POLICY AND PROCEDURES

Office of Generic Drugs

Filing Review of Abbreviated New Drug Applications

Table of Contents

PURPOSE **1**
BACKGROUND **1**
POLICY **2**
RESPONSIBILITIES AND PROCEDURES **2**
REFERENCES **7**
EFFECTIVE DATE **8**
CHANGE CONTROL TABLE **8**
ATTACHMENT 1: ABBREVIATED NEW DRUG APPLICATION (ANDA) FILING CHECKLIST **9**
MODULES 1-5 ..... **9**
ATTACHMENT 2: PK STUDIES **21**
ATTACHMENT 3: CLINICAL ENDPOINT(S) **24**
ATTACHMENT 4: PD ENDPOINTS **28**
ATTACHMENT 5: IN VITRO BINDING STUDY(IES) **31**
ATTACHMENT 6: NASAL PRODUCTS **35**
ATTACHMENT 7: BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS) **42**

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

[1] For purposes of this MAPP, "ANDA" means ANDAs and prior approval supplements (PASs) to approved ANDAs for which the applicant is seeking approval of a new strength of the drug product.

that the ANDA is a substantially complete application, that is, an ANDA that on its face 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. 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 of the bases upon which a submission may be refused for receipt.

- Some applicants submit of a completed checklist with the submission. The DFR Reviewer does not review the applicant's complete checklist during the filing review and may advise applicants, as appropriate, that submission of a completed checklist is not recommended

- 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 the ANDA.[6]

RESPONSIBILITIES AND PROCEDURES

The DFR Reviewer will:

[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 2-7.
[6] See guidance for industry, *ANDA Submissions – Refuse-to-Receive Standards*, as revised, for criteria by which a DFR Reviewer will RTR an ANDA.

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

    - Module 1 (administrative information)

        - Confirm that the following administrative information related to the ANDA is included, but not limited to, the following documents and information:

            - Complete and signed Form FDA 356h and 3674

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

            - Agent appointment letter (as applicable)

                - Assess whether FDA has been authorized to correspond with any applicable agent or persons on behalf of the ANDA applicant and drug master file (DMF) holder(s)

            - Certifications

                - Debarment Certification and List of Convictions

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

            - Patent and exclusivity certifications

                - 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

                - Assess whether an exclusivity statement is submitted

            - Right of reference letter

                - Assess whether FDA has been authorized to access all Type II, Type III, and Type IV DMFs referenced in the ANDA

            - Proprietary name request

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

- Basis of submission

  - 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's petition is required, assess whether a copy of the petition has been provided in the ANDA

- Comparison demonstrating "sameness" to or differences from the RLD within each denoted class

- Environmental impact analysis or request for categorical exclusion

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

- Draft ANDA and RLD labeling

- Assess whether that proposed labeling appears congruent with the applicant's patent certification(s) or statement(s)

- Module 2 (data summaries)

  - Review Module 2 for summaries of the data contained in the ANDA including (see attachments 2-7, as applicable):

    - Quality Overall Summary (QOS) in Question based Review (QbR) format provided in PDF and Word files

    - 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)

- 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
    - 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 (DMF reference is not acceptable)
    - Complete information in all subsections of the Module 3.2.S.4 (specifications, analytical procedures, validation of analytical procedures, batch analysis, and justification of specifications)
    - Complete information on reference standards or materials (DMF reference is not acceptable)
    - Container closure systems and stability data

- Module 3.2.P (drug product)
    - 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[7]
        - Elemental iron calculations
        - Pharmaceutical development report

[7] 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.

- Drug product manufacturer information
    - 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
    - Assess whether that proposed maximum theoretical yield for the commercial batch is no more than 10X scale-up compared to the theoretical yield for the exhibit batch
- Description of the manufacturing process and controls
    - Assess whether complete description of manufacturing process including flow charts, master production batch records, master packaging records (as applicable), product sterilization process (as applicable), and reprocessing statement
    - Submission of critical steps and intermediates information
    - Process validation or evaluation
- 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 of analytical procedures, batch analysis, characterization of impurities, justification of specifications
- 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 and conclusion, and stability data and batch numbers

- Module 3.2.R (regional)

- Review Module 3.2.R for regional information related to the ANDA including:
    - Executed batch records with manufacturing and packaging reconciliation
    - Information on components
    - Comparability protocols (as applicable)
    - Methods validation package (as applicable)
- Module 5 (clinical)
    - Review Module 5 (see attachments 2-7) 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

3. Identify and list all deficiencies noted in review of Modules 1 – 5

4. RTR an ANDA that contains one or more major deficiencies pursuant to the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*, as revised.

5. RTR an ANDA that contains ten or more minor deficiencies pursuant to the guidance for industry *ANDA Submissions – Refuse-to-Receive Standards*, as revised.

6. Send an IR to the applicant if the ANDA contains nine or fewer minor deficiencies, providing the applicant the ability to remedy these deficiencies.
    - RTR the ANDA if the applicant does not remedy all deficiencies within 7 calendar days of FDA sending the IR.

REFERENCES

1. Guidance for industry *ANDA Submissions – Refuse to Receive Standards* (Rev. 2, December 2016)
2. 21 CFR 314.101

EFFECTIVE DATE

This MAPP is effective on September 1, 2017.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
9/1/2017	Initial	N/A

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):
New drug application (NDA) Number:	NDA/ANDA Number:
NDA Holder:	NDA/ANDA Holder:
Drug Product:	Drug Product:

MODULE 1: ADMINISTRATIVE

1.1	**1.1.2**	**Signed and completed application form (356h)** (Prescription (Rx) / Over-the-Counter (OTC) Status) 21 CFR 314.94(a)(1) (original signature) **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
		Comments
		Form FDA 3794 (PDF) GDUFA
		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)

<table>
<tr><td></td><td></td><td>Electronic, fillable copy (if a signed, scanned copy is provided)
Comments</td></tr>
<tr><td rowspan="10">1.3</td><td rowspan="2">1.3.1</td><td><u>Contact/Applicant information</u>
1.3.1.2 U.S. agent appointment letter 21 CFR 314.50(a)(5)
If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided.
Comments</td></tr>
<tr><td>1.3.2</td><td>Field copy certification 21CFR 314.94(d)(5)
(N/A for paper submissions)
Comments</td></tr>
<tr><td>1.3.3</td><td>Debarment certification from applicant Generic Drug Enforcement Act (GDEA)/ 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)
Comments</td></tr>
<tr><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>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</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?</td></tr>
<tr><td></td><td>1.3.5.3 Exclusivity claim
Exclusivity statement: state marketing intentions?
Pediatric exclusivity (new patient population (NPP), pediatric exclusivity (PED))</td></tr>
</table>

		PEPFAR NCE-1 Wavier of Exclusivity
		Comments
1.4	1.4.2	**Statement of right of references** 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
		Comments
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. Inactive ingredient(s) 4. Route of administration(s) 5. Dosage form 6. 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) -OR- **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)** 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically **1.14.1.4 Labeling comprehension studies** Refer to Pharmacy Bulk Package (PBP) Sterility Assurance Table (for PBP's only) See link below for table: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf
		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 a. Container closure system (if different from what is approved for the RLD) i. Vial or ampule vs. prefilled syringe ii. Vial vs. ampule iii. Delivery device that is different from the RLD, e.g. inhalers iv. Bottles vs blisters ("calendarized" packaging) v. Unit of use (dispensable bottle) vs. multiple use bottles (pharmacy bottle) b. Drug product packaged in an IV bag **1.14.3.3 Labeling text for reference listed drug** RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label
		Comments

MODULE 2: CTD SUMMARIES

2.3 QUALITY OVERALL SUMMARY (QOS)

21 CFR 314.50(c)

2.3	**E-Submission: PDF** **MS Word** **Additional information regarding QbR may be found at the following link:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm **Question based review (QbR)**
	Comments
	2.3.S Drug substance (API) 2.3.S.1 General information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of drug substance 2.3.S.5 Reference standards 2.3.S.6 Container closure system 2.3.S.7 Stability
	Comments
	2.3.P Drug product 2.3.P.1 Description and composition of the drug product 2.3.P.2 Pharmaceutical development 2.3.P.2.1 Components of the drug product 2.3.P.2.1.1 Drug substance (API) 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug product oral solids: immediate release or modified release (matrix technology or compressed film coated components) tablet scoring data per guidance for industry, *Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (March 2013) (if applicable) 2.3.P.2.3 Manufacturing process development 2.3.P.2.4 Container closure system 2.3.P.3 Manufacture 2.3.P.4 Control of excipients 2.3.P.5 Control of drug product 2.3.P.6 Reference standards and materials 2.3.P.7 Container closure system 2.3.P.8 Stability
	Comments
2.7	**Clinical summary (BE)** model BE data summary tables 21 CFR 320.21(b) and § 320.24(b) See Attachments 2-7 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. U.S. agent's name (if applicable) 4. Specify function or responsibility 5. Type II DMF number(s) for API(s) 6. Central file number (CFN), facility establishment identifier (FEI), or data universal numbers (DUNS) number (if available) 7. Additional sources of API and information (1 through 6, 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
3.2.S.4	**Control of drug substance (API)**	
	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 of Pharmacopeia (USP) standards or reference made to DMF, **MUST** 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)* 2. Samples-statement of availability and identification (21 CFR §314.50I(1)) a. Name of drug substance 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 API lot numbers
		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)(i) | 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 or Guide (IID or IIG) (per/dose, unit, or maximum daily dose (MDD) justification) (provide justification in a tabular format) 3. Formulation Oral tablet and oral capsules: % to mg/dosage unit Oral suspensions and oral solutions: % to mg/dose (dry powder) Parenterals: same unit of measure as RLD 4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on (maximum daily dose (MDD**)** of the drug product is preferred if this section is applicable) 5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be qualitatively and quantitatively the same (Q1/Q2 same) and must be provided in the package configuration
	Comments
3.2.P.2	**Pharmaceutical development report**

		Comments
		Manufacture
3.2.P.3	3.2.P.3.1	**Drug product manufacturer(s)** Must correlate to 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. U.S. agent's name (if applicable) 4. Specify function or responsibility 5. cGMP Certification from applicant 6. CFN, FEI, or DUNS numbers (if available)
		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) 4. If sterile product 5. Reprocessing Statement (cite 21 CFR 211.115) from applicant
		Comments
	3.2.P.3.4	**Controls of critical steps and intermediates**
		Comments
	3.2.P.3.5	**Process validation and/or evaluation** 1. Terminally sterilized product • Is this pharmacy bulk? (Go to 1.14.1.4) 2. Aseptically filled product • Validation (bacterial retention studies) of sterilizing grade filter(s) • Is this pharmacy bulk? (Go to 1.14.1.4)
		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
3.2.P.5		**Controls of drug product**
	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, must provide verification of USP procedure) Sample - Statement of Availability and Identification (21 CFR §314.50(e)(1)) Finished Dosage Form 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** 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
3.2.P.8		**Stability**

	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** (refer to the guidance for Industry *ANDAs: Stability Testing Drug Substances and Products* (June 2013)) 1. 3 batches? a. Two API lots used per strength? b. All presentations of container closure systems amongst the 3 batches? 2. Additional stability data to support additional API sources (if applicable) 3. Data- At minimum, 6 months (180 days) **and** 3 time points a. Accelerated 1. Significant change occurred 2. If yes, 6 months intermediate stability data b. Long term storage (room temperature) 4. Batch numbers on stability records the same as the test batch 5. Stability study initiated a. Accelerated b. Intermediate (if applicable) c. Long term 6. Date stability sample removed from stability chamber for each testing time point a. Accelerated b. Intermediate (if applicable) c. Long term 7. For liquid and semi-solid products, worst case and non-worst case orientation
		Comments

3.2.R REGIONAL INFORMATION

21 CFR §314.50(d)(1)(ii)(b)

		REGIONAL INFORMATION (DRUG PRODUCT)
3.2.R.P 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) (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.). Refer to the guidance for industry, *ANDAs: Stability Testing Drug Substances and Products, Questions and Answers* (May 2014) a. Two (2) pilot scale and one (1) small scale OR b. Three (3) pilot scale
		Comments
		Batch reconciliation and label reconciliation a. Theoretical yield b. Actual yield 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. 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
		Information on components *Name(s) and address(es) of the API, inactive ingredient(s), and containers and closures in **tabular format**. Hyperlinks are sufficient.*
		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** http://www.fda.gov/ucm/groups/fdagov-public/%40fdagov-drugs-gen/documents/document/ucm073290.pdf
	Comments

5.3	5.3.1	**BA/BE** 1. **Formulation data same?** a. Comparison of all strengths (proportionality of multiple strengths) b. Parenterals, ophthalmics, otics and topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. **Lot numbers and strength of products used in BE study(ies)** 3. **In vivo pharmacokinetic (PK) study(ies)** 4. **In vivo BE study(ies) with clinical endpoint(s)** 5. **In vivo BE study(ies) with pharmacodynamics (PD) endpoints (pilot and pivotal vasoconstrictor)** 6. **In vitro binding study(ies)** 7. **Nasal products (May contain a clinical endpoint or PK study)** 8. **Biopharmaceutics Classification System (BCS)** 9. **In-Vitro Feeding Tube Testing** 10. **Pressurized Metered Dose Inhalation Products** (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) c. Apparatuses and the respective parameters as recommended per the drug product specific guidance 3. In vitro release tests (specifically for acyclovir ointment and some ophthalmic suspensions) a. 90% confidence interval (CI) within 75-133% for 8^{th} and 29^{th} (first stage) b. 90% CI within 75-133% for 100^{th} and 215^{th} (second stage, if first stage failed) c. Study report d. Chromatograms/histograms e. Raw data 4. In vitro comparative physicochemical data 5. In vitro microbial kill test
Note		**See attachments 2-8 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 ▪ Comparative in vitro dissolution data (individual) ▪ Alcohol dose dumping dissolution (if applicable) ▪ ½ tablet dissolution (if applicable) ▪ COA for test and reference products of the bioequivalence (BE) strength (should include potency, assay, content uniformity, date of manufacture and lot number) 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) per the recommendations in the individual product BE guidance
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
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 bioequivalence (BE) studies
Table 3. Summary of skin irritation/sensitization/adhesion study(ies)
#1 Skin irritation/sensitization/adhesion study(ies)
#2 Adhesion data from 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

	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	
	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	
	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 tansport 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) per the recommendations in the product-specific guidance
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) for 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

pH 1.2

pH 3

pH 5

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

1. pH 1.2 T/R ratios of mean phosphate binding
2. pH 3.0 T/R ratios of mean phosphate binding
3. pH 5.0 T/ ratios of mean phosphate binding

Table III.15. In vitro equilibrium binding study results – summary of mean binding data

	Table 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) per the recommendations in the product-specific guidance
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, page 22 to 28 of the document referred in the previous slide); (2) Failure of in vivo BE study with PK endpoint to meet acceptable CI limits is also considered INADEQUATE for filing; (3) In vitro BE test outcomes for nasal products are NOT considered at filing stage (i.e., review issues)
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) per the recommendations in the product-specific guidance**
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) curriculum vitaes (CVs) 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
	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: BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

2.7 Clinical Summary

2.7	**BCS-based study summary and formulation tables** http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM396512.pdf **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. Pivotal permeability study information Table 4. Materials and methods for validation of permeability study Table 5. Permeability validation protocol for each model compound Table 6. Standard operating procedures Table 7. Permeability study validation summary data: permeability coefficients, %recovery for model compounds Table 8. Analytical method validation (for pivotal permeability study) Table 9. Pivotal permeability study design Table 10. Pivotal permeability study: apical-to-basolateral (A-to-B) permeability of test compound and internal standards Table 11. Pivotal permeability study: basolateral-to-apical (B-to-A) permeability of test compound and internal standards Table 12. Pivotal permeability study: ratio of B-to-A papp vs. A-to-B papp Table 13. Gastrointestinal tract instability Table 14. Dissolution method information Table 15. Information of analytical method used to analyze dissolution samples Table 16. 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 (should include potency, assay, content uniformity, date of manufacture and lot number) Table 17. Formulation data Comments

BCS Data

	In vitro solubility testing A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of multiple media with pH ranging from 1 to 6.8 ▪ Solubility testing in multiple pH ranging from 1 to 6.8 ▪ Information on chemical structure, molecular weight, nature of drug substance and dissociation constant (pKa) (multiple locations, i.e., 2.3, 3.2.S) ▪ Test results summarized in tabular format
Comments	
	In vitro permeability testing A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose ▪ Drug substance is 85% or more permeable (performed study or per RLD labeling)
Comments	
	In vitro dissolution testing A drug substance is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 500 mL or less in each of the following media: 0.1 N HCl or pH 1.2 buffer, pH 4.5 buffer, and pH 6.8 buffer ▪ 85% dissolved within 30 minutes in all three media ▪ Mean percent dissolved, range of dissolution and coefficient of variation in tabular format
Comments	