Bridging the Difference: Case Studies that Demonstrate Bioequivalence Assessments for Approved Suitability Petitions

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 8: **Enabling Generics: Changes to Suitability Petitions in GDUFA III**

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objectives

- ❑ List the benefits of a dosage form change
- ❑ Describe a dosage form change approved via suitability petition
- ❑ Consider pharmaceutical equivalence criteria for evaluating a dosage form change via suitability petition
- ❑ Review the structure of a product specific guidance for products approved via suitability petition

Permissible suitability petition changes provided under § 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) include:

- A different active ingredient in a combination product in which the other active ingredients match those of the reference listed drug (RLD)
- A different route of administration*
- A different dosage form
- A different strength

* A (j)(2)(C) petition seeking a change in the route of administration has not been approved to date

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- A different active ingredient in a combination product in which the other active ingredients match those of the RLD
- A different route of administration
- A different dosage form
- A different strength

Case Study

CARBIDOPA AND LEVODOPA: ORAL TABLETS TO ORALLY DISINTEGRATING TABLETS

RLD Product

New Drug Application (NDA)	017555
Proprietary Name	Sinemet
Active Ingredients	Carbidopa and Levodopa
Dosage Form	Tablet
Route	Oral
Strengths	10 mg; 100 mg 25 mg; 100 mg 25 mg; 250 mg
Approval Date	05/02/1975
Labeling Indications	For the treatment of: • Parkinson's disease (PD) • Post-encephalitic parkinsonism • Symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication

A dosage form change of Sinemet offers clinical benefit

- PD and Parkinson-related disorder (PRD) patients develop dysphagia as a result of disease progression likely due to muscle rigidity and bradykinesia
- Dopaminergic medications do not guarantee improved swallowing function
- Orally disintegrating tablets (ODTs), tablets for solutions, and tablets for suspension offer improved dosing options for PD and PRD patients to reduce risk of choking and improve patient compliance

Three suitability petition requests were made for Sinemet dosage form changes

[+]Docket Number	Change from Tablet to:	Status	Petition Status	First ANDA Approved	Suitability Petition Reference Standard (RS)
FDA-2002-P-0217	Orally Disintegrating Tablet	Approved	09/25/2002	08/27/2004	ANDA 076699
01P-0358/CP1	Tablet; for Oral Suspension	Approved	08/09/2002	07/10/2005	ANDA 076643
FDA-1995-P-0005	Powder; for Reconstitution to oral liquid	Withdrawn*	03/26/2007	None Filed	None

*The petition was initially approved May 28th, 1996. However, it was withdrawn in accordance with the Pediatric Research Equity Act of 2003 (PREA) per Federal Register 72 FR 8184 (Feb. 23, 2007)

[+] Regulations.gov & [+]https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/patent-certifications-and-suitability-petitions#petitions

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Carbidopa & Levodopa Orally Disintegrating Tablets
Docket FDA-2002-P-0217

- Petition was approved on September 25, 2002
- Petitioner requested a dosage form change from tablet to ODT
- FDA determined change does not pose questions of safety or efficacy
- FDA evaluated the change with respect to the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients Final Rule (Pediatric Rule) (63 FR 66632) and concluded that investigations are not necessary to demonstrate the safety and effectiveness in the pediatric population because:
  - There is no meaningful therapeutic benefit over existing therapies for pediatric patients
  - The product is not likely to be used in a substantial number of pediatric patients

Four ANDAs were approved based on the suitability petition FDA-2002-P-0217

Marketing Status	Product Name	ANDA #	Strengths	Approval Date	First ANDA Approved	Designated RS for ODT	Basis of Submission
RX	Carbidopa & Levodopa	078690	10 mg; 100 mg 25 mg; 100 mg 25 mg; 250 mg	07/31/2009	No	Yes 25 mg; 250 mg	ANDA 076699
Discontinued*	Parcopa	076699	10 mg; 100 mg 25 mg; 100 mg 25 mg; 250 mg	08/27/2004	Yes	No	NDA 017555
Discontinued	Carbidopa & Levodopa	090631	10 mg; 100 mg 25 mg; 100 mg 25 mg; 250 mg	06/08/2010	No	No	ANDA 076699
Discontinued	Carbidopa & Levodopa	078893	10 mg; 100 mg 25 mg; 100 mg 25 mg; 250 mg	09/18/2008	No	No	ANDA 076699

*Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons

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Pharmaceutical equivalence considerations with switching from tablet to ODT

- Taste Masking
- Tablet Friability and Packaging
- Disintegration
- Selection of the most sensitive administration method for bioequivalence studies
  - Administer with water
  - Administer without water

FDA current thinking on water administration with ODT in bioequivalence studies[+]

RLD Labeling states to:	Applicants should conduct bioequivalence studies:
Administer ODT with or without water	Without water
Administer ODT with water only	With water
Administer ODT without water only	Without water

[+] FDA Guidance for industry, *Bioequivalence studies with pharmacokinetic endpoints for Drugs Submitted Under an Abbreviated New Drug Application (*Aug 2021)

Characteristics of carbidopa and levodopa ODT

- Dosing is initiated with one tablet three times a day and titrated to eight tablets daily.
- Carbidopa and levodopa ODT Formulation
  - Utilized RapiTab technology dosage form
  - Dissolves rapidly (<30 sec) on the tongue with saliva and without chewing
  - Water is not necessary to disintegrate tablet
  - Release of carbidopa and levodopa targeted to occur in 30 mins
  - Mint flavored
  - Packaged in bottles

Carbidopa and levodopa ODT approval basis

1. Suitability petition FDA-2002-P-0217 approving a change from tablet to ODT.
2. A single dose, two-treatment, four-period fully replicate crossover fasting bioequivalence study on the carbidopa and levodopa ODT, 25 mg/250 mg strength against carbidopa and levodopa tablet, 25 mg/250 mg strength based on plasma levels of carbidopa and levodopa.
   - The ODT was administered without additional water
3. Biowaivers for the generic carbidopa and levodopa ODT, 10 mg/100 mg and 25/100 mg, based on:
   - The in vivo fasting bioequivalence study on the generic carbidopa and levodopa ODT tablet, 25 mg/250 mg strength was found acceptable.
   - The in vitro dissolution testing conducted on the generic carbidopa and levodopa tablets, 25 mg/250 mg, 10 mg/100 mg, and 25/100 mg tablets was found acceptable.
   - The generic carbidopa and levodopa tablets, 10 mg/100 mg and 25/100 mg, were found compositionally proportional to the 25 mg/250 mg strength.

Note: Current product specific guidances for carbidopa and levodopa combination products recommend both fasting and fed bioequivalence studies

Case Study

PSG DEVELOPMENT FOR SUITABILITY PETITION PRODUCTS

Case Study: Cefixime Oral Suspension

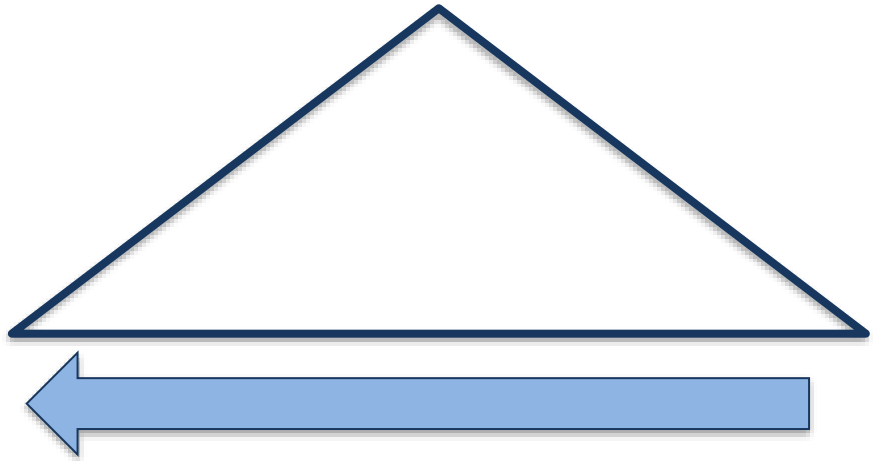
Suprax - NDA 050622 (Held by Lederle)
Dosage: Oral Suspension
Strength: 100 mg/5 mL
Approved: April 28th, 1989
Discontinued*
Listed as RLD

Suprax - ANDA 065129 **(Held by Lupin)**
Strength: 100 mg/5 mL
Approved: Feb 23, 2004
Discontinued
Listed as RLD/RS prior to 200 mg/mL approval

Suitability Petition
2005P-0013/CP1
Change in Strength
Approved: April 8, 2005

10 mL of 100 mg/5 mL used as RLD and RS to support approval of 200 mg/5 mL strength (5 mL administered)

Suprax - ANDA 065355 (**Held by Lupin**)
Strength: 200 mg/5 mL
Approved: April 10, 2007
Current RS
Listed as RLD prior to 500 mg/mL approval



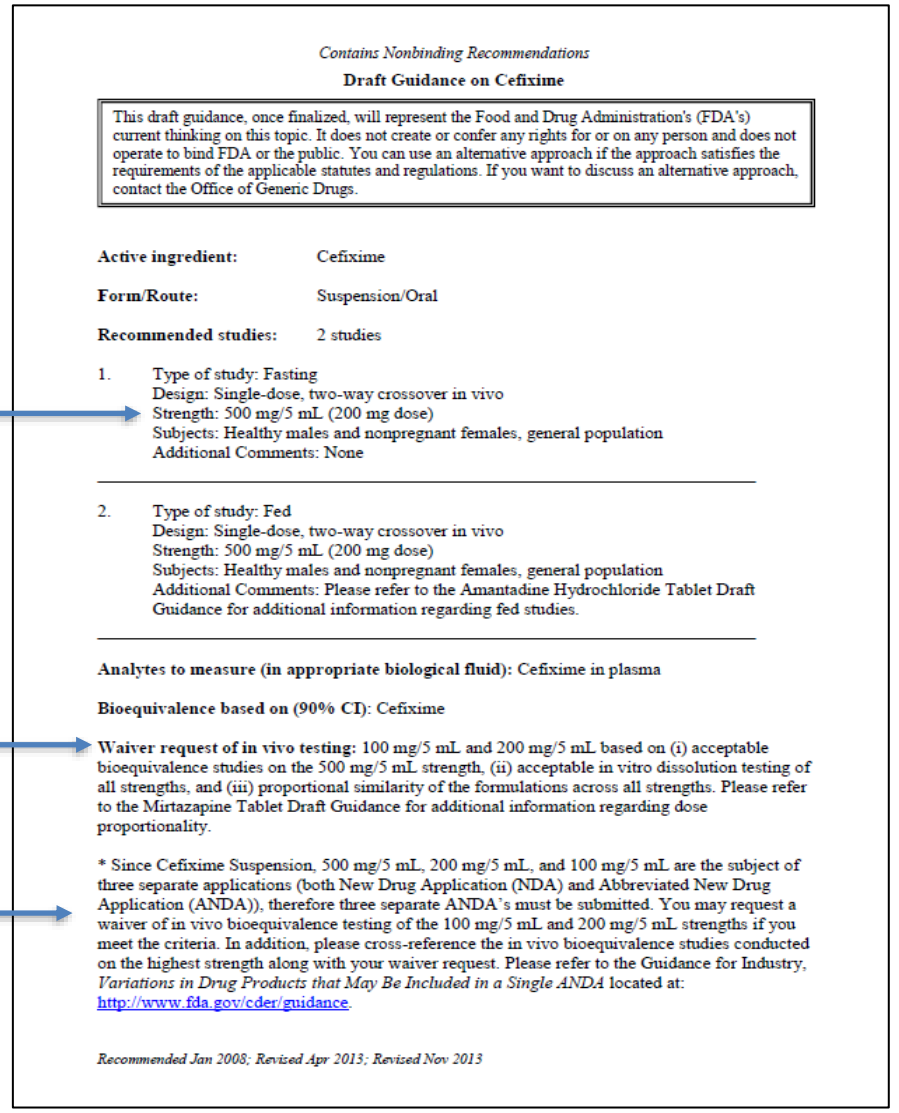
5 mL of 200 mg/5 mL used as RLD and RS to support approval of 500 mg/5 mL strength (2 mL administered)

Suprax - NDA 202091 **(Held by Lupin)**
Strength: 500 mg/5 mL
Approved: Feb 20, 2013
Listed as RLD/RS

Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons

PSG of Cefixime

- 3 strengths of cefixime oral suspension approved based on 1 505(b)(2) NDA, 1 ANDA 505(j) and 1 ANDA 505 (j)(2)(C)
- The 500 mg/5 mL strength is assigned as RLD and RS for cefixime oral suspension
- Waiver of in vivo testing on the lower strengths based on:
  - Lupin's 500 mg/5 mL strength approved based on their 200 mg/5 mL strength
  - Lupin's 200 mg/5 mL strength approved on their 100 mg/5 mL strength
  - OGD considers these 3 strengths as part of the same product line
- A separate ANDA is required to be submitted for each strength



Contains Nonbinding Recommendations

Draft Guidance on Cefixime

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Cefixime

Form/Route: Suspension/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in vivo
   Strength: 500 mg/5 mL (200 mg dose)
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: None

2. Type of study: Fed
   Design: Single-dose, two-way crossover in vivo
   Strength: 500 mg/5 mL (200 mg dose)
   Subjects: Healthy males and nonpregnant females, general population
   Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Cefixime in plasma

Bioequivalence based on (90% CI): Cefixime

Waiver request of in vivo testing: 100 mg/5 mL and 200 mg/5 mL based on (i) acceptable bioequivalence studies on the 500 mg/5 mL strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding dose proportionality.

* Since Cefixime Suspension, 500 mg/5 mL, 200 mg/5 mL, and 100 mg/5 mL are the subject of three separate applications (both New Drug Application (NDA) and Abbreviated New Drug Application (ANDA)), therefore three separate ANDA's must be submitted. You may request a waiver of in vivo bioequivalence testing of the 100 mg/5 mL and 200 mg/5 mL strengths if you meet the criteria. In addition, please cross-reference the in vivo bioequivalence studies conducted on the highest strength along with your waiver request. Please refer to the Guidance for Industry, *Variations in Drug Products that May Be Included in a Single ANDA* located at: http://www.fda.gov/cder/guidance.

Recommended Jan 2008; Revised Apr 2013; Revised Nov 2013

Summary

- A change from tablet to ODT may improve patient compliance for patients who exhibit dysphagia
- Several ANDAs were approved for carbidopa and levodopa ODT based on an approved suitability petition and subsequent approval of an ANDA
- Dosage form changes may have unique product characteristics and special conditions to establish bioequivalence that should be considered
- OGD implements guidance for products approved via suitability petition into their PSG recommendations

Challenge Question

When an ODT label recommends for products to be administered with or without water, the applicant should demonstrate bioequivalence by administering the test and reference product:

A. With Water
B. Without Water
C. The applicant can choose to conduct the BE study with or without water
D. The applicant should conduct two studies; one with water and another study without water

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