

Development of Generic Drug Products under Suitability Petition

Heather J. Boyce, Ph.D.

Lead Pharmacokineticist

Division of Therapeutic Performance II,
Office of Research and Standards

CDER | U.S. FDA

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



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
<u>Dosage Form Switch</u>	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
<u>Strength Change</u>	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Withdrawn	3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.
[fda.gov/cdersbia](https://www.fda.gov/cdersbia)

13 Suitability Petitions have been Granted:*



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

*As of March 1, 2024

[fda.gov/cdersbia](https://www.fda.gov/cdersbia)

The slide features decorative geometric patterns. On the left, a vertical column of triangles in various shades of blue and dark blue. On the right, a vertical column of triangles in various shades of orange and light orange. The main content area is white with the title text in dark blue.

PSG Development on Strengths Approved via Suitability



Three Strengths of Cefixime Oral Suspension Approved under Three Approval Pathways

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

- 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
- 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>.

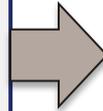
Recommended Jan 2008; Revised Apr 2013; Revised Nov 2013

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

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)

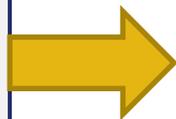
Listed as RS prior to 500 mg/mL approval

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

Contains Nonbinding Recommendations
Draft Guidance on Cefixime

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- 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

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

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* 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 2005; Revised Apr 2013; Revised Nov 2013

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

Bioequivalence consideration for Tablet to ODT

RLD label states:	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

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 mg¹, 50 mg, 100 mg¹, 125 mg¹, 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*.⁴

Document History: Recommended May 2019; Revised November 2023

Unique Agency Identifier: PSG_009170

⁴ 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

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

Challenge Question #1



A permissible suitability petition request does not include:

- A. A different route of administration*
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- C. A different strength
- D. A different salt form of a drug**

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%

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%

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

Questions?

Heather J. Boyce, Ph.D.

Lead Pharmacokineticist

Division of Therapeutic Performance II,

Office of Research and Standards

CDER | U.S. FDA

Heather.Boyce@fda.hhs.gov





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