

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203195Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Final Label and Labeling Review**

Date: May 10, 2012

Reviewer: Aleksander Winiarski, PharmD  
Division of Medication Error Prevention and Analysis

Acting Team Leader Chi-Ming (Alice) Tu, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Suprax (Cefixime) Capsules, 400 mg

Application Type/Number: NDA 203195

Applicant: Lupin Pharmacueticals

OSE RCM #: 2011-3363-1

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the revised container label and carton labeling as well as the revised insert labeling for Suprax (Cefixime) Capsules, 400 mg, for revision to our previous comments to the Applicant in OSE review #2011-3363, dated January 18, 2012.

## 2 MATERIAL REVIEWED

DMEPA reviewed the revised container label, blister label, carton labeling and insert labeling submitted by the Applicant on May 3 and May 7, 2012. See Appendix for samples. We also evaluated our recommendations made in OSE review #2011-3363 to access whether the revisions adequately address our concerns from a medication error perspective.

## 3 CONCLUSIONS AND RECOMMENDATIONS

The revised container label adequately addresses our concerns from a medication error perspective. DMEPA concludes that the proposed container labels are acceptable. However, we recommend the following changes to the insert labeling to minimize the risk of selecting an incorrect Suprax dosage form:

1. Because the 400 mg capsule cannot be divided in half and no data was provided to support an equivalent oral suspension dose to the 200 mg dose (half of the 400 mg tablet), under section 2.3 Renal Impairment, modify the following statement to clearly indicate that the 400 mg tablet is required for the 200 mg dose instead of the capsule or oral suspension dosage forms:

From:

Patients whose clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given [REDACTED] (b) (4)

To:

Patients whose clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given 200 mg daily (i.e. half of the 400 mg tablet).

[REDACTED] (b) (4)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ALEKSANDER P WINIARSKI  
05/10/2012

CHI-MING TU  
05/10/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** April 25, 2012

**To:** Alison Rodgers, Regulatory Project Manager  
Division of Anti-Infective Products (DAIP)

**From:** Christine Corser, Pharm.D., Regulatory Review Officer  
Division of Professional Promotion (DPP)  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA #203195  
Suprax<sup>®</sup> (cefixime) Tablets USP, 400 mg  
Suprax<sup>®</sup> (cefixime) Capsules, 400 mg  
Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 100 mg/5 mL  
Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 200 mg/5 mL

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As requested in your consult dated September 13, 2011, the Division of Professional Promotion (DPP) has reviewed the proposed draft labeling for Suprax<sup>®</sup> (cefixime) tablets, capsules, and oral suspension.

DPP's comments are based on the substantially complete version of the PI titled, "supraxdraftpi-jan-12.doc" which was received via email from Allison Rodgers on April 18, 2012.

DPP's comments are attached in the substantially complete version of the labeling.

If you have any questions about DPP's comments, please contact Christine Corser at 6-2653 or at [christine.corser@fda.hhs.gov](mailto:christine.corser@fda.hhs.gov).

Thank you for the opportunity to provide comments on this proposed PI.

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/s/  
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CHRISTINE G CORSER  
04/25/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 203195	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Suprax Established/Proper Name: cefixime Dosage Form: Capsules Strengths: 400 mg		
Applicant: Lupin Limited		
Date of Receipt: 8-1-11		
PDUFA Goal Date: 6-1-12		Action Goal Date (if different):
Proposed Indication(s): Uncomplicated Urinary Tract Infections; Pharyngitis and Tonsillitis, Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, Uncomplicated Gonorrhea (cervical/urethral)		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 50621	Safety and efficacy of listed drug

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Lupin’s generic Suprax 400 mg tablets were used in a BA/BE study.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
If “NO,” proceed to question #5.  
If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Suprax	50621	Yes

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES X NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Suprax 400 mg Oral Tablet

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO X

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form from tablets to capsule.

This application provides for a change in dosage form from tablets to capsules.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO X

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): No

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES X NO   
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES X NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES X NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):  
generic cefixime oral suspension  
generic cefixime chewable tablets  
generic cefixime tablets

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed    X    *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product? *N/A*

YES     NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

X 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES  NO   
*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES  NO   
*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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ALISON K RODGERS  
04/27/2012

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: April 11, 2012

TO: John Farley, MD, MPH  
Director (Acting)  
Division of Anti-infective Products  
Office of Antimicrobial Products, OND

FROM: Sripal R. Mada, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D., DABT  
Director (Acting)  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 203-195 Suprax (cefixime)  
400 mg capsules from Lupin Limited, India

At the request of the Division of Anti-infective Products (DAIP), the Division of Bioequivalence and GLP Compliance (DBGC) conducted inspections of clinical and analytical portions of the following study:

**LBC-10-044**: "An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three-Sequence, Three-Period Crossover Oral Bioequivalence Study of Reference product (Treatment A) SUPRAX<sup>®</sup> (Cefixime 400 mg) Tablets, manufactured by Lupin Limited Mumbai 400098, India for Lupin Pharmaceuticals, Inc. 111 South Calvert Street Baltimore, Maryland 21202 USA, and Test product (Treatment B) Cefixime Capsules 400 mg manufactured by Lupin Limited, India, under fasting conditions and Food effect study of Test product Cefixime Capsules 400 mg manufactured by Lupin Limited, India administered under fasting (Treatment B) and fed (Treatment C) conditions in Healthy, Adult, Human Male Subjects"

The inspections of clinical and analytical portions were conducted at **Lupin Bioresearch Center, Pune, India** (March 19-23, 2012). Following the inspections, no Form FDA-483 was issued.

**Conclusion:**

The clinical and analytical data are acceptable for your review.

Sripal R. Mada, Ph.D.  
Bioequivalence Branch, DBGC, OSI

**Final Classification:**

**NAI - Lupin Bioresearch Center, Pune, India (Clinical and Analytical)**

FEI: 3008355456

cc:

OSI/Ball/Moreno

OSI/DBGC/Taylor/Dejernett

OSI/DBGC/BB/Haidar/Skelly/Mada

OND/OAMP/DAIP/Farley/Rodgers/Alexander/Blank

OCP/DCP4/Lazor/Chilukuri/Noory

ORA/KAN-DO/Kuchenthal

Draft: SRM 04/09/2012

Edit: MFS 04/09/2012

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SRIPAL R MADA  
04/11/2012

SAM H HAIDAR  
04/13/2012

WILLIAM H TAYLOR  
04/13/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: January 25, 2012

Reviewer(s): Aleksander Winiarski, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name(s): Suprax (Cefixime) Capsules, 400 mg

Application Type/Number: NDA 203195

Applicant/sponsor: Lupin Pharmaceuticals

OSE RCM #: 2011-3363

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed labels and labeling for Suprax (Cefixime) to identify areas of vulnerability that can lead to medication errors. This review is in response to a request from the Division of Anti-Infective Products (DAIP). This new NDA requests approval for a 400 mg capsule that will be added to the existing Suprax product line.

### 1.1 REGULATORY HISTORY

The original approval for Suprax, NDA 050621, was on April 28, 1989, under Lederle Pharmaceuticals. Lederle Pharmaceuticals (b) (4) granted the use of the proprietary name to Lupin Pharmaceuticals, Inc. This is a 505 (b)(2) application, and the reference listed drug (RLD) is Suprax (Cefixime) 400 mg tablets, ANDA 065130, which was approved on February 12, 2004 for Lupin Pharmaceuticals, Inc

In response to an information request sent on October 17, 2011, Lupin Pharmaceuticals provided the following information:

- (b) (4)
- (b) (4)
- Lupin intends to have dedicated insert labeling specific to the 400 mg capsules and separate from other approved dosage forms; however, Lupin acknowledges that the proposed insert labeling references other dosage forms of Suprax.
- The label of the individual blisters (b) (4)

DMEPA previously reviewed the labels and labeling for Suprax chewable tablets 100 mg, 150 mg and 200 mg (ANDA 065380) in OSE Review 2007-2292 dated January 15, 2008. The chewable tablets were approved with a dedicated package insert labeling on October 25, 2010 but are not currently marketed. We also previously reviewed the labels and labeling for (b) (4) in OSE Review (b) (4)

### 1.2 PRODUCT INFORMATION

Table 1 below summarizes the proposed and currently marketed product information for Suprax contained in the insert labeling.

Table 1. Suprax Insert Labeling Product Information

	Proposed Suprax Capsule Insert	Suprax Tablets (RLD) and Suspension Insert
Dosage Forms and Strengths	Capsule 400 mg	Tablet 400 mg (scored) Suspensions: <ul style="list-style-type: none"> <li>• 100 mg/5 mL</li> <li>• 200 mg/5 mL</li> </ul>
Usual Dose	Adults: 400 mg once daily or divided twice daily (using 200 mg tablet*†) Children: 8mg/kg/day (once daily or divided twice daily) †‡	Adults: 400 mg once daily or divided twice daily (using 200 mg tablet*) Children: 8mg/kg/day (once daily or divided twice daily)
Dose Adjustments	Renal Adjustments CrCl 21 to 60 mL/min <ul style="list-style-type: none"> <li>• 300 mg daily‡</li> </ul> CrCl < 20 mL/min <ul style="list-style-type: none"> <li>• 200 mg daily‡</li> </ul>	Renal Adjustment CrCl 21 to 60 mL/min <ul style="list-style-type: none"> <li>• 300 mg daily**</li> </ul> CrCl < 20 mL/min <ul style="list-style-type: none"> <li>• 200 mg daily</li> </ul>
Indications	Uncomplicated UTI Pharyngitis and Tonsillitis Acute bronchitis Acute exacerbations of chronic bronchitis Uncomplicated gonorrhea (cervical/urethral)	Uncomplicated UTI Pharyngitis and Tonsillitis Acute bronchitis Acute exacerbations of chronic bronchitis Uncomplicated gonorrhea (cervical/urethral) Acute otitis media***
References made to other dosage forms <u>not</u> listed in the how supplied sections of the insert labeling	200 mg tablet* Suspension 100 mg/5 mL Suspension 200 mg/5 mL	200 mg tablet*
<p>* Product no longer available  † Unclear why children dosing is included if insert labeling is dedicated to the single strength capsules  ‡ Dose not achievable using products listed in the how supplied section of the insert  ** Dose only achievable using the suspension dosage forms listed in the how supplied section of the insert  *** AOM should only be treated with the suspension (or chewable tables when and if they become available)</p>		

The absorption pharmacokinetics significantly differ between the liquid and solid oral dosage forms of Suprax. Therefore Suprax 400 mg capsules or tablets should not be substituted for the oral suspension in children with otitis media. If approved, the proposed capsules will be available in bottles containing 50 capsules and unit-dose blisters for professional samples.

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup>, the principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container labels submitted on 06/28/2011
- Blister labels submitted on 06/28/2011
- Carton labeling submitted on 06/28/2011
- Insert Labeling submitted on 10/14/2011

We compared the proposed Suprax labels and labeling to the currently marketed Suprax labels and labeling to identify any potential safety concerns. We also reviewed our label and labeling recommendations from OSE review 2007-2292 dated January 15, 2008 and OSE review [REDACTED]<sup>(b) (4)</sup>, to determine whether recommendations from those reviews are applicable to our proposed labels and labeling.

Additionally, since Suprax is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Suprax. The October 13, 2011 AERS search used the following search terms: active ingredient “cefixime and cefixime anhydrous”, trade name “Suprax”, and verbatim terms “Supr%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. The time frame of the search was not limited.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review.

Reports excluded from the case series include cases that did not describe a medication error (i.e., adverse events unrelated to a medication error). Additionally, medication error cases where labels and labeling were not identified as a cause of medication error (i.e., name confusion, improper dose, product quality issue) were also excluded. See appendix F for a summary of exclusions. Following exclusions, one case was determined to be relevant to this review.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### **3 RESULTS AND DISCUSSION**

The following section describes the findings of our AERS search and label and labeling risk assessment.

#### **3.1 AERS SEARCH**

A total of 43 cases were retrieved from AERS using methodology described in section 2. Following exclusions we evaluated one case that was relevant to this review. The case is described below.

##### Label Design and Readability (n=1)

The case (ISR 5714131) involved a reporter who was concerned about the design of the peel-off labels on the Suprax suspension bottles. The reporter stated that the peel-off labels often cause the labels underneath with the reconstitution directions to tear, making them difficult to read. Because the products vary in amount of drug per bottle and concentrations, there are different dilution volumes needed for reconstitution. The reporter was concerned that the label design and the difficulty in reading the directions could cause medication errors. Since the current suspension labels are not designed as peel-off labels and because this case is not related to the solid oral dosage forms of Suprax, we find that this case does not have a significant effect on our label and labeling recommendations.

#### **3.2 CONTAINER LABELS**

The following deficiencies were noted:

- Overly prominent net quantity statement due to color blocking.
- The statement “Each capsule contains 400 mg of cefixime as the trihydrate,” creates clutter and decreases the readability of the principal display panel (PDP).

#### **3.3 BLISTER LABEL**

The following deficiencies were noted:

- Customary placement of the established name is located below the proprietary name, and in this case, the established name is next to proprietary name, which may lead to product name confusion.
- There is no indication where the lot number and expiration will appear.

#### **3.4 CARTON LABELING**

The following deficiencies were noted:

- Customary placement of the established name is located below the proprietary name and in this case the established name is next to proprietary name, which may lead to product name confusion.
- The current net quantity description of [REDACTED] <sup>(b) (4)</sup> is confusing and requires further clarification. The net quantity statement should reflect the total

number of blisters included in one carton as well as the fact that each blister contains one capsule.

- Overly prominent net quantity statement using color blocking, as compared to the statement of strength
- The statement “Each capsule contains 400 mg of cefixime as the trihydrate,” creates clutter and decreases the readability of the principal display panel (PDP).

### 3.5 INSERT LABELING

The sponsor intends to market with a separate, dedicated insert labeling for the capsules only; however, the proposed insert labeling contains references to other dosage forms (tablets and suspension) and dosing regimens, including dosing in children using the suspension and dose adjustments in renal impairment using the oral tablets. Although there are references to other dosage forms, the insert labeling only lists the 400 mg capsules in the *How Supplied* and *Dosage Forms and Strengths* sections of the Full Prescribing Information (FPI). Provision of some, but not all, information regarding other dosage forms may lead to confusion with regards to dosing, dose adjustments, and switching between formulations.

Further consultation with Lillie Golson, Team Leader in the Office of Generic Drugs (OGD), Division of Labeling and Program Support (DLPS), Labeling Review Branch (LRB), revealed that there exists regulatory precedent allowing information from NDAs and ANDAs to be combined into one insert (see Timentin insert which combines information from NDAs 50-658, 50-590, and ANDA 62-691). Based on this information, DMEPA recommends combining the information of all the marketed Suprax products into one insert labeling.

We also identified the following deficiencies in Section 2.2 Children of the FPI:

- There is inadequate prominence of the statement regarding lack of bioequivalence between the tablet/capsule and the suspension.
- The statement regarding children weighing more than 50 kg or who are older than 12 years old should be treated with the recommended adult dose, could be misunderstood as direction to use the capsules; however, there is additional information which states that otitis media should be treated with the suspension. As currently presented, this may cause confusion.
- The dosing chart does not contain weight ranges, only a reference weight without indicating if the appropriate dose is above that weight or up to that weight, which may lead to dosing confusion.
- The dosing chart contains both suspension concentrations side by side and two different methods of dosing using mL and teaspoonfuls in the same table, which decreases the chart’s readability and increases the chance for dosing errors.
- The statement “In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of Cefixime should be administered at least 10 days” is under the children section, which implies that it only applies to children and it is unclear if this information should apply to the adults as well.

Additionally, we identified the use of dangerous or unclear abbreviations and symbols throughout the insert labeling. Our recommendations are listed below in Section 4.

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes that the proposed labeling is vulnerable to confusion which can lead to medication errors. We advise the following recommendations be implemented prior to approval:

##### **A. Container Label**

1. As currently presented, the net quantity statement competes with the statement of strength due to the use of overly prominent color blocking, which may lead to confusion. Remove the color blocking for the net quantity statement and debold the font.
2. The statement “Each capsule contains 400 mg of cefixime as the trihydrate,” creates clutter on the principal display panel (PDP). To decrease clutter and ensure that the proprietary name, established name and strength are the most prominent information on the PDP, relocate this statement to the side panel. In order to accommodate this change, consider condensing the manufacturer and distributor statements per 21 CFR 201.1(h)(5).

##### **B. Blister Label**

1. Customary placement of the established name is located below the proprietary name. In order to improve readability and facilitate the identification of the most important information on the label, move the established name below the proprietary name and the strength below the established name as follows:

Suprax  
Cefixime Capsule  
400 mg

2. There is no indication where the expiration date and lot number will appear. Ensure the lot and expiration numbers are printed on the label.

##### **C. Carton Labeling**

1. See comments A1, A2, and B1 above.
2. The current net quantity description of (b) (4) is confusing and requires further clarification. Per 21 CFR 201.51, the net quantity statement should reflect the total number of blisters included in one carton as well as the fact that each blister contains one capsule.

##### **D. Insert Labeling**

The sponsor intends to market with separate, dedicated insert labeling for the capsules only; however, the proposed insert labeling contains references to other dosage forms (tablets and suspension) and dosing regimens, including dosing in children using the suspension and dose adjustments in renal impairment using the oral tablets. Although there are references to other dosage forms, the insert labeling only lists the 400 mg

capsules in the *How Supplied* and *Dosage Forms and Strengths* sections of the Full Prescribing Information (FPI). Provision of some, but not all, information regarding other dosage forms may lead to confusion with regards to dosing, dose adjustments, and switching between formulations.

In order to minimize confusion on available dosage forms, dosing, dose adjustments, and switching between formulations, DMEPA recommends combining the prescribing information for all of the currently marketed Suprax formulations into one insert labeling. The recommendations below are consistent with such an approach.

Should the Division have concerns with regard to combining the prescribing information of all the marketed Suprax products into one insert, DMEPA would be willing to meet with the Division for further discussion. Additional recommendations will be conveyed during labeling negotiation meetings as required.

We have the following recommendations for the proposed insert:

1. Under section 2.2 of the FPI, Children, there is inadequate prominence of the statement regarding lack of bioequivalence between tablet/capsule and the suspension, which may lead to inappropriate switches between formulations. We recommend increasing the prominence of this statement and to include it in the “*Highlights of Prescribing Information*” of the insert labeling.
2. Under section 2.2 of the FPI, Children, there is a confusing statement regarding dosing children who weigh more than 50 kg or are older than 12 years. It states that they should be treated with the recommended adult dose, which may lead to the use of capsules for otitis media resulting in under dosing. Consider changing the current statement to specify the conditions under which it is appropriate for children older than 12 years or weighing more than 50 kg to use the capsule/tablet formulations and at what dose.
3. Under section 2.2 of the FPI, Children, the pediatric dosing chart provides one reference weight without indication if the corresponding dose is above that weight or up to that weight, which may lead to dosing confusion. Additionally, if the intended dose is based on up to the listed reference weight then there is a missing dose for children weighing between 37.5 kg to 50 kg. In order to prevent dosing confusion, revise the pediatric dosing chart to include patient weight ranges.
4. Under section 2.2 of the FPI, Children, the pediatric dosing chart contains both suspension concentrations (side by side) which decreases the chart’s readability and increases the chance for dosing errors. To improve readability and minimize the chance for dosing errors, delineate the two concentrations in the table by using appropriate methods, such as bolded borders.
5. Under section 2.2 of the FPI, Children, the pediatric dosing chart two different methods of dosing using mL and teaspoonfuls in the same table. This decreases the chart’s readability and increases the chance for dosing errors. To improve readability and minimize the chance for dosing errors, include only mL for dosing the suspension (metric).
6. Under section 2.2 of the FPI, Children, the location of the statement “In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of

Cefixime should be administered at least 10 days” implies that it only applies to children and it is unclear if this information should apply to the adults as well. If this information applies to adults then this information should be clarified and relocated appropriately.

7. In Section 2.3 of the FPI, Renal Impairment, the information is written in paragraph format which decreases readability. To improve readability consider providing this information in a table format. Additionally some of the doses specified are not achievable using the capsule formulation (200 mg or 300 mg) or the current tablet formulation (300 mg). Please indicate how the intended 200mg (e.g. split 400 mg scored tablet) and 300 mg dose will be achieved.
8. The error prone symbol, <, is utilized in Section 2.3, Renal Impairment, of the FPI. Additionally, the abbreviation QD is utilized in Sections 6 and 14 of the FPI. The symbol ‘<’ and the abbreviation ‘QD’ are included in the Institute for Safe Medication Practices’ (ISMP) ‘List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>2</sup>’. The symbol ‘<’ has been misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol, and the abbreviation ‘QD’ has been misinterpreted as QID. As part of a national campaign to decrease the use of dangerous symbols, the FDA agreed not to use such error-prone symbols or abbreviations in the approved labeling of products because they can be carried over to prescribing. Therefore DMEPA recommends that “<” be replaced with “less than” and “QD” be replaced with “daily.”
9. In Sections 6 and 14 of the FPI, Adverse Reactions and Clinical Studies, (b)  
(4) is utilized. To improve clarity of the information, we recommend replacing (b)  
(4)” with twice daily.
10. In sections 12.2, 12.3 and 14 of the FPI, Pharmacodynamics, Pharmacokinetics and Clinical Studies, there are hyphens used between numbers to indicate ranges (3-4 hrs, 21-60 mL/min, 40%-50%, 25-50%, 10%-25%, and 30%-31%). Hyphens between numbers have been shown to cause confusion, especially if they are overlooked. We recommend replacing hyphens with the word “to” when expressing a range between numbers.

If you have further questions or need clarifications, please contact, Brantley Dorch, OSE project manager, at 301-796-0150.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>2</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

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/s/  
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ALEKSANDER P WINIARSKI  
01/25/2012

IRENE Z CHAN  
01/26/2012

CAROL A HOLQUIST  
01/26/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: October 28, 2011

TO: Associate Director  
International Operations Drug Group  
Division of Foreign Field Investigations

From: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority PDUFA NDA Pre-Approval Data  
Validation Inspection**, Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 203195  
DRUG: Suprax (cefixime) 400 mg capsules  
SPONSOR: Lupin Limited  
Maharashtra, India

This memo requests an inspection of the clinical and analytical portions of the following bioequivalence study. **The site should not be informed in advance of the application, drug name(s), the names of the clinical and analytical investigators, the studies to be audited and the focus of the inspection.** This information should be provided to the firm only at the start of the inspection. **Per the request of the Review Division, the inspection should be completed before April 1, 2012.**

**Study Number:** LBC-10-044  
**Study Title:** An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three-Sequence, Three-Period Crossover Oral Bioequivalence Study of Reference product (Treatment A) SUPRAX® (Cefixime 400 mg) Tablets, manufactured by Lupin Limited Mumbai 400098, India for Lupin Pharmaceuticals, Inc. 111 South Calvert Street Baltimore, Maryland 21202 USA, and Test product (Treatment B) Cefixime Capsules 400 mg manufactured by Lupin Limited, India, under fasting conditions and Food effect study of Test product Cefixime Capsules 400 mg

manufactured by Lupin Limited, India administered under fasting (Treatment B) and fed (Treatment C) conditions in Healthy, Adult, Human Male Subjects

**Clinical Site:** Lupin Bioresearch Center, (b) (4)  
Pashan, Pune - 411021, India  
Mr. Manoj Bob (Study Director)  
Ph.: +91-020-66219212  
manojbob@lupinpharma.com  
Dr. Ravisekhar Kasibhatta (Head, Lupin Bioresearch)  
Ph.: +91-020-66219200  
Fax: +91-020-66219270

**Clinical Investigator:** Dr. Shalini B.Khanna, M.B.B.S

Please check the batch numbers of the test and reference formulations used in the studies with the descriptions in documents submitted to the Agency. The sites conducting the above bioequivalence study are responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please confirm whether reserve samples were retained as required by 21 CFR 320.38 and 320.63. Samples of the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening. Please obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample.

Please have the records of all subjects in the study audited. The subject records in the submission should be compared to the original documents at the firm. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were

administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. Also, please determine if the subjects met the protocol inclusion/exclusion criteria.

**Analytical Site:** Lupin Bioresearch Center, (b) (4)  
(b) (4)  
Pashan, Pune - 411021, India  
Ph.: +91-020-66219200  
Fax: +91-020-66219270  
Mr. Manoj Bob (Bioanalytical Research Head)  
manojbob@lupinpharma.com

**Bioanalytical Investigator:** Mr. Sachin Deokar, M.Sc

**Analytical Methods:** LC-MS/MS

All pertinent items related to the analytical method for the measurement of cefixime concentrations should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the firm. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized. In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A scientist from DBGCC, OSI with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise.** Please contact DBGCC upon receipt of this assignment to arrange scheduling of the inspection.

Page 4 - BIMO Assignment, NDA 203195, Suprax (cefixime) 400 mg capsules

Headquarters Contact Person: Arindam Dasgupta, Ph.D.  
(301) 796-3326

Page 5 - BIMO Assignment, NDA 203195, Suprax (cefixime) 400 mg capsules

CC:

CDER DSI PM TRACK

OSI/DBGC/Salewski/Haidar/Skelly/Dasgupta/Cho/Dejernet/CF

HFC-130/ORA HQ DFFI IOB BIMO

OCP/DCP4/John Lazor/Dakshina Chilukura/Assadollah Noory

Draft: SC 10/28/2011

Edit: MFS 10/28/2011

DSI: 6264; O:\BE\assigns\bio203195.doc

FACTS: \_\_1351629\_\_

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/s/  
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SEONGEUN CHO  
11/01/2011

MICHAEL F SKELLY  
11/01/2011

We have only the single e-mail address available.

Skelly signing on behalf of Dr. Haidar

**Division of Anti-Infective Products**  
**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** 203195

**Name of Drug:** Suprax (cefixime capsules), 400 mg

**Applicant:** Lupin Limited

**Labeling Reviewed**

**Submission Date:** 6-28-11

**Receipt Date:** 8-1-11

**Background and Summary Description:** Lupin Limited submitted NDA 203195 as a 505(b)(2) application on June 28, 2011.

**Review**

The following issues/deficiencies have been identified in the proposed labeling and will be forwarded to the sponsor:

- Highlights Limitation Statement – Must be placed at the beginning of HL, bolded, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- Use in Specific Populations – Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

**Recommendations**

Please address the identified deficiencies/issues and re-submit labeling by October 15, 2011. This updated version of labeling will be used for further labeling discussions.

Regulatory Project Manager

Date

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Chief, Project Management Staff

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
09/27/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203195 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Suprax Established/Proper Name: Cefixime Dosage Form: Capsules Strengths: 400 mg		
Applicant: Lupin Limited, India Agent for Applicant (if applicable): Lupin Pharmaceuticals, Inc.		
Date of Application: June 28, 2011 Date of Receipt: August 1, 2011 Date clock started after UN:		
PDUFA Goal Date: June 1, 2012	Action Goal Date (if different):	
Filing Date: September 30, 2011	Date of Filing Meeting: September 12, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Uncomplicated Urinary Tract Infections; Pharyngitis and Tonsillitis, Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, Uncomplicated Gonorrhea (cervical/urethral)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): NA				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b> <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</a></p>		<p>X</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		Sponsor notified of need to submit – 8-30-11
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>		X		
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	Name already approved.
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> <i>If yes, distribute minutes before filing meeting</i>		X		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** September 12, 2011

**BLA/NDA/Supp #:** 203195

**PROPRIETARY NAME:** SUPRAX®

**ESTABLISHED/PROPER NAME:** cefixime

**DOSAGE FORM/STRENGTH:** capsules, 400 mg

**APPLICANT:** Lupin Limited

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Uncomplicated urinary tract infections, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, uncomplicated gonorrhea (cervical/urethral)

**BACKGROUND:** Lupin Limited submitted NDA 203195 as a 505(b)(2) application for Suprax (cefixime capsules), 400 mg on August 1, 2011. Lupin referenced ANDA #065130. However, this is not the correct product to reference. Lupin has been directed to reference the innovator product, NDA 50621, instead. They will submit a new 356H and patent certification.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Alison Rodgers	Yes
	CPMS/TL:	Maureen Dillon-Parker	Yes
Cross-Discipline Team Leader (CDTL)	Dakshina Chilukura		Yes
Clinical	Reviewer:	James Blank	Yes
	TL:	John Alexander	Yes
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial</i> )	Reviewer:	Avery Goodwin	Yes

<i>products)</i>			
	TL:	Fred Marsik	Yes

Clinical Pharmacology	Reviewer:	Assad Noory	Yes
	TL:	Dakshina Chilukuri	Yes
Biostatistics	Reviewer:	Mark Gamalo	Yes
	TL:	Thamban Valappil	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Nostrandt	Yes
	TL:	Wendy Schmidt	Yes
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Maotang Zhou	Yes
	TL:	Dorota Matecka	Yes
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	NA	
	TL:	NA	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	
	TL:	TBD	
OSE/DRISK (REMS)	Reviewer:	NA	
	TL:	NA	
OC/DCRMS (REMS)	Reviewer:	NA	
	TL:	NA	

Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Yes
	TL:	Susan Thompson	No
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers: ONDQA Biopharmaceutics	Tien Mien Chen		Yes
Other attendees	Fuqiang Liu		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b> The sponsor referenced the wrong product, their own ANDA. They need to reference the innovator product, NDA 50621.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Sponsor needs to submit pediatric plan. Sponsor needs to reference correct product.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> No clinical studies were submitted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><b><i>If no, for an original NME or BLA application, include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p>Reason:</p>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<p>X Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p>X Not Applicable  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  X FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  X FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p>X YES  <input type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  X FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p>	<p><input type="checkbox"/> Not Applicable  X FILE  <input type="checkbox"/> REFUSE TO FILE</p>

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
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<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<b><u>CMC Labeling Review</u></b>	
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority: John Farley, MD, MPH</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b> Mid-Cycle Meeting: 1-18-12, Wrap-Up: 4-23-11	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  X No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  X Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ALISON K RODGERS  
09/27/2011

**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** 8-31-11

**TO:** Associate Director for Bioequivalence  
 Division of Scientific Investigations, HFD-48

**THROUGH:** John Farley, MD, MPH  
 Acting Director  
 Division of Anti-Infective Products

John Lazor, Pharm. D.  
 Director, Division of Clinical Pharmacology 4

**FROM:** Alison Rodgers, Regulatory Project Manager, Division of Anti-Infective Products

**SUBJECT: Request for Biopharmaceutical Inspections**  
 NDA 203195  
 Suprax (cefixime capsules), 400 mg

**Study/Site Identification:**

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
LBC-10-044	Lupin Bioresearch Center [REDACTED] (b) (4) Pashan, Pune – 411021 India Phone: +91-020-66219200 Fax: +91-020-66219270	Lupin Bioresearch Center [REDACTED] (b) (4) Pashan, Pune – 411021 India


**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **April 15, 2012**. We intend to issue an action letter on this application by **June 1, 2012**.

Should you require any additional information, please contact Alison Rodgers, Regulatory Project Manager, 301-796-0797.

Concurrence:

John Alexander, MD, Clinical Team Leader

Dakshina Chilukura, PhD, Acting Clinical Pharmacology Team Leader

James Blank, MD, Medical Officer

Assadollah Noory, PhD, Clinical Pharmacology Reviewer

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/s/  
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ALISON K RODGERS  
09/13/2011

JOHN J FARLEY  
09/13/2011

JOHN A LAZOR  
09/16/2011