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ABBREVIATED NEW DRUG APPLICATION (ANDA) FILING CHECKLIST

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ABSTRACT

This paper is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This guidance details the information that should be provided in each section of the common technical document (CTD) format for human pharmaceutical product applications and identifies supporting guidance documents and recommendations issued by FDA to assist applicants in preparing their ANDA submission. This guidance identifies the information that an applicant should include to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance documents on the filing process, including the guidance for industry about refuse-to-receive standards, and common, recurring deficiencies which should be reviewed thoroughly prior to submission of an ANDA. ANDA Content Differences with 505(b)2 Emerging Initiatives Summary ANDA Submission Checklist FDA ANDA Review Checklist ANDA Process for Generic Drugs ANDA Checklist for CTD or ECTD Format for Completeness and Acceptability of an Application for Filing Guidance for Industry Organization of an ANDA.

KEYWORDS: Abbreviated New Drug Application (ANDA), Common Technical Document (CTD), Check List, USFDA.

1. INTRODUCTION

ANDA Submissions — Content and Format Guidance for Industry[1-4]

This project is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance details the information that should be provided in each section of the common technical document (CTD) format for human pharmaceutical product applications and identifies supporting guidance documents and recommendations issued by FDA to assist applicants in preparing their ANDA submission. This guidance identifies the information that an applicant should include to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance documents on the filing process, including the guidance for industry about refuse-to-receive standards, and common, recurring deficiencies which should be reviewed thoroughly prior to submission of an ANDA.

ANDA submission requirements for Generic drugs[5,6]

The Food and Drug Administration (FDA or US FDA) is an agency of the United States department of Health and Human Services one of the United States federal executive departments. The USFDA is considered as the most stringent standards in approving the drug products into the market. “ANDA” is the abbreviation for “Abbreviated New Drug Application”. It contains data which when submitted to FDA’s Center for Drug Evaluation & Research, Office of Generic Drug, provides for the review & ultimate approval of a generic drug product. The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. In the ANDA submission to FDA CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness.

“A drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use”. It termed "abbreviated" because they generally not required including preclinical and clinical data to establish safety and effectiveness.

CTD FORMAT[7-9]

The CTD format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in an attempt to streamline the

submission requirements for Japan, the European Union, and the United States. The CTD collects quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. The electronic CTD (eCTD) is the standard format for electronic regulatory submissions for ANDAs.

As of May 5, 2017, ANDAs and submissions to ANDAs (which includes amendments, supplements, and reports) must be submitted to FDA electronically in eCTD format.

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

The CTD is comprised of the following modules

- Module 1: Administrative Information and Prescribing Information
- Module 2: Summaries
- Module 3: Quality
- Module 4: Nonclinical
- Module 5: Clinical

NOTE: Module 4 * Nonclinical are not performed for the generic drugs because the bioequivalence studies are already performed for branded drugs.

2. RESEARCH METHODOLOGY

Introduction to the role of regulatory affairs in pharmaceutical industries

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Introduction to the ANDA filling checklist

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ANDA submission requirements for generic drugs

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The main objective is to understand the regulations and guidelines of ANDA checklist

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Review of literature

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↓

Study & discussions

↓

Conclusion

3. STUDY & DISCUSSIONS[9-15]

MODULE 1: ADMINISTRATIVE

1.1 Signed and completed application form (356h) (Prescription (Rx) / Over-the Counter (OTC) Status) 21 CFR 314.94(a)(1) (original signature)

1.1.2 Electronic, fillable copy (if a signed, scanned copy is provided) Refer to the links provided for the newly revised form 356h and updated instructions.

- **Form FDA 3794 (PDF) GDUFA**

1.2 Cover letter

Is the drug product subject to REMS Requirements.

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)

1.3 Contact/Applicant information

1.3.1 U.S. agent appointment letter 21 CFR 314.50(a)(5) If the applicant identifies a U.S. Agent on the 356h,

U.S. Agent Appointment letter should be provided

1.3.2 Field copy certification 21CFR 314.94(d) (5) 1.3.2 (N/A for paper submissions)

1.3.3 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)

1.3.4 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)

1.3.5 Patent and exclusivity

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)
2. Pediatric extension

a. Expiration of pediatric extension

1.3.5.3 Exclusivity claim Exclusivity statement: state marketing intentions? Pediatric exclusivity (new patient population (NPP), pediatric

(LoA) received from DMF holders)

1. Type II DMF authorization letterexclusivity (PED)

1.4 Statement of right of references 21 CFR 314.50(g)(1) DMF written statement of authorization for reference (copy of letter of authorization (s) or synthesis for Active Pharmaceutical Ingredient (API)

2. Type II DMF#
3. Type III DMF authorization letter(s) for container Closure

1.12.4 Request for comments and advice – proprietary name requested if yes, the applicant provided the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing.

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)

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)

1.12.14 Environmental analysis from applicant

Environmental assessment (EA)

If applicable, environmental impact statement (EIS) Claim of categorical exclusion statement

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)

1.14 Draft labeling

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)

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)

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 syring

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

MODULE 2: CTD SUMMARIES

2.3 Quality Overall Summary (QOS)

In Question based Review (QbR)

2.3. SDrug 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

2.3.1. S.7 Stability

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

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

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)

3.2. S.1General 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

3.2. S.2.1Manufacturer

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)

3.2. S.3Characterization

All potential impurities should be listed in tabular format

3.2. S.4Control of drug substance (API)

3.2. S.4.1 Specification

Testing specifications and data from drug substance manufacturer(s)

3.2. S.4.2 Analytical procedures

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

2. Samples-statement of availability and identification (21 CFR §314.50I(1))

a. Name of drug substance

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

3.2. S.4.5 Justification of specifications

All Potential Impurities Should Be Listed In Tabular Format

3.2. S.5 Reference standards or materials (Do NOT refer to DMF)

3.2. S.6 Container closure systems

3.2. S.7 Stability

1. Retest date or expiration date of API(s)

3.2. P DRUG PRODUCT

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

3.2. P.2 Pharmaceutical development report

3.2. P.3 Manufacture

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)

3.2. P.3.2 Batch formula

Largest intended commercial batch size

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

3.2. P.3.4 Controls of critical steps and intermediates

3.2. P.3.5 Process validation and/or evaluation

1. Terminally sterilized product

• Is this pharmacy bulk?

2. Aseptically filled product

• Validation (bacterial retention studies) of sterilizing grade filter(s)

• Is this pharmacy bulk?

3.2. P.4 Controls of excipients (inactive ingredients)

Source of inactive ingredients identified

3.2. P.4.1 Specifications

1. Testing specifications (including identification and characterization)

2. Supplier's COA (specifications and test results)

3.2. P.4.2 Analytical procedures

3.2. P.4.3 Validation of analytical procedures

3.2. P.4.4 Justification of specifications (as applicable)

Applicant COA

3.2. P.5 Controls of drug product

3.2. P.5.1 Specification(s)

3.2. P.5.2 Analytical procedures

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

3.2. P.5.4 Batch analysis

Certificates of Analysis for finished dosage form

Lot number(s) and strength of drug product(s)

3.2. P.5.5 Characterization of impurities

3.2. P.5.6 Justification of specifications

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

c. Injectables with rubber stoppers: extractables

5. Source of supply and supplier's addresss

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)

3.2. P.8.2 Post-approval stability protocol and stability commitment

1. Post-Approval Protocol and Commitment from applicant

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

3.2. R REGIONAL INFORMATION

3.2. R.P REGIONAL INFORMATION (DRUG PRODUCT)

3.2. R.P.1 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, 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,

3.2. R.P.3 Methods validation package

Methods validation package (Required for Non-USP drugs)

MODULE 5: CLINICAL STUDY REPORTS

5.2 Tabular listing of clinical studies

5.3 BA/BE

5.3.1

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 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 8th and 29th (first stage)

b. 90% CI within 75-133% for 100th and 215th (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

4. CONCLUSION

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

5. REFERENCES

1. Definition for the Food and Drug Administration (FDA or US FDA) [Internet]. Wikipedia; 2018 [cited 2018 Jun 20] Available from: https://en.wikipedia.org/wiki/Food_and_Drug_Administration

2. Details of “ANDA” are the abbreviation for “Abbreviated New Drug Application” [Internet]. REGULATORY ONE; 2018 [cited 2012 Jan 24]. Available from: http://www.regulatoryone.com/2012/01/anda.html
3. Role of FDA's Center for Drug Evaluation and Research (CDER) [Internet]. U.S FDA; 2015 [cited 2015 Aug 18]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/
4. Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) [Internet]. U.S FDA; 2018 [cited 2018 May 17]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/default.htm
5. Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) [Internet]. U.S FDA; 2018 [cited 2018 May 17]. Available from: https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/default.htm
6. History of Generic Drug Approval [Internet]. Health day; 2018 [cited 2018 Jan 20]. Available from: https://consumer.healthday.com/encyclopedia/drug-center-16/misc-drugs-news-218/history-of-generic-drugs 646390.html
7. History of Generic drug approval [Internet]. Wikipedia; 2018 [cited 2018 May 21]. Available from: https://en.wikipedia.org/wiki/Generic_drug
8. Indispensability grounds for Generics [Internet]. SSlide share; 2012 [cited 2018 May 17]. Available from: hcopgnt.com/admin/uploads/anda%20filing.pptx
9. Sokal and Bart A. Gerstenblith article about the hatch-waxman act: encouraging innovation and generic drug competition Hatch-Waxman Act [Internet]. Finnegan; 2018 [cited 2018 May 23]. Available from: https://www.finnegan.com/en/insights/the-hatch-waxman-act-encouraging-innovation-and-generic-drug.html
10. General provisions of the act Recent additions to the Hatch-Waxman Act Under the “Medicare Prescription Drug and Modernization Act”, 2003 [Internet]. Slide share; 2012 [cited 2018 May 25]. Available from: hcopgnt.com/admin/uploads/anda%20filing.pptx

11. ANDA certification clauses [Internet]. Gphaonline; 2018 [Cited 2018 May 11]. Available from: https://www.gphaonline.org/media/wysiwyg/Meetings/Fall_2016/Joseph_Sobecki.pdf
12. Brahmaiah Bonthagarala, Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic Goods Administration, International Journal of Advanced Scientific and Technical Research, ISSN 2249-9954, November-December 2016; 6(6): 144-157.
13. Brahmaiah Bonthagarala, Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, November-December 2016; 6(6): 1-19.
14. Brahmaiah Bonthagarala, Regulatory process and ethics for clinical trials in India (CDSCO)- A Review, The Pharma Innovation Journal, ISSN (E): 2277-7695, ISSN (P): 2349-8242, 2017; 6(4): 165-169.
15. Brahmaiah Bonthagarala, Evaluation of Pharmaceutical Regulatory Systems & Present Scenario of Indian Pharmaceutical Industry, World Journal of Pharmaceutical Research, ISSN 2277–7105, 2017; 6(5): 368-379.