.2.R REGIONAL INFORMATION

21 CFR § 314.50(d)(1)(ii)

		REGIONAL INFORMATION (DRUG PRODUCT)
	3.2.R.1.P	**Executed batch records** Copies of executed batch records with equipment specified, including packaging records (packaging and labeling procedures) for the following: a. Two (2) pilot scale and one (1) small scale OR b. Three (3) pilot scale For (a) and (b) above: 1. Two API lots used per strength? 2. All presentations of container closure systems amongst the 3 batches?
		Comments
		Batch reconciliation (Refer to batch size and packaging information that meet the minimum threshold amount for specified dosage forms, i.e., solid oral dosage forms, oral powders/solutions/suspensions, parenteral drug products, ophthalmic/otic drug products, transdermal patches, topicals (i.e., creams, lotions, gels, inhalation solutions, nasal sprays, etc.). See the guidance for industry, *ANDAs: Stability Testing Drug Substances and Products, Questions and Answers* (May 2014)) a. Theoretical yield b. Actual yield i. Manufacturing minimum threshold met for each strength? c. Packaged yield
		Comments
		Bulk package reconciliation for all bulk packaging considered a commercial container is recommended if bulk packaging is used to achieve the minimum package requirement for stability testing (interpreting 314.50(d)(1)(ii)(*a*) and 211.166(a)(3) and addressed in the guidance for industry, *ANDAs: Stability Testing of Drug Substances and*

		Products, Questions and Answers (May 2014)), or to satisfy an alternative approach. Provide the following information in their respective sections: a. Bulk package label (1.14.1) b. Bulk package stability (3.2.P.8) 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months 2. If bulk is only warehoused for repackaging, provide room temperature stability data at 0,3,6 months *c.* Bulk package container closure information (3.2.P.7)
		Comments
	3.2.R.3.P	**Methods validation package** Methods validation package (Required for Non-USP drugs)
		Comments

MODULE 5: CLINICAL STUDY REPORTS

21 CFR 314.94(a)(7)

5.2		**Tabular listing of clinical studies** https://www.fda.gov/media/93569/download
		Comments
5.3	**5.3.1**	**BE** (21 CFR 314.94(a)(7)) (The following is a non-exhaustive list of BE studies that comply with 21 CFR 314.94(a)(7)) 1. **In vivo pharmacokinetic (PK) study(ies)** 2. **In vivo BE study(ies) with clinical endpoint(s)** 3. **In vivo BE study(ies) with pharmacodynamics (PD) endpoints (pilot and pivotal vasoconstrictor)** 4. **In vitro binding study(ies)** 5. **Nasal products (May contain in-vitro, clinical endpoint and/or PK study)** 6. **Pressurized Metered Dose Inhalation Products** 7. **Biopharmaceutics Classification System (BCS) Studies** 8. **In-Vitro Feeding Tube Study** (Continue with the appropriate study type box below)
		Comments
Study Type		**Miscellaneous** 1. Drug Efficacy Study Implementation (DESI) Drug Product (in Module 2.7) a. Table 5 Dissolution b. Table 6 Formulation data 2. Quantitative capsule rupture testing (liquid-filled capsule products) a. Study report b. Release profile per the drug product-specific guidance (demonstrates the time points at which 80% of the drug is released from the capsule), or explanation of an alternative approach

	c. Apparatuses and the respective parameters as recommended per the drug product specific guidance, or explanation of an alternative approach 3. In vitro release tests a. 90% confidence interval (CI) within 75-133% for 8th and 29th (first stage), or explanation of an alternative approach b. 90% CI within 75-133% for 100th and 215th (second stage, if first stage failed), or explanation of an alternative approach c. Study report d. Chromatograms/histograms e. Raw data 4. In vitro comparative physicochemical data 5. In vitro microbial kill test
Note	**See attachments 2-9 for specific data sets**

ATTACHMENT 2: PK Studies

2.7 Clinical Summary

2.7

Clinical summary (bioequivalence (BE)) model BE data summary tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf

E-Submission: PDF
MS Word

2.7.1 Summary of biopharmaceutic studies and associated analytical methods

2.7.1.1 Background and overview

Table 1. Submission summary
Table 4. Bioanalytical method validation
Table 6. Formulation data
Table 10. Study information
- Long-term stability studies (LTSS) data location and hyperlink

Table 11. Product information
Table 17. Comparative physiochemical data of ophthalmic solution products

Comments

2.7.1.2 Summary of Results of Individual Studies

Table 5. Summary of in vitro dissolution
- All proposed strengths (test and RLD) tested
  - 12 dosage units of test and RLD
    - Multi -media dissolution (if applicable)
    - Alcohol dose dumping dissolution (if applicable)
    - ½ tablet dissolution (if applicable)
- *COA for test and reference products of the bioequivalence (BE) strength*

Table 9. Reanalysis of study samples
Table 12. Dropout information
Table 13. Protocol deviation
Table 14. Summary of standard curve and quality control (QC) data for BE sample analysis

Comments

2.7.1.3 Comparison and analyses of results across studies

Table 2. Summary of bioavailability (BA) studies
Table 3. Statistical summary of the comparative BA data:
1. Unscaled average – Table A
2. Reference-scaled average BE studies – Tables A **and** B BE Studies

Table 16. Composition of meal used in fed bioequivalence study

Comments

2.7.1.4 Appendix

Table 15. Standard operating procedures (SOPs) regarding bioanalytical repeats of study samples

	Comments
	2.7.4 Summary of clinical safety
	2.7.4.1.3 Demographic and other characteristics of study population
	Table 7. Demographic profile of subjects completing the bioequivalence study
	Comments
	2.7.4.2.1.1 Common adverse events
	Table 8. Incidence of adverse events in individual studies
	Comments

5.3.1.2 and 5.3.1.4

	BE Study(ies) required by 314.94(a)(7)(i) and (iii)(A) per the recommendations in the individual product BE guidance or explanation of alternative approach
Comments	
	Clinical report Fasting Fed Other
Comments	
	Individual and mean data Fasting Fed Other
Comments	
	Graphs, linear, & ln Fasting Fed Other
Comments	
	SAS datasets Fasting Fed Other
Comments	
	Statistical report (including SAS output) Fasting Fed Other
Comments	
	Method validation report Fasting Fed Other
Comments	
	LTSS data

	Fasting Fed Other
Comments	
	Study bioanalytical or analytical report Fasting Fed Other
Comments	
	Chromatograms, 20% Fasting Fed Other
Comments	
	Raw numerical data Fasting Fed Other
Comments	

ATTACHMENT 3: Clinical Endpoint(s)

2.7 Clinical Summary

2.7	**Clinical endpoint summary tables for comparative clinical endpoint bioequivalence studies** https://www.fda.gov/media/119053/download **E-Submission: PDF** ***MS Word*** **Select** Table 1. Submission summary **Select** Table 2. Source of comparative clinical endpoint bioequivalence (BE) study data **Select** Table 3. Protocol review **Select** Table 4. FDA product-specific guidance deviations (if applicable) **Select** Table 5. Summary of comparative clinical endpoint BE studies with continuous primary endpoint (if applicable) **Select** Table 6. Summary of comparative clinical endpoint BE studies with binary primary endpoint (if applicable) **Select** Table 7. Study center information **Select** Table 8. Study inclusion/exclusion criteria **Select** Table 9. Prohibited concomitant medication list **Select** Table 10. Product information **Select** Table 11. Study schedule (for example) **Select** Table 12. Subject populations **Select** Table 13. Summary of protocol deviations **Select** Table 14. Summary of subject discontinuation/early termination from the study **Select** Table 15. Demographic characteristics at baseline for the safety population, (M)ITT population, and per-protocol population **Select** Table 16. Primary endpoint analysis result for a comparative clinical endpoint BE study **Select** Table 17. Summary of adverse events in safety population **Select** Table 18. Formulation **Select** a. For a waiver of BE study requirements or for a test product that requires qualitative and quantitative sameness to the reference listed drug (RLD), if applicable Comments

2.7 Clinical Summary - Irritation/Sensitization/Adhesion (I/S/A) Studies

2.7	**Clinical endpoint summary tables for I/S/A studies, specifically for transdermal and topical delivery systems (TDS)** https://www.fda.gov/media/119055/download **E-Submission: PDF** ***MS Word***

		Table 1.	Submission summary
		Table 2.	Source of I/S/A study data
		Table 3.	Protocol review
		Table 4.	FDA product-specific guidance deviations (if applicable)
		Table 5a.	Summary of skin I/S/A study(ies)
		Table 5b.	Adhesion data from a two-way crossover PK BE & adhesion study
		Table 5c.	Two-way crossover or parallel design adhesion study
		Table 6.	Study center information
		Table 7.	Study inclusion/exclusion criteria
		Table 8.	Prohibited concomitant medication list
		Table 9.	Product information
		Table 10.	Study schedule (for example)
		Table 11.	Subject populations
		Table 12.	Summary of protocol deviations
		Table 13.	Summary of subject discontinuation/early termination from the study
		Table 14.	Demographic characteristics at baseline for the safety population and per protocol population
		Table 15a.	Summary Statistics for the Mean Irritation and Mean Adhesion Scores (per protocol population)
		Table 15b.	Non-inferiority analysis results for a skin irritation study – mean irritation score (per protocol population)
		Table 15c.	Non-inferiority analysis results for a skin adhesion study – mean adhesion score (per protocol population)
		Table 15d.	Number (N) and frequency (%) of sensitization reactions during the challenge phase (per protocol population)
		Table 16a.	Frequency tables - induction phase irritation scores (combined dermal response and other effect scores) for per protocol population
		Table 16b.	Frequency tables - induction phase irritation scores (dermal response) for per protocol population
		Table 16c.	Frequency tables - induction phase irritation scores (other effects) for per protocol population
		Table 16d.	Frequency tables - irritation scores (combined dermal response and other effects scores) for per protocol population during challenge phase/re-challenge phase
		Table 16e.	Frequency tables - irritation scores (dermal response) for per protocol population during challenge phase/re-challenge phase
		Table 16f.	Frequency tables - irritation scores (other effects) for per protocol population during challenge phase/re-challenge phase
		Table 16g.	Frequency tables - adhesion scores for per protocol population
	Select	Table 17.	TDS removal or move due to skin irritation score > 3
	Select	Table 18.	Proportion of subjects with adhesion score of 2 or more and 3 or more per treatment
	Select	Table 19.	Duration of TDS wear prior to adhesion score >2 in the per protocol population (specific for skin adhesion studies)

	Select Table 20.	Summary of adverse events in safety population
	Select Table 21.	Formulation
	Select Table 21a.	For a waiver of bioequivalence study requirements or for a test product that requires qualitative and quantitative sameness to the RLD, if applicable
Comments		

5.3.1.2 and 5.3.1.4

	All studies **(#)**
Comments	
	Study report
Comments	
	Protocol (original and amendments)
Comments	
	Placebo formulation
Comments	
	Date of data unblinded
Comments	
	Date of data locked
Comments	
	Clinical site(s) and study investigator(s) list (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population) Study investigator(s) curriculum vitaes (CVs)
Comments	
	Statistical analysis plan
Comments	
	IRB approval Approval letters for protocol Approved consent/assent forms (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)
Comments	
	Consent forms
Comments	
	Case report forms *(at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)*
Comments	
	Data definition file (describes the variables in each data set)
Comments	
	Provides all SAS programs and list of all programs (Used to generate the analysis datasets and efficacy results)
Comments	

SAS dataset (XPT) Randomization Schedule
Demographic data
Reasons for discontinuation from the study, if discontinued
Adverse events
Concomitant medications
Individual subject's scores/data per visit
Protocol deviations
Raw data (no "last observation carried forward" (NO-LOCF))
LOCF data
Summary data (usually the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset)
Identification of the modified intention to treat (mITT) population Reasons for exclusion If transdermal, Identification of adhesion population Reason for exclusion
Identification of the per protocol population Reasons for exclusion If transdermal, Identification of irritation population Reasons for exclusion When applicable, Identification of sensitization population Reasons for exclusion
Comments

Clinical endpoint study (#Study Number)

Primary endpoint Defined (within BE limits) Superiority over placebo
Comments
Secondary endpoint Defined (within BE limits) Superiority over placebo
Comments

Non-transdermal study (#Study Number)

SAS dataset (XPT) Subject's measurements/visits/dates Data to evaluate treatment compliance
Comments

Irritation/sensitization study (#Study Number)

Applicant indicates no worse skin irritation and sensitization properties of the test product compared to that of the RLD (within non-inferiority limit, T-[1.25X R] < 0)
Comments
SAS dataset (XPT) Subject's irritation measurements (i.e., time points, scores, visit #, dates) Subject's sensitization measurements (if applicable) (i.e., time points, scores, visit #, dates)
Comments

Adhesion study (#Study Number)

Applicant indicates no worse skin adhesion properties of the test product compared to that of the RLD (within non-inferiority limit, T-[1.25X R] < 0)
Comments
SAS dataset (XPT) Adhesion measurements per patch (i.e., time points, scores, visit #, dates)
Comments

ATTACHMENT 4: PD endpoints

(e.g., topical corticosteroid pilot and pivotal vasoconstrictor assay studies, metered dose inhalers (MDIs), Acarbose, Orlistat, Megletol)

2.7 Clinical Summary

2.7	**Topical dermatologic corticosteroids in vivo Bioequivalence (BE) study summary tables and SAS transport formatted tables for dataset submission** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM379421.pdf **E-Submission: PDF** ***MS Word*** **I. Pre-study method validation** Table 1. Chroma meter validation Table 2. Skin site validation Table 3. Intra-subject and inter-site validation Table 4. Operator validation Comments **II. Summary of Studies** Table 5. Summary of the pilot dose duration-response study Table 6. Summary of the pivotal bioequivalence study Table 7. Summary of the pivotal bioequivalence study (pharmacodynamic (PD) Parameters, Area Under Curve (AUC), etc.) Table 8. Listing of relevant standard operating procedures (SOPs) for pre-study method validation and pilot dose duration-response and pivotal BE studies Comments **III. Pilot Dose Duration-Response Study** Table 9. Study information Table 10. Product information Table 11. Demographics profile of subjects completing the pilot dose duration-response study product information Table 12. Dropout information, pilot dose duration-response study Table 13. Study adverse events, pilot dose duration-response study Table 14. Protocol deviations, pilot dose duration-response study Table 15. Median effective dose (ED_{50}) and maximum drug effect (Emax) values calculated Comments **IV. Pivotal BE study** Table 16. Study information Table 17. Product information Table 18. Demographics profile of subjects completing the pivotal BE study Table 19. Dropout information, pivotal BE study

	Table 20. Study adverse events, pivotal BE study Table 21. Protocol deviations, pivotal BE study Table 22. Area under the effect curve (AUEC) and 90% confidence intervals (CIs) Table 22. Test product formulation
	Comments

5.3.1.2 and 5.3.1.4

	Pilot and pivotal studies submitted
Comments	

	BE study(ies) required by 314.94(a)(7)(i) and (iii)(A) per the recommendations in the product-specific guidance or explanation of alternative approach
Comments	
	Clinical report Pilot dose duration-response study Pivotal BE study Other
Comments	
	Individual and mean data Pilot dose duration-response study Pivotal bioequivalence study Other
Comments	
	Graphs, linear Pilot dose duration-response study Pivotal bioequivalence study Other
Comments	
	Statistical report (including SAS Output) Pilot dose duration-response study Pivotal BE study Other
Comments	
	Method validation report Pilot dose duration-response study Pivotal bioequivalence study Other
Comments	
	SAS dataset (XPT) (for pilot dose duration-response study and pivotal BE study) **Pilot dose duration-response study data** Table 24. Chroma meter raw data
	Table 25. Baseline-adjusted, chroma meter raw data
	Table 26. Baseline-adjusted, untreated site-corrected chroma meter raw data

Table 27. AUEC, all subjects at each dose duration
Pivotal BE study data submission format
Table 28. Chroma meter raw data
Table 29. Baseline-adjusted, chroma meter raw data
Table 30. Baseline-adjusted, untreated site-corrected, chroma meter raw data
Table 31. AUEC, all subjects at each dose duration
Comments

ATTACHMENT 5: In Vitro Binding study(ies)

2.7 Clinical Summary

2.7	**In vitro binding bioequivalence (BE) study summary tables and SAS transport formatted tables for dataset submission** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf **E-Submission: PDF** ***MS Word*** **I. For calcium acetate drug products** Table I.1. Submission summary Table I.2. Summary of In vitro binding study Table I.3. Pre-study analytical method validation Table I.4. Summary of In vitro dissolution studies, if applicable Table I.5. Formulation data Table I.6. Reanalysis of study samples Table I.7. Study information Table I.8. Product information Table I.9. Assay validation 1. Phosphate 2. Calcium Table I.10. Standard operating procedures (SOPs) dealing with analytical repeats Table I.11. Calcium amount in the supernatant after binding Table I.12. Phosphate amount in the supernatant after binding Comments **II. For a polymer drug that binds to either phosphate (e.g., sevelamer) or bile acid (e.g., colesevelam, cholestyramine, or colestipol)** Table II.1. Submission summary Table II.2. In vitro equilibrium binding studies 1. Summary of constants k_1 and k_2- without acid pre-treatment (if applicable) 2. Summary of constants k_1 and k_2- with acid pre-treatment (if applicable) Table II.3. Pre-study analytical method validation Table II.4. Summary of in vitro disintegration studies Table II.5. Formulation data Table II.6. Reanalysis of study samples Table II.7. Study information (separate table for each in-vitro binding BE study) Table II.8. Product information (separate table for each in-vitro binding BE study) Table II.9. Study design 1. In vitro kinetic binding study 2. In vitro equilibrium binding study Table II.10. Assay validation

Table II.11. SOPs for analytical repeats
Table II.12. In vitro kinetic binding study results
1. Test/Reference (T/R) ratios of mean phosphate/bile acid binding
2. With acid pre-treatment (if applicable)
Table II.13. In vitro equilibrium binding study results
1. Summary of mean binding data (without acid pre-treatment)
1. Summary of mean binding data (with acid pre-treatment) (if applicable)

Comments

III. For lanthanum drug products

Table III.1. Submission summary
Table III.2. Summary of mean binding data (refer to PSG for pH recommendations)

Table III.3. Summary of dissolution bioequivalence data
Table III.4. Pre-study analytical method validation (for in vitro binding study sample analysis)
Table III.5. Pre-study analytical method validation (for in vitro dissolution bioequivalence study sample analysis)
Table III.6. Summary of in vitro dissolution studies (for both in vitro dissolution BE studies and regulatory dissolution studies)
Table III.7. Formulation data
Table III.8. Reanalysis of study samples
Table III.9. Study information
Table III.10. Product information
Table III.11. Study design
1. In vitro kinetic binding study
2. In vitro equilibrium binding study
Table III.12. Assay validation
Table III.13. SOPs for Analytical repeats
Table III.14. In vitro kinetic binding study results (refer to PSG for pH recommendations)

Table III.15. In vitro equilibrium binding study results – summary of mean binding data
Table III.16. Composition of meal used in fed BE study

Comments

5.3.1.2 and 5.3.1.4

	Study(ies) meets BE criteria (90% CI of 80-120, k2)
Comments	

	BE study(ies) required by 314.94(a)(7)(i) and (iii)(A) per the recommendations in the product-specific guidance or explanation of alternative approach
Comments	
	Clinical report Equilibrium binding Kinetic binding Other
Comments	
	Individual and mean data Equilibrium binding Kinetic binding Other
Comments	
	Graphs, linear, & ln Equilibrium binding Kinetic binding Other
Comments	
	SAS datasets Equilibrium binding Kinetic binding Other
Comments	
	SAS datasets (XPT) (For all but binding studies of calcium acetate drug products) Equilibrium binding (separate dataset for each binding condition per product-specific guidance) Kinetic binding (separate dataset for **each** binding condition per product-specific guidance (e.g., different concentrations of adsorbate, different pH, with/without acid treatment)) Other
Comments	
	Statistical report (including SAS output) Equilibrium binding Kinetic binding Other
Comments	
	Method validation report Equilibrium binding Kinetic binding Other
Comments	

ATTACHMENT 6: Nasal Products

2.7 Clinical Summary

2.7	**Bioequivalence (BE) summary tables for aqueous nasal spray products** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf **E-Submission: PDF** ***MS Word*** Table 1. Formulation table Table 2. Batch information Table 3. Device comparability Table 4. Actuation methods **Table 5. Single actuation content through container life test** Table 5.1. Study information Table 5.2. Analytical method validation for high-performance liquid chromatography (HPLC) Table 5.3. Calibration of manual and/or automated spray pump actuator (for single actuation content and priming/repriming studies) Table 5.3.1. Precision Table 5.3.2. Ruggedness (by date) Table 5.3.3. Ruggedness (by analyst) Table 5.3.4. Ruggedness (unit to unit if more than one unit is used) Table 5.4. Results summary **Table 6. Priming and re-priming test** Table 6.1. Study information Table 6.2. Analytical method validation for HPLC (if different from table 5.2) Table 6.3. Results summary – priming and re-priming **Table 7. Droplet size distribution by laser diffraction test** Table 7.1. Study information Table 7.2. Validation summary tables for droplet size distribution by laser diffraction Table 7.2.1. Precision Table 7.2.2. Intermediate precision (by date) Table 7.2.3. Intermediate precision (by analyst) Table 7.3. Results summary – droplet size distribution by laser diffraction **Table 8. Drug in small particles/droplets by cascade impactor test** Table 8.1. Study information Table 8.2. Validation summary table for particle size distribution by cascade impactor – analytical method validation for HPLC Table 8.3. Validation tables for cascade impaction Table 8.3.1. Precision Table 8.3.2. Intermediate precision (by date)

	Table 8.3.3.	Intermediate precision (by analyst)
	Table 8.4.	Results summary – drug in small particles/cascade impactor
	Table 9.	**Spray pattern test**
	Table 9.1.	Study information
	Table 9.2.	Validation summary tables for spray pattern
	Table 9.2.1.	Precision
	Table 9.2.2.	Intermediate precision (by date)
	Table 9.2.3.	Intermediate precision (by analyst)
	Table 9.3.	Results summary – spray pattern
	Table 10.	**Plume geometry test**
	Table 10.1	Study information
	Table 10.2.	Validation summary tables for plume geometry
	Table 10.2.1.	Precision
	Table 10.2.2.	Intermediate precision (by date)
	Table 10.2.3.	Intermediate precision (by analyst)
	Table 10.2.4.	Robustness for varies parameters (the selection of parameters is optional)
	Table 10.3.	Results – plume geometry
	Comments	

2.7	**Clinical endpoint summary tables** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM400548.pdf **E-Submission: PDF** ***MS Word*** Table 1. Submission summary Table 2. Summary of clinical endpoint BE studies Table 3. Summary of skin irritation/sensitization/adhesion study(ies) #1 Skin irritation/sensitization/adhesion study(ies) #2 Adhesion data from pharmacokinetic (PK) study #3 Adhesion study Table 4. Study center information Table 5. Study inclusion/exclusion criteria Table 6. Prohibited concomitant medication list Table 7. Product information Table 8. Study schedule (for example) Table 9. Study populations (general) Table 10. Subject populations (specific for nasal spray products) Table 11. Subject populations (specific for skin irritation/sensitization/adhesion studies) Table 12. Summary of protocol deviations Table 13. Summary of patient discontinuation/early termination from the study Table 14. Demographic characteristics at baseline for the safety population, modified intention to treat (M)ITT population, and per protocol population Table 15. Primary endpoint analysis result for a clinical endpoint BE study Table 16. Non-inferiority analysis result for a skin irritation/sensitization/adhesion study A. Irritation and adhesion scores B. Sensitization analysis Table 17. Frequency tables (specific for skin irritation/sensitization/adhesion studies) A. Irritation scores(combined irritation and other effect scores) for per protocol population B. Adhesion scores for per protocol population C. Irritation scores (combined irritation and other effect scores) for per protocol population during challenge period/re-challenge period Table 18. Patch removal or move date due to significant skin irritation (specific for skin irritation/sensitization/adhesion studies) Table 19. Proportion of subjects with adhesion score of 2 or more and 3 or more per treatment (specific for skin irritation/sensitization/adhesion studies) Table 20. Summary of adverse events Table 21. Formulation a. For a waiver of BE study requirements or for a test product that requires

	qualitative and quantitative sameness to the reference listed drug (RLD)
Table 22	OGD excipient/impurity toxicology data table
Comments	

5.3.1.2 and 5.3.1.4 BE In vitro

NASALLY ADMINISTERED DRUG PRODUCT (in vitro) (1) Lack of SAS data in CORRECT format is considered INADEQUATE for filing (See SAS Data Tables for Aqueous Nasal Spray Product In Vitro Bioequivalence Study Data Submission); (2) Failure of in vivo BE study with PK endpoint to meet acceptable CI limits is also considered INADEQUATE for filing, unless there is an explanation of an alternative approach; (3) In vitro BE test outcomes for nasal products are NOT considered at filing stage (i.e., review issues) Explanation of alternative approach should be provided if recommendations are not followed. It is recommended that reference should be made to the PSG for additional tests.
Recommended in vitro studies Single actuation content through container life Droplet size distribution by laser diffraction Drug in small particles/droplets, or by particle/droplet size distribution by cascade impactor Spray pattern Plume geometry Priming and repriming
Comments
Sufficient number of test and reference lots (3) Single actuation content through container life Droplet size distribution by laser diffraction Drug in small particles/droplets, or by particle/droplet size distribution by cascade impactor Spray pattern Plume geometry Priming and repriming
Comments
For suspensions, 3 distinct API lots and pump container closure lots
Comments
Study report Single actuation content through container life Droplet size distribution by laser diffraction Drug in small particles/droplets, or by particle/droplet size distribution by cascade impactor Spray pattern Plume geometry Priming and repriming
Comments
Statistical report (including SAS output)
Comments
SAS output (XPT) Single actuation content through container life

	Priming and repriming Droplet size distribution by laser diffraction Plume geometry Spray pattern Drug in small particles/droplets by cascade impactor
Comments	

5.3.1.2 and 5.3.1.4 BE In-Vivo

Select	**BE study(ies) required by 314.94(a)(7)(i) and (iii)(A) per the recommendations in the product-specific guidance** or explanation of alternative approach
Comments	
	BE study protocol Fasting Other
Comments	
	Clinical report Fasting Other
Comments	
	Individual and mean data Fasting Other
Comments	
	Graphs, linear, & ln Fasting Other
Comments	
	SAS datasets (XPT) Fasting Other
Comments	
	Statistical report (including SAS output) Fasting Other
Comments	
	Method validation report Fasting Other
Comments	
	Study bioanalytical or analytical report Fasting Other
Comments	
	Chromatograms, 20%

	Fasting Other
Comments	
	Raw numerical data Fasting Other
Comments	

5.3.1.2 and 5.3.1.4 Division of Clinical Review (DCR) in vitro

	All Studies (#)
Comments	
	Study report
Comments	
	Protocol (original and amendments)
Comments	
	Placebo formulation
Comments	
	Date of data unblinded
Comments	
	Date of data locked
Comments	
	Clinical site(s) and study investigator(s) list (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population) Study investigator(s) CVs
Comments	
	Statistical analysis plan
Comments	
	IRB approval **Approval letters for protocol** **Approved consent/assent forms** (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)
Comments	
	Consent forms
Comments	
	All case report forms *(at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)*
Comments	
	Data definition file (describes the variables in each data set)
Comments	
	Primary endpoint Defined (within BE limits)

	Superiority over placebo
Comments	
	Secondary endpoint Defined (within BE limits) Superiority over placebo
Comments	
	Provides all SAS programs and list of all programs (Used to generate the analysis datasets and efficacy results)
Comments	
	SAS dataset (XPT) Randomization schedule
	Demographic data
	Reasons for discontinuation from the study, if discontinued
	Adverse events
	Concomitant medications
	Individual subject's scores/data per visit
	Protocol deviations
	Raw data (no "last observation carried forward" (NO-LOCF))
	LOCF data
	Identification of the modified intention to treat (mITT) population Reasons for exclusion
	Identification of the per protocol population Reasons for exclusion
	Summary data (usually the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset)
Comments	

ATTACHMENT 7: Metered Dose Inhaler (MDI) Products

2.7 Clinical Summary

2.7

Bioequivalence (BE) summary tables for MDI products
https://www.fda.gov/media/119054/download

E-Submission: PDF
MS Word

Table 1.	Formulation table
Table 2.	Batch information
Table 3.	Device comparability
Table 4.	Actuation methods
	Single actuation content through container life test
Table 5.1.	Study information
Table 5.2.	Analytical method validation for high-performance liquid chromatography (HPLC)
	Calibration of manual and/or automated metered dose inhaler (MDI) actuation (for single actuation content)
Table 5.3.	Precision and ruggedness
Table 5.4.	Results summary – single actuation content
Table 5.4.1.	Summary of population bioequivalence results
	Priming and re-priming test
Table 6.1.	Study information
Table 6.2.	Analytical method validation for HPLC (if different from Table 5.2)
Table 6.3.	Precision and ruggedness (if different from Table 5.3)
Table 6.4.	Results summary – priming and re-priming
Table 6.4.1.	Summary of population bioequivalence results
	Aerodynamic particle size distribution (APSD) by cascade Impaction
Table 7.1.	Study information
	Validation summary tables for APSD by cascade impaction
Table 7.2.	Analytical method validation for HPLC
Table 7.3.	Method validation for cascade impaction
Table 7.4.	Results summary – APSD by cascade impaction
Table 7.5.	Summary of population bioequivalence results
	Spray pattern test
Table 8.1.	Study information
	Validation summary table for spray pattern
Table 8.2.	Precision and ruggedness
Table 8.3.	Results summary – spray pattern

	Table 8.3.1.	Summary of population bioequivalence results
		Plume geometry test
	Table 9.1	Study information
		Validation summary table for plume geometry
	Table 9.2.	Precision and ruggedness
	Table 9.3.	Robustness for various parameters (the selection of parameters is optional)
	Table 9.4.	Results – plume geometry
		Pharmacodynamic (PD) Bioequivalence (BE) Bronchoprovocation Study
	Table 10.1.	Study information
	Table 10.2.	Product information
	Table 10.3.	Demographic profile of subjects completing the BE study
	Table 10.4.	Dropout information
	Table 10.5.	Incidence of adverse events in the PD BE study
	Table 10.6.	Protocol deviations
	Table 10.7.	Statistical summary for the PD BE Study
	Table 10.7a.	Point estimates and 90% confidence intervals, raw data
	Table 10.7b.	Point estimates and 90% confidence intervals, bootstrapping procedure
	Table 10.8.	PD BE study, additional information
	Table 10.9.	SAS data table for MDI product in vivo PD BE study data submission
	Comments	

2.7	**<u>Clinical endpoint summary tables</u>** <u>https://www.fda.gov/media/119053/download</u> **E-Submission: PDF** ***MS Word***	
	Table 1.	Submission summary
	Table 2.	Source of comparative clinical endpoint bioequivalence (BE) study data
	Table 3.	Protocol review
	Table 4.	FDA product-specific guidance deviations (if applicable)
	Table 5.	Summary of comparative clinical endpoint BE studies with continuous primary endpoint (if applicable)
	Table 6.	Summary of comparative clinical endpoint BE studies with binary primary endpoint (if applicable)
	Table 7.	Study center information
	Table 8.	Study inclusion/exclusion criteria
	Table 9.	Prohibited concomitant medication list
	Table 10.	Product information

	Table 11.	Study schedule (for example)
	Table 12.	Subject populations
	Table 13.	Summary of protocol deviations
	Table 14.	Summary of subject discontinuation/early termination from the study
	Table 15.	Demographic characteristics at baseline for the safety population, (M)ITT population, and per-protocol population
	Table 16.	Primary endpoint analysis result for a comparative clinical endpoint BE study
	Table 17.	Summary of adverse events in safety population
	Table 18.	Formulation
		a. For a waiver of BE study requirements or for a test product that requires qualitative and quantitative sameness to the reference listed drug (RLD), if applicable
	Comments	

5.3.1.2 and 5.3.1.4 BE (MDI)

METERED DOSE INHALER (MDI) DRUG PRODUCT

(1) Lack of SAS data in CORRECT format is considered INADEQUATE for filing (For SAS Data Tables for MDI product In Vitro Bioequivalence Study Data Submission, please refer to the related section in "Bioequivalence Summary Tables for Aqueous Nasal Spray Products," pg 22-28 available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf); (2) Failure of in vivo BE study with PK endpoint to meet acceptable CI limits is also considered INADEQUATE for filing, unless there is an explanation of an alternative approach; (3) In vitro BE test outcomes for inhaled products are NOT considered at filing stage (i.e., review issues)

Explanation of alternative approach should be provided if recommendations are not followed.

Recommended studies

Single actuation content through container life
Priming and repriming
Aerodynamic particle size distribution (APSD) by cascade impaction
Spray pattern
Plume geometry
Pharmacodynamic (PD) Bioequivalence (BE) bronchoprovocation

Comments

Sufficient number of test and reference lots (1 for PD BE bronchoprovocation; 3 for all other studies)

Single actuation content through container life
Priming and repriming
APSD by cascade impaction
Spray pattern
Plume geometry
PD BE bronchoprovocation

Comments

Study report

Single actuation content through container life
Priming and repriming
APSD by cascade impaction
Spray pattern
Plume geometry
PD BE bronchoprovocation

Comments

Statistical report (including SAS output)

Comments

SAS output (XPT)

Single actuation content through container life
Priming and repriming
Plume geometry
Spray pattern
APSD by cascade impaction

PD BE bronchoprovocation (for more information, refer to module 2.7, Table 10.9)
Comments

5.3.1.2 and 5.3.1.4 BE in-vivo (MDI)

	BE study(ies) required by 314.94(a)(7)(i) and (iii)(A) per the recommendations in the product-specific guidance or explanation of alternative approach
Comments	
	BE study protocol Fasting Other
Comments	
	Clinical report Fasting Other
Comments	
	Individual and mean data Fasting Other
Comments	
	Graphs, linear, & l Fasting Other
Comments	
	SAS datasets (XPT) Fasting Other
Comments	
	Statistical report (including SAS output) Fasting Other
Comments	
	Method validation report Fasting Other
Comments	
	Study bioanalytical or analytical report Fasting Other
Comments	
	Chromatograms, 20% Fasting Other
Comments	
	Raw numerical data

	Fasting Other
Comments	

5.3.1.2 and 5.3.1.4 Division of Clinical Review (DCR) in-vivo (MDI)

	All studies (#Study Number)
Comments	
	Study report
Comments	
	Protocol (original and amendments)
Comments	
	Placebo formulation
Comments	
	Date of data unblinded
Comments	
	Date of data locked
Comments	
	Clinical site(s) and study investigator(s) list (if no U.S. sites used, ask for justification whether the sponsor's study population is representative of the disease state in the U.S. population) Study investigator(s) CVs
Comments	
	Statistical analysis plan
Comments	
	IRB approval **Approval letters for protocol** **Approved consent/assent forms** (IRB letter/memo with stamped date of approval and/or IRB letterhead with date showing approval)
Comments	
	Consent forms (Evidence of consent given by subjects. These can be embedded within completed CRFs or provided as separate forms)
Comments	
	All case report forms *(at minimum, should have for all patients who were dropped from the analysis population, demonstrated protocol deviations, demonstrated protocol violations, experienced serious adverse events, and a random sample of 10% of all enrolled patients)*
Comments	
	Data definition file (describes the variables in each data set)
Comments	
	Primary endpoint Defined (within BE limits) Superiority over placebo
Comments	

	Secondary endpoint Defined (within BE limits) Superiority over placebo
Comments	
	Provides all SAS programs and list of all programs (Used to generate the analysis datasets and efficacy results)
Comments	
	SAS dataset (XPT) Randomization schedule
	Demographic data
	Reasons for discontinuation from the study if discontinued
	Adverse events
	Concomitant medications
	Individual subject's scores/data per visit
	Protocol deviations
	Raw data (no "last observation carried forward" (NO-LOCF))
	LOCF data
	Identification of the modified intention to treat (mITT) population Reasons for exclusion
	Identification of the per protocol population Reasons for exclusion
	Summary data (usually the ADSL.xpt dataset with efficacy measures or the combined dataset of ADSL.xpt and efficacy dataset)
Comments	

ATTACHMENT 8: Biopharmaceutics Classification System (BCS)

2.7 Clinical Summary

2.7	**BCS-based study summary and formulation tables** https://www.fda.gov/media/148433/download **E-Submission: PDF** ***MS Word*** Table 1. Method validation for solubility testing Table 2. Solubility data for (drug name) in different buffered media at (pH range) Table 3. Standard Operating Procedures Table 4. Permeability Study Method Validation Information Table 5. Permeability study validation summary data: permeability coefficients, % recovery for model compounds Table 6. Analytical method validation (for pivotal permeability study) Table 7. Pivotal Permeability Study Information Table 8. Pivotal permeability study: apical-to-basolateral (A-to-B) permeability of test compound and internal standards Table 9. Pivotal permeability study: basolateral-to-apical (B-to-A) permeability of test compound and internal standards Table 10. Pivotal permeability study: ratio of B-to-A papp vs. A-to-B papp Table 11. Drug Substance Stability in the Gastrointestinal Tract (if applicable) Table 12. Dissolution Method Information (For BCS Classification) Table 13. Information of analytical method used to analyze dissolution samples Table 14. Dissolution data ▪ Comparative in vitro dissolution data (12-unit individual data test vs. reference listed drug (RLD)) ▪ COA for test and reference products of the bioequivalence (BE) strength Table 15. Formulation Table 16. Core Excipient Data (for BCS Class III biowaiver, if applicable) Comments

BCS Data to support bioequivalence under 320.24(b)(6)

In vitro solubility testing

- Solubility testing in multiple pH ranging from 1.2 to 6.8 (at least 3 pHs within this range, including pH 1.2, 4.5 and 6.8)

Comments

In vitro permeability testing

- (1) Permeability testing performed or (2) reference made to RLD labeling or other human in vivo data derived from published literature.

Comments

In vitro dissolution testing

- pH 1.2 buffer
- pH 4.5 buffer
- pH 6.8 buffer
- In addition, dissolution studies per PSG (OGD media/USP media), if applicable

Explanation of alternative approach

ATTACHMENT 9: In-vitro Feeding Tube Testing

2.7 Clinical Summary

2.7	**In vitro feeding tube study summary and formulation tables** https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApplicationsforFDAApproval/AbbreviatedNewDrugApplicationANDAGenerics/UCM509461.pdf **E-Submission: PDF** ***MS Word*** Table 1. Product information Table 2.1 Information for oral syringe Table 2.2 Information for feeding tube (e.g., NG/G/J) Table 3. Comparative sedimentation data (if applicable) Table 4. Particle size distribution method validation Table 5. Particle size distribution data (arithmetic mean) Table 6. pH profiles before dispersion (initial pH) and after administration through feeding tube Table 7.1 Comparative recovery study at exit of oral syringe (arithmetic mean) Table 7.2 Comparative recovery study at exit of feeding tube (arithmetic mean) Table 8.1 Acid resistance stability data after delivery through the syringe Table 8.2 Acid resistance stability data after delivery through the feeding tube Table 9. SAS transport formatted tables for submission of data from in-vitro feeding tube studies A. Particle size distribution data B. Recovery study Comments