Development of Generic Drug products under Suitability Petition

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Facilitating Generic Product Development Through
Product-Specific Guidances (PSGs) – April 25, 2024

Learning Objectives

- ❑ Describe changes permissible via suitability petition
- ❑ Understand how GDUFA III Reauthorization FY 2023-2027 affects suitability petitions
- ❑ Summarize the effect of GDUFA III on suitability petition submissions since FY 2024
- ❑ Review the structure of a product-specific guidance (PSG) for products approved via suitability petition

Permissible Suitability Petition Changes* 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

*Provided under § 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
**A (j)(2)(C) petition seeking a change in the route of administration has not been approved to date

GDUFA III Resulted in Goal Dates for Suitability Petitions Submitted FY 2024-2027

- The following goals are implemented:

Fiscal Year:	% Submissions reviewed in 6 months	Maximum Petitions eligible for goal
2024	50 (n = 25)	50
2025	70 (n = 49)	70
2026	80 (n = 64)	80
2027	90 (n = 81)	90

As of March 1, 2024,* FDA has Received

Monthly Submissions (FY'24)

Oct*	Nov	Dec	Jan	Feb
54	9	6	7	1
			Total	**77**

*The GDUFA III start date for FY 2024 was October 1, 2023.

Tablet to Orally Disintegrating Tablet (ODT) is the Most Frequent Dosage Form Petition

Type of Switch Petitioned	# Petitions
Dosage Form Switch	**32**
Tablet → ODT	15
Solution → Powder for reconstitution	4
Tablet or Capsule → Solution/Suspension	4
Lyophilized powder → Ready to use injection	4
Other - specialized	5
Strength Change	**52**
Intravenous injection (Convenience dosing/waste elimination)	18
Tablet/Capsule	17
Other	17

FDA Action on FY'24 Suitability Petitions:*

Final Response Issued:	**28**
Denied	12
Withdrawn	3
Partial Grant/Deny	1
Granted	13
On Hold/Information Request	**2**
Pending	**46**

*As of March 1, 2024.

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13 Suitability Petitions have been Granted:*

Granted	**13**
Tablet to ODT (Cyclobenzaprine Tablet to ODT)	1
Strength Change	**12**
Intravenous injection – Convenience dosing/Waste elimination (Concentration typically remains the same)	8
Tablet/Capsule Strength additions	4

*As of March 1, 2024

PSG Development on Strengths Approved via Suitability

Three Strengths of Cefixime Oral Suspension Approved under Three Approval Pathways

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

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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

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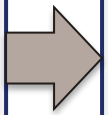
Case Study: Cefixime Oral Suspension

Basis for all cefixime oral suspensions

Suprax - NDA 050622
Applicant Holder: **Lederle**
Application Type: **505(b)(1)**
Dosage: Oral Suspension
Strength: **100 mg/5 mL**
Approved: April 28th, 1989
Discontinued*
Original RLD;
Currently listed RLD



Suprax - ANDA 065129
Applicant Holder: **Lupin**
Application Type: **505(j)**
Dosage: Oral Suspension
Strength: **100 mg/5 mL**
Approved: Feb 23, 2004
Discontinued**
Was listed as RS prior to 200 mg/mL approval

*Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons
**No Federal Register determination

Case Study Continued: Cefixime Oral Suspension

Suitability Petition Approved
2005P-0013/CP1
Change in Strength:
100 mg/5ml → 200 mg/ 5 mL
Approved: April 8, 2005

Bioequivalence Approach for Suitability Petition

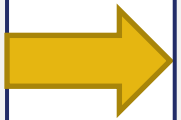
- NDA 050622 was discontinued
- ANDA 065129 identified as RS
  - The dose tested was 200 mg:
  - 10 mL of the 100 mg/5 mL was tested against 5 mL of the 200 mg/ 5 mL proposed suspension

Suprax - ANDA 065355
Applicant Holder: **Lupin**
Application Type: **505(j)(2)(C)**
Dosage: Oral Suspension
Strength: **200 mg/5 mL**
Approved: April 10, 2007
Current reference standard (RS)
Listed as RS prior to 500 mg/mL approval

Case Study Continued: Cefixime Oral Suspension

Approach for 505(b)(2) submission

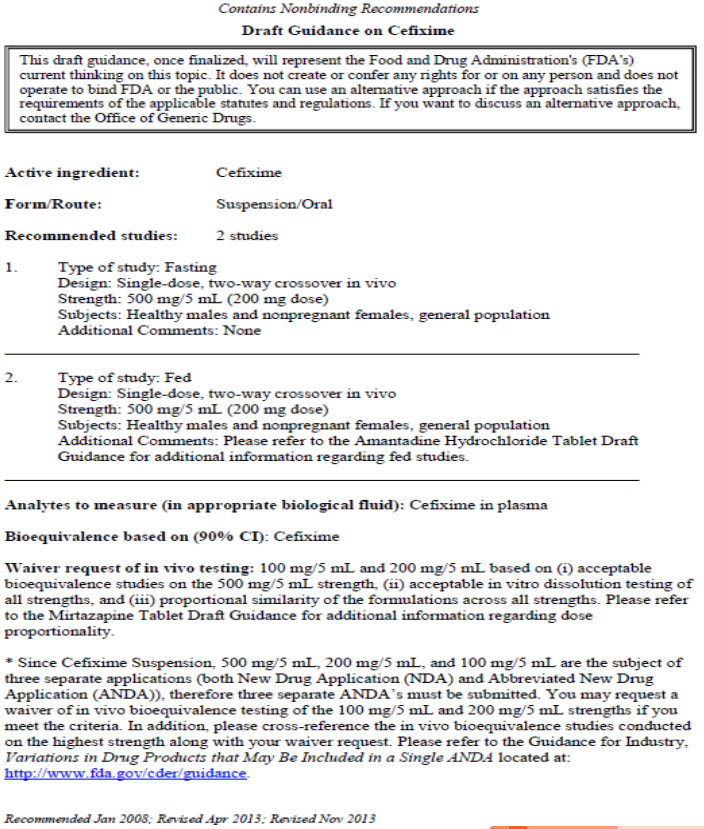
- ANDA 065355 (200 mg/5 mL) selected as the listed drug
  - The dose tested was **200 mg**
  - 5 mL of the 200 mg/5 mL was tested against 2 mL of the 500 mg/ 5 mL proposed suspension



Suprax - NDA 202091
Applicant Holder: **Lupin**
Application Type: **505(b)(2)**
Dosage: Oral Suspension
Strength: **500 mg/5 mL**
Approved: Feb 20, 2013
Listed as current RLD/RS

Anatomy of the Cefixime PSG

- Three strengths of cefixime oral suspension approved based on a:
  - 505(b) NDA / 505(j) ANDA
  - ANDA 505 (j)(2)(C)
  - 505(b)(2) NDA
- 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 three strengths as part of the same product line
- A separate ANDA is required to be submitted for each strength



Contains Nonbinding Recommendations

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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.

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Recommended Jan 2008; Revised Apr 2013; Revised Nov 2013

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PSG Development on Dosage Form Changes Permissible to File via a Suitability Petition

Example: Tablet to an ODT and Pharmaceutical Equivalence Considerations

- Taste Masking
- Tablet Friability and Packaging
- Disintegration
- Intended label claims for petitioned ANDA that differ from the tablet
- Selection of the most sensitive administration method for bioequivalence studies
  - Administer with water
  - Administer without water

Special Administration for ODT Tablets in Bioequivalence Studies

Bioequivalence consideration for generic approval of an ODT referencing an ODT

ANDA labeling intends to state:	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

Bioequivalence consideration for Tablet to ODT

Petitioned ANDA labeling intends to state:	Applicants should conduct bioequivalence studies:
Administer ODT with or without water	Conduct study both with and without water
Administer ODT with water only	With water
Administer ODT without water only	Without water

Future of PSG and Suitability Petitions

PSG will Proactively Support Recommendations for Approved Suitability Petition

- Traditionally, FDA incorporates our recommendations for the additional strengths into the PSG only *after a petitioned ANDA has been approved*
- Moving forward, FDA will attempt to proactively incorporate our recommendations for petitioned strengths into our PSG *prior to a petitioned ANDA being approved*
  - Example – Primidone
- In the future, you may see strengths and dosage forms in the PSG recommendation that are not in the Orange Book
  - This will be because there is an approved suitability petition

Primidone PSG Example

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Primidone

November 2023

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In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Primidone

Dosage Form: Tablet

Route: Oral

Strengths: 25 mg[1], 50 mg, 100 mg[1], 125 mg[1], 250 mg

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 50 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 50 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: None

Analyte to measure: Primidone in plasma

Bioequivalence based on (90% CI): Primidone

[1] Strengths identified are the subject of an approved suitability petition (FDA-2009-P-0482).

Recommended May 2019; Revised Nov 2023

Waiver request of in vivo testing: 25 mg, 100 mg, 125 mg and 250 mg strengths based on (i) acceptable bioequivalence studies on the 50 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application.

If any strength of the tablet product has a functional score, additional dissolution profile testing should be conducted for each segment of the split tablet after manual and mechanical splitting as per the most recent version of the FDA guidance for industry on *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*.[a]

Document History: Recommended May 2019; Revised November 2023

Unique Agency Identifier: PSG_009170

[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Recommended May 2019; Revised Nov 2023

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Challenge Question #1

A permissible suitability petition request does not include:

A. A different route of administration*

B. A different dosage form

C. A different strength

D. A different salt form of a drug

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Challenge Question #2

By 2027, FDA commits to reviewing what percentage of suitability petitions in 6 months?

A. 30%

B. 60%

C. 90%

D. 100%

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A. 30%

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C. 90%

D. 100%

Summary

- GDUFA III commitment goals in FY'24 related to suitability petitions have been met
- Industry has successfully leveraged the revamped suitability pathway evident by the number of submissions received
- FDA is proactively providing PSG recommendations for petitioned strengths
  - Dosage form changes may have unique product characteristics and special conditions to establish bioequivalence that should be considered
  - Additional strengths are likely eligible for a waiver of in vivo testing; special considerations may need to be made

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Questions?

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