CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202091Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 202091	NDA Supplement #: N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Suprax Established/Proper Name: Cefixime Dosage Form: Oral Suspension Strengths: 100 mg/mL		
Applicant: Lupin Limited		
Date of Receipt: August 20, 2012 (Class 2 Resubmission)		
PDUFA Goal Date: February 20, 2013	Action Goal Date (if different): N/A	
Proposed Indication(s): Treatment of: Uncomplicated Urinary Tract Infections; Otitis Media; Pharyngitis and Tonsillitis; (b) (4) 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 X

*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)
SUPRAX® [Cefixime 200 mg/5 mL for Oral Suspension USP])	Dosage forms and strengths (3.0); Clinical Pharmacology (12.0); Microbiology (12.1)

*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)

The applicant bridged the proposed product to the reference product via BA/BE Study 312-07/313-07: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover bioequivalence study of two formulations of cefixime oral suspension 200 mg in healthy adult human male subjects under fasted or fed conditions.

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 X

*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 X 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® Cefixime for Oral Suspension USP, 200 mg/5mL	NDA# 50-622	Y

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 X 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 X

*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 X

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

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

c) Described in a monograph?

YES ☐ NO X

*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 (Lederle) NDA 50-621
Suprax (Lederle) NDA 50-622

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 a change in concentration of suspension from 200 mg/5mL to 100 mg/mL.

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):

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 ☐

Suprax (cefixime) Capsules (NDA 203195) – Approved 6/1/12

*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): There are generic oral suspensions, generic tablets, and generic chewable tablets as well as discontinued tablets (NDA 50621) listed in the Orange Book.

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?

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 <u>and</u> 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 ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH C DAVI
02/11/2013

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, Labeling, Packaging and Human Factors Study Results Review

Date:	February 7, 2013
Reviewer:	Aleksander Winiarski, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Associate Director	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Suprax (Cefixime) for Oral Suspension, 500 mg/5 mL
Application Type/Number:	NDA 202091
Applicant:	Lupin Pharmaceuticals
OSE RCM #:	2012-2110

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

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Suprax (Cefixime) for Oral Suspension, 500 mg/5 mL for areas of vulnerability that could lead to medication errors. Additionally, this review evaluates the results of the user testing discrimination study for Suprax labels and labeling.

1.1 REGULATORY HISTORY

Suprax (Cefixime) for Oral Suspension, 100 mg/5 mL and 200 mg/5 mL, were approved in 1989 and 2007 respectively. On October 25, 2010, the Applicant pursued approval (NDA 202091) for an additional strength (500 mg/5 mL) of the suspension (b) (4) (b) (4). The DMEPA review of the proposed product's label, labeling, and (b) (4), dated August 5, 2011, identified several deficiencies that predispose this formulation to errors. Our findings were sent to the Applicant in the Complete Response (CR) letter for the application, dated August 26, 2011. Additionally, the CR letter requested that the Applicant conduct a human factors study that would validate the differentiation of the proposed strength and to validate that the use of the proposed label enhancements is effective. Furthermore, the CR letter requested that the Applicant ensure the Patient Instructions For Use (PIFU) are appropriate and demonstrate that the (b) (4) (b) (4).

The Applicant submitted a user testing study protocol on December 28, 2011. DMEPA provided extensive comments to the Applicant in OSE review #2012-52, dated May 15, 2012. In our comments to the Applicant, DMEPA suggested that the Applicant submit a revised final protocol and submit all of the materials (b) (4), container labels, and carton labeling) prior to initiating the study for comment. The Applicant chose to revise their protocol and execute the study without further evaluation from DMEPA. The Applicant submitted the study results together with the labels, labeling, and proposed (b) (4) in the current submission, dated August 17, 2012.

(b) (4)

1.2 PRODUCT INFORMATION

The following product information is provided in the December 12, 2012 labeling submission.

- Active Ingredient: Cefixime
- Indication of Use: Uncomplicated urinary tract infections, otitis media, acute exacerbations of chronic bronchitis, uncomplicated gonorrhea (cervical/urethral), pharyngitis, and tonsillitis
- Route of Administration: Oral
- Dosage Form: Powder for oral suspension
- Strength: 500 mg/5 mL
- Dose and Frequency: Adults: 400 mg daily, Children 8 mg/kg/day (dose may be divided and administered every 12 hours)
- How Supplied: 10 mL and 20 mL bottles
- Storage: Prior to reconstitution store at room temperature, following reconstitution may be stored at room temperature or under refrigeration for up to 14 days.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Suprax medication error reports. We also reviewed the Suprax user testing study results, labels, and insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1. This search timeframe addressed the gap from the previous Adverse Event Reporting System (AERS) search in OSE review #2012-52, dated May 15, 2012. The previous review did not identity any cases relevant to our review.

Table 1: FAERS Search Strategy

Date	February 22, 2012 to December 26, 2012
Drug Names	Cefixime Cefixime\Water Suprax
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database retrieved zero reports; therefore we had no post-marketing cases relevant to our review.

2.2 USABILITY STUDY, LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 20, 2012 (Appendix A)
- Carton Labeling submitted August 20, 2012 (Appendix B)
- Insert Labeling submitted December 12, 2012
- User testing study results submitted August 20, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the risk assessment of the Suprax 500 mg/5 mL labels and labeling based on the user testing study, as well as the associated label and labeling.

3.1 DMEPA'S ASSESMENT OF THE USER TESTING STUDY DESIGN

A. Study Objective

1. The study objective: "to determine whether pharmacists and pharmacy technicians in two different kinds of setting (retail pharmacies and hospital pharmacies) could choose the correct concentration of the drug (based on a simulated prescription or hospital order) and correctly fill a prescription for Suprax suspension from the three alternative concentrations", addresses our concerns as outlined in the CR letter regarding potential selection errors and need for differentiation between product labels.

B. Methodology

1. The study includes participants (pharmacists and pharmacy technicians) to represent users from the inpatient and outpatient pharmacy settings, which are appropriate to test the study objective. However, the limited geographical area (3 locations including Salt Lake City UT, Louisville KY, and Birmingham AL), and limited number of inpatient sites, may not be fully representative of the varying standards of practice from different areas of the United States. Although a more diverse group of locations would be preferred, the implications on the results of this study may be minimal, because we are only evaluating the ability of the participants to select the correct products from the shelf and understand the preparation procedures as listed on the label.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

C. Criteria for Participation

1. The number of participants (15 for each of the 4 user groups) to represent both pharmacist and pharmacy technician end users in the two pharmacy settings are adequate. However, the experience level of the participants appears to favor more experienced practitioners, (ranges not provided, average experience: 8.5 years Hospital Technicians, 18.4 years Retail Technicians, 16.2 years Hospital Pharmacists, 18.4 years Retail Pharmacists). It would have been preferred that additional criteria were used to ensure equal proportions of newer and experienced practitioners who participated in the study.

D. Study Materials

1. The package sizes used in the study do not match all available packaging configurations for the 100 mg/5 mL and 200 mg/5 mL concentrations. Although DMEPA suggested using all of the proposed packaging configurations in the testing scenarios, the Applicant only used 2 bottle sizes of each concentration. Table 2 below indicates which package configurations were included and excluded in the testing scenarios.

   It is unclear why the Applicant did not include all of the packaging configurations in the test; however they noted that about a third of the participants stated that it is unlikely that their pharmacy would stock all of the different packaging configurations and concentrations, which we acknowledge. However, the Applicant failed to acknowledge that they excluded some of the packaging configurations which overlap in size between the different concentrations. Inclusion of all the package sizes in the testing scenarios would have provided a more complete test for the users, where the amount to be dispensed would overlap (75 mL or 100 mL) or may appear similar on the prescription (100 mL vs. 10 mL or 25 mL vs. 20 mL).

Table 2: Surpax for Oral suspension package sizes

Product Strength	**Included Sizes**	**Excluded Sizes**
100 mg /5 mL	50 mL and 100 mL	75 mL
200 mg /5 mL	50 mL and 75 mL	25 mL, 37.5 mL, and 100 mL
500 mg /5 mL	10 mL and 20 mL	Not Applicable

E. Interview Procedures

1. Participants were interviewed in a private or semi-private area of each pharmacy at the site designated for interviews. The proposed scenarios in both pharmacy settings tested the pharmacist's and pharmacy technician's ability to fill a prescription using a simulated prescription/order for one of the concentrations of the drug. They were asked to select the product they would use from a mock pharmacy shelf and then describe in detail how they would reconstitute the product.

2. After the participant was through with the description of the reconstitution process, the interviewer asked follow-up questions about any step the process requires that the respondent failed to mention.

   Based on the description of the simulated prescriptions, mock pharmacy shelf and settings, all of the interview procedures seem adequate to evaluate the correct selection and preparation of the product by pharmacy staff, although as previously noted the Applicant failed to incorporate all oral suspension package configurations in their testing.

F. Statistics and Criteria for Success

1. The Applicant used an 85% correct performance target as the criterion for any individual part of the use process. This target was chosen based on the assumption that virtually all pharmacies have procedures in place that require triple-checking each prescription. Therefore, an 85% criterion for any individual part of the process would result in an effective error rate for the pharmacy of less than 1% (0.15 x 0.15 x 0.15 = 0.0034).

   However, the Applicant's assumption does not accurately depict current pharmacy practice in terms of the number of checks that occur prior to a medication being dispensed. In many pharmacies there is only a single technician who selects the product and a single pharmacist who performs the final check, and in some pharmacies (especially lower volume retail stores), the pharmacist may be selecting the product and also performing the only check. Therefore, assuming that multiple checks will be preformed prior to dispensing the product and choosing an 85 % rate of correctly preformed tasks as the threshold of risk is not appropriate. The entire process needs to be performed correctly in order to ensure that the product can be dispensed without performing a medication error. Thus each task that failed should be further assessed to determine the likelihood of it resulting in a medication error.

3.2 USER TESTING RESULTS AND ASSESSMENT

A. Product Selection

1. All pharmacists in both practice settings performed the task of selecting the concentration and bottle size correctly.

2. One of 15 hospital technicians selected a correct bottle size but the wrong concentration; further details explaining the root cause were not provided. Additionally, 1 of 15 retail technicians selected the incorrect concentration and bottle size [chose 20 mL of the 500 mg/5 mL concentration vs. the prescribed 50 mL of the 200 mg/5 mL concentration]. She stated that she focused on the quantity (20 mL) rather than the concentration.

   The Applicant concluded that 93% of the technicians (28 of 30 subjects) selected the correct product (concentrating and net quantity). The follow up questions with the two technicians that failed to select the correct product indicate a performance

deficit of focusing on the bottle size and not the concentration. This type of error would be difficult to mitigate, because it would require eliminating all overlapping numbers in the concentrations and the net quantity statements. However, increasing the prominence of the concentration or strength statement may decrease the risk of practitioners focusing their attention on net quantity statement.

B. Product Preparation

1. Seven of 15 hospital pharmacist stated that their internal preparation protocols differ from the labeling instructions to add half the water, shake, then add the remaining half of the water, and require the addition of the entire contents of water at once and to shake adequately to suspend the entire contents of the bottle. The Applicant did not state that deviating from the preparation instructions resulted in an incorrectly prepared product. Thus, it does not appear that this part of the preparation instructions was a critical task. In addition, if practitioners knowing follow institutional protocols and disregard manufacturer's preparation instructions, then it will be difficult to mitigate this type of behavior and error unless there is a documented negative outcome that can be conveyed to the practitioners.

2. Three of 15 hospital technicians stated they would add all of the water to the bottle at once. As stated above their failures do not appear to be a critical task and would still result in an acceptable reconstitution of the product.

3. One of 15 hospital technicians made an error in calculating the correct dose for the child. This failure was a performance deficit that could not be directly attributed to the introduction of the 500 mg/5 mL concentration.

C. Overall Summary of Results

1. All of the pharmacists selected the correct concentration from the mock shelf based on the simulated prescription, and 93% (28 of 30) of the technicians selected the correct concentration. The Applicant concluded that the errors in selecting the correct concentration were not related to the novelty of the higher concentration and that each of the two errors resulted from inattention to the details of the mock prescription. The Applicant's follow up questions with the technicians that failed this task indicate a performance deficit due to the technician focusing on the net quantity to select the product and not on the concentration. This type of performance deficit related error could occur with any of the Suprax oral suspensions. However, increasing the prominence of the concentration or strength statement may decrease the risk of practitioners focusing their attention on the net quantity statement.

2. Additionally, the Applicant noted that the participants didn't find it challenging to select a correct product. They found that the color coding was helpful in identifying the right concentration and bottle size needed to fill a prescription. DMEPA agrees with the Applicant that color coding of the concentration and adequate differentiation of the labels improves the likelihood of correctly selecting the product.

3. Also, the Applicant noted that other factors implemented in pharmacy procedures will likely decrease the potential for an error such as: several checks preformed by humans and utilizing computer systems at different stages in the process of filling the prescription. DMEPA agrees that appropriate pharmacy procedures help to mitigate the potential for a selection error, however the Applicant fails to acknowledge that some pharmacies lack adequate computer systems or multiple checks in the dispensing processes and that dispensing procedures vary widely across pharmacies in the United States.
4. Finally, the Applicant states that an error arising form an addition of a higher concentration of Suprax is extremely small and that there is nothing about the Suprax product line that appears to be problematic. DMEPA agrees that the risk of a selection error is mitigated by label variability between different concentrations; however we conclude that additional improvements to the labels may be warranted to further decrease the potential of a selection error.

3.3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

There were two errors made by pharmacy technicians who selected the incorrect concentrations. One of the technicians reported that she focused on the net quantity (20 mL) rather than the concentration. Both of these errors suggest that the net quantity statement competes for prominence with the product strength. Current review of the container label and carton labeling revealed that the net quantity statement appears to be in the same font size as the strength statement and the quantities are highlighted in a similar manner as the strength statement, which may compete for prominence with the strength. Based on these findings, our recommendations are listed in section 5.1.

Review of the integrated insert labeling (all formulations of Suprax), revealed that under the Dosing and Administration section, reference to the Suprax chewable tablets is confusing. It appears that the Applicant intends to convey that the chewable tablets are bioequivalent to the suspension; however this information needs to be further clarified with the Applicant and revised under this section for clarity.

(b) (4)

Also under section 2.3, Renal Impairment, the information refers to several dosage forms and several doses in one single paragraph, which may be confusing. We suggest that the Division considers replacing this text with a table. Our recommendations are listed in section 5.1.

We also note that the proposed concentration and strength is presented as 500 mg/5 mL. However, after a review of the Dosage and Administration section we realized that 500 mg is not an approved dose. Normally for a liquid product the strength is presented in a usual dosage measurement of 5 mL (teaspoon), 15 mL (tablespoon), or 1 mL. If one of these measurements is not an approved dose, then the concentration is usually

presented as xx mg/mL. In this case, we note that the two currently approved suspension strengths are presented as 100 mg/5 mL and 200 mg/5 mL and that the Applicant studied the 500 mg/5 mL strength presentation. Therefore, we feel it is appropriate to present the concentration and strength as 500 mg/5 mL. However, in order to help further differentiate this higher concentration from the other two concentrations we are recommending to highlight the phrase "each mL contains 100 mg" of cefixime.

4 CONCLUSIONS

DMEPA concludes the Human Factor Study indicates pharmacists and technicians can differentiate and select the correct concentration or strength of oral suspension. However, the proposed container label, carton and insert labeling can still be improved to increase the readability and prominence of important information and to clarify important information to promote the safe use of the product.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of the NDA:

1. Under section 2, Dosage and Administration, in the full prescribing information, the Applicant includes the following statement:

   > "Suprax (cefixime) chewable tablets, 100 mg are appropriate for a 100 mg dose, Suprax (cefixime) chewable tablets, 150 mg are appropriate for a 150 mg dose and Suprax (cefixime) chewable tablets, 200 mg are appropriate for a 200 mg dose."

   DMEPA suggests removing this statement as it may cause confusion.

   If the Division feels the statement is clinically important to include for practitioners to inform that the chewable tables may be used interchangeably with other formulations, then consider revising the statement to provide additional context and clarity. Consider if a statement similar to the following may be helpful: "Suprax (cefixime) chewable tablets may be interchanged with other Suprax formulations with an equivalent dose".

2. Under section 2.2, Pediatric Patients, in the full prescribing information, the Pediatric Dosage Chart provides equivalent doses in mLs for all of the concentrations of Suprax. We propose revising the chart as specified below (new weight ranges and rounded doses were provided by the Division). Additionally, we suggest adding the following statement to the section to refer the healthcare provider to the chart for correct prescribing: "Note: A suggested dose has been determined for each pediatric weight range. Refer to Table 1. Ensure all orders that specify a dose in milliliters include a concentration, because Suprax for oral suspension is available in three different concentrations (100 mg/5 mL, 200 mg/5 mL, and 500 mg/5 mL)."

Table 1. Suggested doses for pediatric patients

PEDIATRIC DOSAGE CHART **Doses are suggested for each weight range and rounded for ease of administration**					
		Suprax (cefixime) for Oral Suspension			**Suprax (cefixime) Chewable Tablet**
		100 mg/5 mL	**200 mg/5 mL**	**500 mg/5 mL**	
Patient Weight (kg)	**Dose/Day (mg)**	**Dose/Day (mL)**	**Dose/Day (mL)**	**Dose/Day (mL)**	**Dose**
5 to 7.5*	50	2.5	1.2	0.5	--
7.6 to 10*	80	4	2	0.8	--
10.1 to 12.5	100	5	2.5	1	1 tablet of 100 mg
12.6 to 20.5	150	7.5	4	1.5	1 tablet of 150 mg
20.6 to 28	200	10	5	2	1 tablet of 200 mg
28.1 to 33	250	12.5	6	2.5	1 tablet of 100 mg and 1 tablet of 150 mg
33.1 to 40	300	15	7.5	3	2 tablet of 150 mg
40.1 to 45	350	17.5	9	3.5	1 tablet of 150 mg and 1 tablet of 200 mg
45.1 or greater	400	20	10	4	2 tablet of 200 mg
*The preferred concentrations of oral suspension to use are 100 mg/5 mL or 200 mg/5 mL for pediatric patients in these weight ranges.					

3. Under section 2.3, Renal Impairment, we propose the Division considers revising the information from the current paragraph format to the following:

   "Refer to Table 2 for dose adjustments for adults with renal impairment."

Table 2. Doses for Adults with Renal Impairment

Renal Dysfunction	**Suprax (cefixime) for Oral Suspension**			**Tablet**	**Chewable Tablet**
Creatnine Clearance (mL/min)	**100 mg/5 mL**	**200 mg/5 mL**	**500 mg/5 mL**	**400 mg**	**200 mg**
	Dose/Day (mL)	Dose/Day (mL)	Dose/Day (mL)	Dose/Day	Dose/Day
60 or greater	Normal dose	Normal dose	Normal dose	Normal dose	Normal dose
21 to 59 * OR renal hemodialysis*	13	6.5	2.6	Not Appropriate	Not Appropriate
20 or less OR continuous peritoneal dialysis	Dose to be determined by DAIP	Dose to be determined by DAIP	Dose to be determined by DAIP	0.5 tablet	1 tablet
* The preferred concentrations of oral suspension to use are 200 mg/5 mL or 500 mg/5 mL for patients with this renal dysfunction Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body					

5.2 COMMENTS TO THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this NDA:

A. All Container Labels and Carton Labeling

1. The net quantity statements compete for prominence with the strength presentation. In order to ensure that the proprietary name, established name and strength are the most prominent information on the principal display panel (PDP), increase the prominence of the strength presentation by significantly increasing its size.

B. Carton Labeling

1. Increase the prominence of the statement "each mL contains 100 mg" by only bolding that portion of the current phrase, to appear as: "When reconstituted **each mL contains 100 mg** of cefixime as the trihydrate".
2. Decrease the prominence of the statement "This package contains 1 g cefixime as the trihydrate" by debolding the sentence.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

(b) (4)

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/s/

ALEKSANDER P WINIARSKI
02/07/2013

JAMIE C WILKINS PARKER
02/07/2013

SCOTT M DALLAS
02/07/2013

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

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

Memorandum

Date: January 24, 2013

To: J. Christopher Davi, MS, Regulatory Project Manager
Division of Anti-Infective Products

John Alexander, MD, MPH, Cross Discipline Team Leader
Division of Anti-Infective Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion

Subject: NDA #202091
Suprax® (cefixime) Tablets USP, 400 mg
Suprax® (cefixime) Capsules, 400 mg
Suprax® (cefixime) Chewable Tablets, 100 mg, 150 mg, and 200 mg
Suprax® (cefixime) for Oral Suspension USP, 100 mg/5 mL
Suprax® (cefixime) for Oral Suspension USP, 200 mg/5 mL
Suprax® (cefixime) for Oral Suspension USP, 500 mg/5 mL

As requested in your consult dated January 17, 2013, OPDP has reviewed the draft labeling for Suprax® (cefixime).

The Division of Professional Drug Promotion (DPDP) has reviewed the proposed PI. Our comments are based on the substantially complete version of the labeling titled, "Lupin18Jan13PLRclean.doc" which was sent via email from Chris Davi on January 18, 2013.

DPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about our comments, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

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

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/s/

CHRISTINE G CORSER
01/24/2013

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:	August 5, 2011
Reviewer(s):	Denise V. Baugh, PharmD, BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Associate Director	Kellie Taylor, PharmD, MPH Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Suprax (Cefixime) Oral Suspension 100 mg/mL
Application Type/Number:	NDA 202091
Applicant:	Lupin Pharmaceuticals, Inc.
OSE RCM #:	2010-2602

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

1 INTRODUCTION

This review evaluates the potential for medication errors with the proposed 505(b)(2) application for Suprax (Cefixime Oral Suspension) which allows for a more concentrated strength of 100 mg per mL. The currently marketed concentrations are 100 mg/5 mL and 200 mg/5 mL. This review also evaluates the proposed [redacted] (b) (4) with this new concentration.

1.1 BACKGROUND

This review responds to a request from the Division of Anti-infective Products (DAIP) for assessment of the container label, carton and insert labeling, and drug delivery device for Suprax (Cefixime Oral Suspension), 100 mg/mL, NDA 202091.

1.2 REGULATORY HISTORY

Suprax (Cefixime) for Oral Suspension 100 mg/5 mL was initially approved April 28, 1989 (NDA 050622, Lederle). Suprax suspension is currently marketed with the concentration of 100 mg/5 mL (Lupin ANDA 065129 approved February 23, 2004) and 200 mg/5 mL (Lupin ANDA 065355 approved April 10, 2007).

The Applicant submitted a NDA for its proposed product, Suprax (Cefixime) Oral Suspension 100 mg/mL utilizing the 505(b)(2) pathway. The Reference Listed Drug (RLD) is ANDA 065355.

1.3 PRODUCT INFORMATION

Suprax (Cefixime) for Oral Suspension is a cephalosporin antibiotic indicated for Uncomplicated Urinary Tract Infections, Otitis Media, Pharyngitis and Tonsilitis, [redacted] (b) (4) Acute Exacerbations of Chronic Bronchitis, and Uncomplicated Gonorrhea. The recommended dose for children is 8 mg/kg/day of the suspension which may be given as a single daily dose or may be divided into two doses (e.g., 4 mg/kg every 12 hours). (See following Table for weight based dosing). Children weighing more than 50 kg or older than 12 years of age should be treated with the recommended adult dose. This strength will be available in a 10 mL and 20 mL bottle size and should be stored at 20°C to 25°C (68°F to 77°F) prior to reconstitution.

2 METHODS AND MATERIALS REVIEWED

2.1 LABEL AND LABELING

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted October 27, 2010
- Carton Labeling submitted October 27, 2010
- Insert Labeling submitted October 27, 2010
- Drug Delivery Device received February 16, 2011

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS) CASES

Since Suprax is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Suprax. The April 24, 2011 search used the following terms: active ingredient "Cefixime", trade name "Suprax", and verbatim terms "cefix%" and "Suprax%". The reaction terms used were the MedDRA High Level Term (HLT) "Maladministrations" and the Preferred Term (PT) "Accidental Overdose". No time limitations were set.

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 this product, the case was considered pertinent to this review.

A total of 40 cases were retrieved in the AERS search and after excluding cases as described above, four of the 40 cases remained. All four cases dealt with improper dilution of the product. They are described as follows:

- In three of the four cases the pharmacist neglected to add diluent to the product (ISR 4198134-2, ISR 4209896-X, and ISR 4097961-X). One patient received

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

two doses of dry powder, the second patient noticed the error prior to using the product, and no details were given in the third case. No adverse outcomes were reported with these cases. Our review of the labels and labeling identified the directions for reconstitution of this product are clearly stated and are prominent on the labels and labeling.

- The fourth case (ISR 4534142-7) was a complaint concerning the inability to read the volume of water to be added to the powder on the label. Specifically, the reporter stated that "the peel-off top label often causes the direction label underneath to tear which makes the dilution quantity impossible to read". The reporter suggests that the dilution quantity needs to be in very bold print for easy legibility and improved accuracy. This case cited the labeling of a different Applicant (i.e., Lederle) that has since been discontinued in the marketplace. Our evaluation of the label for this Applicant, Luprin, found this information to be clear and prominent.

3 DEFICIENCIES IDENTIFIED

The following sections summarize our evaluation of the introduction of the 100 mg/mL concentration into the marketplace and the proposed dosing delivery device.

3.1 INTRODUCTION OF THE 100 MG/ML STRENGTH

The proposed Suprax Oral Suspension 100 mg/mL introduces a third concentration into the marketplace (i.e., 100 mg/mL, 100 mg/5 mL, and 200 mg/5 mL). This new concentration has a numeric overlap with and is 5 times more concentrated than the currently marketed 100 mg/5 mL. Drug usage data demonstrates that Suprax is currently prescribed by concentration and a corresponding teaspoon or mL dose. However, despite the inclusion of a concentration on the prescription, errors within the Suprax product line may occur during the prescribing and dispensing of Suprax.

We have determined that the introduction of this new overlapping numeric strength increases the potential for dosing errors with Suprax, and increases the potential for under dosing or over dosing if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product. Currently there is a similar risk of over and under dosing with the available product concentrations. However, the clinical team is concerned with the potential of a five fold overdose and characterizes this risk as nausea and vomiting causing dehydration and the increased potential for seizures. The introduction of this new strength increases the potential for under dosing or over dosing due to the numeric overlap with the currently marketed strength, 100 mg/5 mL.

The following paragraphs describe how some of the prescribing and dispensing errors within the Suprax product line may occur.

- The wrong concentration may be selected during prescribing in an electronic Computerized Prescriber Order Entry (CPOE) System and at the point of data entry into the pharmacy computer (100 mg/mL chosen instead of 100 mg/5 mL). This risk is also present with the 100 mg/5 mL and 200 mg/5 mL concentrations to a lesser extent. Based on our post-marketing experience with other drug products having similar expressions of concentration, we have determined that there is a heightened risk of confusion between the 100 mg/mL and 100 mg/5 mL products since healthcare providers may misinterpret 100 mg/5mL as 100 mg/mL (or vice versa) due to the numeric overlap in the expression of concentration. Because the dose of Suprax is most commonly expressed in volume

(i.e. teaspoonfuls or X mL), these errors would go undetected and could result in an over or underdose depending on the strength selected as compared to the strength prescribed.

- Prescribers may order the "100 mg/mL" concentration but the pharmacist/pharmacy technician erroneously misinterprets the prescription as "100 mg/5 mL" to dispense to the patient because they misread the prescription or selected the wrong concentration (on a computer screen or from the shelf) because they are not aware of the availability of the new concentration. If the directions were expressed in volume (i.e., teaspoonfuls or X mL) the patient would receive a five-fold underdose.
- Prescribers may order the "100 mg/5 mL" concentration but the pharmacist/pharmacy technician erroneously misinterprets the prescription as "100 mg/mL" because they misread the prescription or selected the wrong concentration (on a computer screen or from the shelf) because they are not aware of the availability of the new concentration. If the directions were expressed in volume (i.e., teaspoonfuls or X mL) the patient would receive a five-fold overdose.
- During prescribing, healthcare providers may confuse the 100 mg/mL and 100 mg/5 mL concentrations when calculating the doses. Prescribers may be confused over the two 100 mg concentrations and while converting the dose in mg to the corresponding volume, they may calculate the corresponding volume teaspoon or mL dose incorrectly thereby misdosing the patient.

We acknowledge that some of these errors may also occur due to confusion between the 100 mg/5 mL and 200 mg/5 mL concentrations. However, to date, we have not identified any such confusion between these two concentrations. Additionally, as previously mentioned, we have determined that there is a greater risk of confusion between the 100 mg/mL and 100 mg/5 mL concentrations than with the other Suprax concentrations due to the numeric overlap in the expression of concentration. This determination is supported by post-marketing evaluation of errors with other drug products bearing similar expressions of strengths. A similar overlap in strength was experienced with morphine oral solution 20 mg/mL and 20 mg/5 mL. FDA has received post-marketing reports of errors between these concentrations, some of which resulted in death (OSE review 2007-1786/2007-1808, dated February 6, 2008).

Of greatest concern are the errors related to confusion between the Suprax 100 mg/mL and 100 mg/5 mL concentrations which could result in 5 fold overdoses of Suprax. Such overdoses represent a significant safety concern because it is our understanding from the clinical team patients who receive this magnitude of overdose with Suprax are at risk for adverse events including nausea and vomiting causing dehydration, as well as increased potential for seizures.

Since preliminary drug usage information indicates that most directions for the currently marketed Suprax products are written in a teaspoonful unit of measurement and Suprax 100 mg/5 mL is the concentration with which the medical community is most familiar, it is plausible that the five-fold overdose would occur if the 100 mg/mL concentration is allowed into the marketplace.

There are some options available that could lessen the risk of confusion between Suprax 100 mg/mL and 100 mg/5 mL. The Applicant could alternatively label the concentration in a similar manner to the currently marketed Suprax formulations, 500 mg/5 mL, 200 mg/5 mL, and 100 mg/5 mL, which would help to highlight the fact that the 100 mg/mL concentration is more concentrated than the 100 mg/5 mL or 200 mg/5mL concentration. This would help lessen the risk of confusion in prescribing, ordering, and dispensing. However, some electronic databases

and texts in used in the healthcare setting may still display the concentration as 100 mg/mL, and therefore even the alternate expression of strength as 500 mg/5 mL may not fully eliminate the risk of error. Another option to lessen the risk of errors with the introduction of Suprax 100 mg/mL is to revise the container labels and carton labeling to enhance the visual differentiation between the Suprax products. This would only address the potential for shelf selection errors, which is only one area of risk for this product.

Although these options should be considered and implemented to reduce the risk of errors with Suprax 100mg/mL, we believe that there is still risk of medication errors within the Suprax product line if the 100 mg/mL concentration is approved. Because these errors represent a safety concern and we believe it is unlikely that the potential for such errors can be fully mitigated through labeling efforts, DAIP should consider requiring Human Factors testing to validate that differentiating the strength with different colors or other label enhancements is effective.

(b) (4)

4 CONCLUSIONS

We have determined that the introduction of this new overlapping numeric strength increases the potential for dosing errors with Suprax and increases the potential for under dosing or over dosing if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product. (b) (4) We provide recommendations to address the medication error concerns in section 5 below.

5 RECOMMENDATIONS

Our greatest concern is the errors related to confusion between the Suprax 100 mg/mL and 100 mg/5 mL concentrations which could result in 5 fold overdoses of Suprax and the introduction of the proposed (b) (4). It is our understanding from the clinical team that a 5 fold overdose represents significant safety concerns for patients who receive this magnitude of overdose of Suprax. Adverse events include: nausea and vomiting causing dehydration, as well as increased potential for seizures. Additionally, the proposed (b) (4) introduces vulnerabilities that can lead to wrong drug errors. As such measures should be taken to minimize these potential risks prior to approval. If the applicant wishes to pursue this concentration despite our safety concerns, we recommend the following:

A. Product Concentration

- Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.

- Some electronic databases and texts used in the healthcare setting may still display the concentration as 100 mg/mL despite displaying the concentration on the immediate container and carton labeling as 500 mg/5 mL. Therefore, we recommend the container labels and carton labeling be revised so that the labels, labeling, and packaging of this new strength be visually different than the currently marketed concentrations.

- Conduct Human Factors testing to validate that differentiating the strength and the use of other label enhancements is effective in minimizing the risk of confusion between the Suprax 100 mg/mL concentration and the currently marketed Suprax 100 mg/5 mL and 200 mg/5 mL concentrations.

B. (b) (4)

(b) (4)

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(b) (4)

Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the Applicant pertaining to this issue. If the Division has further questions or need clarifications, please contact Brantley Dorch, OSE Safety Regulatory Project Manager, at 301-796-0150.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

TODD D BRIDGES
08/05/2011
Also signing for Denise Baugh

CAROL A HOLQUIST on behalf of KELLIE A TAYLOR
08/05/2011
for Kellie Taylor

CAROL A HOLQUIST
08/05/2011

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 # 202091 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Suprax Established/Proper Name: cefixime for oral suspension, (b) (4) Dosage Form: oral suspension Strengths: (b) (4)		
Applicant: Lupin Limited Agent for Applicant (if applicable): N/A		
Date of Application: October 25, 2010 Date of Receipt: October 27, 2010 Date clock started after UN:		
PDUFA Goal Date: August 27, 2011	Action Goal Date (if different):	
Filing Date: December 26, 2010	Date of Filing Meeting: December 7, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indication(s)/ Treatment of: Uncomplicated Urinary Tract Infections; Otitis Media; Pharyngitis and Tonsillitis; (b) (4) Acute Exacerbations of Chronic Bronchitis; Uncomplicated gonorrhea (cervical/urethral)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) X 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	X Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)	

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	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)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X (S)			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***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.***	Payment for this application: x Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: X Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
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)].**		X		
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)]?** ***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***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**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) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

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

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

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

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				Submitted in PLR format
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			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			X	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 7, 2010

BLA/NDA/Supp #: NDA 202091

PROPRIETARY NAME: Suprax

ESTABLISHED/PROPER NAME: cefixime for oral suspension

DOSAGE FORM/STRENGTH: 100 mg/mL

APPLICANT: Lupin Limited

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of: Uncomplicated Urinary Tract Infections; Otitis Media; Pharyngitis and Tonsillitis; (b) (4) Acute Exacerbations of Chronic Bronchitis; Uncomplicated gonorrhea (cervical/urethral)

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kyong Hyon	Y
	CPMS/TL:	Janice Pohlman	Y
Cross-Discipline Team Leader (CDTL)	Kimberly Bergman		Y
Clinical	Reviewer:	James Blank	N
	TL:	Janice Pohlman	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerry Snow	Y
	TL:	Frederic Marsik	Y

Clinical Pharmacology	Reviewer:	Yongheng Zhang	Y
	TL:	Kimberly Bergman	Y
Biostatistics	Reviewer:	Daniel Rubin	Y
	TL:	Thamban Valappil	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Nostrandt	N
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Andrew Yu	Y
	TL:	Rapti Madurawe	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Kassa Ayalew	Y
	TL:	Jean Mulinde	N
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:	Brantley Dorch	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Mar Seggel: Biopharmaceutics reviewer		Y
Other attendees	Althea Cuff: ONDQA PM Wiley Chamber:Acting Division Director Katherine Laessig:Deputy Director Kassa Ayalew:DSi reviewer Sumathi Nambiar:Deputy Director for Safety		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues: 1. DMF (b) (4) titled, (b) (4) " is listed in Form 356h-Annexture 3, but a letter of authorization (LOA) to the DMF is not included in Module 1-section 1.4. Provide an LOA to DMF (b) (4).	☐ Not Applicable X YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**: Acceptable	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: No clinical study conducted	☐ YES X NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: X NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**: Information Request send in 74d letter dated 11/18/2010	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: One review issue identified and communicated in 74D letter.	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	X Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	X Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Katherine Laessig

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): 1. DMF (b) (4) titled, "(b) (4) IH" is listed in Form 356h-Annexture 3, but a letter of authorization (LOA) to the DMF is not included in Module 1-section 1.4. Provide an LOA to DMF (b) (4). Review Classification:

	X Standard Review ☐ Priority Review
	ACTIONS ITEMS
☐	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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) • notify DMPQ (so facility inspections can be scheduled earlier)
X	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
☐	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: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
X	Other; Send Advice and Information request letter for the followings: **CHEMISTRY:** (b) (4) [redacted] **CLINICAL MICROBIOLOGY:** • Submit to the NDA data describing the in vitro antibacterial activity of cefixime against recently collected isolates of pathogens sought in the indications for the drug (including *Escherichia coli*, *Proteus mirabilis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Neisseria gonorrhoeae*). This information

may come from studies conducted by your company or from the recent literature. At least 500 clinical isolates should be listed for each bacterial species, and should include drug resistant phenotypes. Submitted data should include pertinent information for each isolate, including susceptibility test results to cefixime and appropriate comparators, geographic source of the tested isolate, clinical specimen source for each isolate, date of specimen collection, geographic origin, and date of susceptibility test. Tabular data summaries should include MIC_{90}, MIC_{50}, and MIC_{range} values for each species and resistance phenotype.

BIOPHARMACEUTICS:

- The approved Suprax suspension products provide 200 mg/5 mL and 100 mg/5 mL. The approved dissolution requirement for both is NLT (b) (4) (Q) dissolved after 30 minutes. For the new product, you are proposing NLT (b) (4) (Q) after 30 minutes (in one place you also mention NLT (b) (4) Q after (b) (4) minutes). Please provide your justification for Q of (b) (4) (include the dissolution data supporting the proposed specification-time point and specification value).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KYONG M HYON
04/25/2011

FRANCES V LESANE
04/27/2011