

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
50-821

OTHER REVIEW(S)

MEMORANDUM

To: J. Christopher David, MS
Division of Anti-Infective and Ophthalmology Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: April 16, 2010

Re: Comments on draft labeling for cefepime for injection and dextrose injection
NDA 50-821

We have reviewed the proposed label for cefepime for injection and dextrose injection (FDA version dated 4/6/10 and received by SEALD on 4/8/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

17 pages have been withheld in full immediately following this page as B4 (Draft Labeling)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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/s/

IRIS P MASUCCI
04/20/2010

LAURIE B BURKE
04/20/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: March 16, 2010

To: Wiley A Chambers, MD, Acting Director
Division of Anti-Infective and Ophthalmology Products

Through: Kellie Taylor, PharmD, MPA, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Chi-Ming Tu, PharmD, Safe Medication Management Fellow
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Container and Carton Labeling Review

Drug Name(s): Cefepime for Injection and Dextrose Injection in the Duplex
Container

Application Type/Number: NDA 050821

Applicant: B Braun Medical Inc.

OSE RCM #: 2010-444

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EXECUTIVE SUMMARY

This review describes the Division of Medication Error Prevention and Analysis (DMEPA)'s evaluation of the container labels and carton labeling for Cefepime for Injection and Dextrose Injection in the Duplex Container (NDA 050821). According to the Applicant, the advantages of the Duplex system include decreased potential for admixture errors or contamination of the drug product and decreased risk of needle stick injuries with the needle-free system.

Before approval of this New Drug Application, DMEPA recommends the Applicant make the recommended changes to the container labels to reduce unnecessary information and provide more space for strength differentiation on the container label, and improve the carton's readability.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a February 24, 2010 request from the Division of Anti-Infective and Ophthalmology Products (DAIOP) for review of the container labels and carton labeling for Cefepime for Injection and Dextrose Injection in the Duplex Container (NDA 050821). Six other Duplex products by B. Braun have been approved by the Agency for other antimicrobial products.

1.2 REGULATORY HISTORY

B. Braun Medical, Inc. submitted NDA 050821, Cefepime for Injection and Dextrose for Injection in the Duplex Container on September 25, 2008. The application was submitted in accordance with the 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The reference listed drug (RLD) (NDA 050679, Maxipime) is approved for the following indications: pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections, empiric therapy for febrile neutropenic patients, and complicated intraabdominal infections.

1.3 PRODUCT INFORMATION

1.3.1 *Cefepime for Injection and Dextrose Injection in the Duplex Container*

Cefepime is a fourth generation cephalosporin antibacterial agent with broad spectrum activity against Gram positive and Gram negative aerobic bacteria. Cefepime was initially approved in 1996 for the treatment of pneumonia (moderate to severe), uncomplicated and complicated urinary tract infections (including pyelonephritis), and uncomplicated skin and skin structure infections.

A meta-analysis by Yahav, et al. in *Lancet Infectious Diseases*, May 2007, described a higher rate of all-cause mortality in patients treated with cefepime compared to other β -lactam antibacterial agents, particularly in the subgroup of patients with fever and neutropenia. Cefepime is the only drug approved by the FDA for empiric treatment of patients with fever and neutropenia. FDA issued an Early Communication on November

14, 2007, and an update on May 14, 2008, indicating that it was working with the Bristol-Myers Squibb, the manufacturer of Maxipime, to further evaluate the risk of death in patients treated with cefepime.

B. Braun Medical Inc. received initial approval for the use of the Duplex Container system with Cefazolin for Injection USP and Dextrose Injection USP in the Duplex Container in July 2000. The Duplex Container system is a dual chamber bag filled with powder (drug substance) and diluent (dextrose) in separate chambers (Appendix A). Pressure is applied to the diluent chamber which breaks the seal between chambers, allowing the powder to be reconstituted with the diluent. The system is designed for single use administration. According to the Applicant, the advantages of this system include decreased potential for admixture errors or contamination of the drug product and decreased risk of needle stick injuries with the needle-free system. The Cefepime for Injection and Dextrose for Injection in the Duplex Container application is the seventh cephalosporin duplex container application submitted to the FDA.

2 MATERIALS REVIEWED

2.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) SEARCHES

Since Cefepime Hydrochloride is currently marketed, the Division of Medication Error Prevention and Analysis searched the Adverse Event Reporting System (AERS) database to identify medication error reports related to the use of this product and thus relevant to this review. We searched the AERS database using the trade name term “Maxipime,” the active ingredient term “Cefepime,” “Cefepime hydrochloride,” and “cefepime hydrochloride (arginine formulation)” on March 3, 2010 and the verbatim term “Cefep%” on March 17, 2010 with the MedDRA high level group term “Medication Errors” and “Product Quality Issues.”

The reports were manually reviewed to determine if a medication error occurred. Those reports that did not describe a medication error were excluded from further analysis. If an error occurred, the staff reviewed the reports to determine if the root cause could be associated with the carton and container labels of the product, and thus pertinent to this review.

3 RESULTS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) SEARCHES

The AERS searches identified a total of 50 cases (n=50). Duplicate cases were identified and placed together as one case, resulting in 48 unique cases. Of these cases, 39 were excluded from further evaluation for one of the following reasons: no medication error was identified, Cefepime was a concurrent medication not involved in the medication error described in the case, product compliant describing lack of consistency in color after reconstitution, name confusion with the trade name Maxipime, and/or the reported error occurred with a Cefepime product marketed in a foreign country.

The remaining 9 cases (n=9) involved a medication error and thus are relevant to this review.

3.1.1 Overdose (n=3)

Three cases (n=3) involved the overdose of cefepime injection. Two of these cases reported a failure to adjust dosage to creatinine clearance and one reported failure to adjust dosage to body weight. In one case (n=1), a consumer reported a patient previously diagnosed with chronic renal failure (creatinine clearance 20 – 30 mL/min) received Cefepime 2 grams every 12 hours. One day after the drug was started, the patient became comatose. Cefepime was discontinued, and two days later the patient was awake and recovering. The patient passed away thirteen days later but assessment for cause of death was not reported. The other medication error involving failure to adjust dosage to creatinine clearance resulted in temporary confusion and mental impairment, and the patient recovered after Cefepime was discontinued. Another case reported a 28 year old patient who weighed 33 kg received Cefepime 1 gram twice daily. The 2 grams per day dose exceeded the maximum 1.65 gram daily dose for her body weight. The patient suffered temporary confusion and mental impairment, but returned to baseline health after discontinuation of Cefepime.

3.1.2 Wrong Drug (n=2)

Two cases (n=2) involved wrong drug medication error that did not reach the patient. One case involved the trade name product Maxipime being used to reconstitute Fungizone orders. The second case involved dispensing Aztreonam with a Cefepime label to the floor. Details of these incidents were not reported in both cases.

3.1.3 Label confusion (n=1)

A reporter stated “I called [manufacturer]. They admitted (Pharm D). That columns at top say incorrect information of omission. All generics are same for impaired renal function. Doses vary 400% what does each of 4 columns vertical say – nothing.” No details describing the specific part of the label were reported.

3.1.4 Wrong Route (n=1)

One case (n=1) involved Cefepime being administered to a patient in a wrong route but details of the incident were not provided in the report.

3.1.5 Monitoring Error (n=2)

Two cases (n=2) involved patients who received Cefepime with documented allergy to penicillin or ceftin. Both cases required additional monitoring and intervention.

4 DISCUSSION

The Applicant states the Duplex system is designed for single use administration. According to the Applicant, the advantages of this system include decreased potential for admixture errors or contamination of the drug product and decreased risk of needle stick injuries with the needle-free system. The Cefepime for Injection and Dextrose for Injection in the Duplex Container application is the seventh cephalosporin duplex container application submitted to the FDA.

The Duplex Container packages Cefepime powder and Dextrose solution in separate chambers together in one dual chamber bag. To reconstitute the Cefepime powder and Dextrose diluent, the seal between the two separated chambers are broken by applying pressure to the container. The Duplex system simplifies the steps needed to reconstitute the admixture and does not require syringe or needles in reconstituting the product. We agree that the Cefepime for Injection and Dextrose Injection in the Duplex Container reduces potential for admixture errors or contamination of the drug product and decreases the risk of needle stick injuries with the needle-free system.

However, we note that the proposed Cefepime for Injection and Dextrose Injection in the Duplex Container cannot provide for all dosages and thus the risk of infusing the wrong amount of drug is still present. For patients with decreased renal function and their weight falls outside the reference range, healthcare practitioners will need to infuse partial volume contained in the Duplex Container.

In our search of AERS, we identified three cases of overdose due to failure to adjust to creatinine clearance or failure to calculate dose by body weight; and one report of label confusion. Renal dosing information is provided in SECTION 2.4 DOSAGE AND ADMINISTRATION of the label, but the currently proposed Table 2 (Appendix B) does not present information on indication and duration, thus presents a potential risk in the wrong dose being prescribed, dispensed, and administered to the patient. DMEPA notes that a similar table appears in the Maxipime labeling and that any updates relating to cefepime safety should also be considered to Cefepime for Injection and Dextrose Injection in the Duplex Container.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO DIVISION

As it relates to this pending supplement, we recommend changes to the container labels and carton labeling be implemented prior to approval (see Section 5.2) to improve the carton's readability and reduce unnecessary information on the container label and provide more space for strength differentiation.

We also identified medication error cases in the search of the Adverse Events Reporting System (AERS) database related to Cefepime overdose due to failure to adjust to creatinine clearance or failure to calculate dose by body weight. Review of the Cefepime prescribing information identified potential confusion related to the presentation of information in Table 2 (Appendix B) in Section 2.4 Patients with Renal Impairment of the label. These findings are also applicable to the Maxipime label (NDA 050679) which uses a similar table for renal dosing. If the division feels these cases are significant enough to warrant changes to the information in these tables, DMEPA is willing to provide further recommendations as to how this table can be improved. The improvements to the prescribing information do not require implementation prior to marketing of the Duplex Container packages.

5.2 COMMENTS TO THE APPLICANT

- A. Cefepime/Dextrose Duplex Carton (all strengths) (Appendix C)

1. Present the strength “Equivalent to 1 g Cefepime (5% w/v Dextrose)” and “Equivalent to 2 g Cefepime (5% w/v Dextrose)” in the same font size as or greater than the company logo “B|BRAUN”
- B. Cefepime/Dextrose Duplex Container Label (all strengths) (Appendix D)
1. Delete the statement “U.S. Patent Nos D388.168... and 6,996.951” and include this information in the insert labeling.
 2. Delete the statement “Duplex® Drug Delivery System” and “Duplex is a registered trademark of B. Braun Medical Inc.” and include this information in the insert labeling.
 3. Delete B. Braun Medical Inc.’s address as this information is included in the insert labeling.
- C. Cefepime/Dextrose Duplex Container Label - Drug Chamber Label (all strengths) (Appendix E)
1. Revise the statement [REDACTED] (b) (4) with “Peel foil strip only when ready for use to visually inspect drug prior to reconstitution”
 2. Delete the statement [REDACTED] (b) (4) as this information is included in the Container Label.

6 REFERENCES

DATABASES

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 manufactures 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.

5 pages have been withheld in full immediately following this page as B4 (draft labeling).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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/s/

CHI-MING TU
05/05/2010

KELLIE A TAYLOR
05/05/2010

CAROL A HOLQUIST
05/05/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 50-821	NDA Supplement #: N/A	Efficacy Supplement: N/A
Proprietary Name: N/A Established/Proper Name: Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container Dosage Form: Solution for Injection Strengths: 1g and 2g		
Applicant: B. Braun Medical, Inc.		
Date of Receipt: September 25, 2008		
PDUFA Goal Date: July 25, 2009		Action Goal Date (if different): July 25, 2009
Proposed Indication(s): Indicated for the treatment of the following infections caused by susceptible strains of the following microorganisms: pneumonia, empiric therapy for febrile neutropenic patients, uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated skin and skin structure infections and complicated intra-abdominal infections.		

GENERAL INFORMATION

1. Is this application for a drug that is an “old” antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

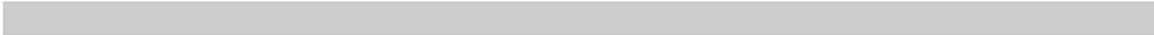
YES X NO

If “YES,” proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide 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)**

3. 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)
Refers to approved drug Maxipime® in the Add-Vantage Vials as RLD (NDA 50-679)	Safety and efficacy

4. 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).

Applicant only proposes to package cefepime in the Duplex® container. No bridging studies are necessary from a bioequivalence standpoint.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

NO

If “NO,” proceed to question #6.

- (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 #6

If “YES,” list the listed drug(s) identified by name and answer question #5(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 #6-10 accordingly.

6. 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

If “NO,” proceed to question #11.

7. 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)
Maxipime® in the Add-Vantage Vials as RLD	NDA 50-679	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.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A

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

9. Were any of the listed drug(s) relied upon for this application:

a. Approved in a 505(b)(2) application? NO

b. Approved by the DESI process? NO

c. Described in a monograph? NO

Name of drug(s) described in a monograph: Maxipime®

d. Discontinued from marketing? NO

Name of drug(s) discontinued from marketing: N/A

1. Were the products discontinued for reasons related to safety or effectiveness?

(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.)

10. 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 approval to market Cefepime for Injection USP and Dextrose Injection, USP in the Duplex®, which is bioequivalent to the RLD, Maxipime®, in the 1g and 2g strengths.

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.

11. (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.

No

If “NO,” to (a) proceed to question #12.

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

If **“YES”** and there are no additional pharmaceutical equivalents listed, proceed to question #13.

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 that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): NDA 50-817
ANANDA 65-441
ANANDA 65-369

12. (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

If **“NO”**, proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES

NDA 50-817
ANANDA 65-441
ANANDA 65-369

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #13.

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 that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all 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): There are no unexpired patents for Maxipime in the Orange Book Database (no patent numbers are provided).

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES

The RLD, Maxipime® is subject to the exemption provisions of Section 125 of Title I of the FDA Modernization Act of 1997. Patent certification is not required.

15. 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 solely based on published literature that does not cite a specific innovator product or for an “old antibiotic” (see question 1.))
- 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):
- 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)
- Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

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

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

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

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 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):

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/s/

Christopher Davi
6/5/2009 03:23:18 PM
CSO

ACTION PACKAGE CHECKLIST

Application Information		
BLA # N/A NDA # 50-821	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: N/A Established Name: Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container Dosage Form: Injection/Intravenous Infusion		Applicant: B. Braun Medical, Inc.
RPM: J. Christopher Davi, MS, Division of Anti-Infective and Ophthalmology Products		Division: DAIOP Phone: (301) 796-0702
NDA Application Type: 505(b)(2) Efficacy Supplement: N/A	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Maxipime® (Bristol Myers Squibb)	
❖ User Fee Goal Date ❖ Action Goal Date (if different)		July 24, 2009
❖ Actions		
• Proposed action		CR: July 24, 2009
• Previous actions (<i>specify type and date for each action taken</i>)		None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		Requested in AP letter <input type="checkbox"/> Received and reviewed N/A
Application Characteristics		
Review priority: Standard Chemical classification (new NDAs only): New Molecular Entity (NME) 4010900 NDAs, BLAs and Supplements: Fast Track		
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies		
NDAs and NDA Supplements		
Other comments: None		
Application Integrity Policy (AIP)		
• Applicant is on the AIP		No
• This application is on the AIP		No

<ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	N/A
<ul style="list-style-type: none"> OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	N/A
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	No
<ul style="list-style-type: none"> Press Office notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	Included
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> NDA: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> NDA: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> NDA: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	No No No No
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	Verified <input checked="" type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) 21 CFR 314.50(i)(1) Verified
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire

- [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).*
- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

N/A
 Verified

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other

paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

Summary Reviews

Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Deputy Division Director
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A

• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Included
✓ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	N/A
❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input checked="" type="checkbox"/> Memos of Mtgs

Administrative Documents

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	Included
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	X Included
Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	X None
• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)	N/A
• Incoming submission documenting commitment	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	N/A
• Pre-NDA/BLA meeting (<i>indicate date</i>)	X No mtg
• EOP2 meeting (<i>indicate date</i>)	X No mtg
• Other (e.g., EOP2a, CMC pilot programs)	None
❖ Advisory Committee Meeting	X No AC meeting
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

CMC/Product Quality Information

CMC/Product review(s) (<i>indicate date for each review</i>)	Pending
Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	Pending
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

❖ Environmental Assessment (check one) (original and supplemental applications)	
• <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	N/A
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input type="checkbox"/> Pending
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: <input type="checkbox"/> Acceptable <input checked="" type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	
• Facility review (<i>indicate date(s)</i>)	N/A
• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	May 14, 2009
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

Clinical Information

❖ Clinical review(s) (<i>indicate date for each review</i>)	June 5, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	N/A
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	Completed as part of clinical review
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
• Clinical Studies	N/A
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
Statistical Review(s) (<i>indicate date for each review</i>)	May 26, 2009
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	May 22, 2009

Appendix A to Action Package Checklist

.1 NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's Office of Regulatory Policy representative.