

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 50-792

Administrative/Correspondence

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA: 50-792

Supplement Type (e.g. SE5):N/A

Stamp Date: September 30, 2003

Action Date: July 29, 2004

HFD-520

Trade and generic names/dosage form: NDA 50-792 Cefotaxime for Injection USP
and Dextrose Injection in DUPLEX® Container

Applicant: B. Braun Medical, Inc.

Therapeutic Class: Priority

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of patients with serious infections caused by susceptible strains of the designated microorganisms.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg ____ mo. ____ yr. ____ Tanner Stage ____
Max ____ kg ____ mo. ____ yr. ____ Tanner Stage ____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min __ kg__ mo. ____ yr. ____ Tanner Stage ____
Max ____ kg__ mo. ____ yr. ____ Tanner Stage ____

Comments: No additional studies in pediatric patients are required. Claforan, the reference listed drug is labeled for use in children and cefotaxime in duplex container includes labeling stating that it is inappropriate for use in smaller pediatric patients who do not require the full dose of the drug (1 gram or two grams). Hence, cefotaxime in duplex container is not expected to be used in children weighing less than 20 kgs.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 50-792

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Sumathi Nambiar
8/12/04 02:41:42 PM

6/28/04

To: Vidra, James D

Cc: Peat, Raquel

Subject: Teleconference Minute (Draft) with B. Braun on NDA 50-792 - unknown impurity level in API

Background:

NDA 50-792 provides for two APIs for cefotaxime sodium, both made by [redacted]; Process-A and 2) Process B. Process-A material meets unknown impurity at NMT [redacted] while Process B material fails to meet unknown impurity at NMT [redacted] and has a concentration at NMT [redacted]. The reviewer has requested that Process-B material be reduced to NMT [redacted]. B. Braun has submitted [redacted] showing that the [redacted] and wished to discuss the options available to pursue the NDA successfully in case [redacted] fails to improve the Process-B material to NMT [redacted] before the NDA is due.

Date: 6/22/04

Attendee: J. Vidra, Andy Yu from FDA and R. Bourne and David Schuk from B. Braun.

Three options were discussed during the meeting on API source from [redacted]

Option 1

B. Braun would amend the NDA with the Process-B material, having its unknown impurity specification reduced to NMT [redacted]. B. Braun would commit not to use any Process-B material until the manufacturing process was refined to meet unknown impurity specification at NMT [redacted]. This could be called a "tentative specification".

Option 2

B. Braun and [redacted] would refine the Process-B material such that specification will be reduced to or less than [redacted].

Option 3

[redacted] would submit qualification data (animal studies) showing that the unknown [redacted] impurity was qualified.

B. Braun should act quickly within two weeks to resolve this issue. The option of B. Braun withdrawing the Process-B material from the NDA was discussed but not well received. FDA will await a full DMF response for deficiencies from [redacted] in the meantime.

Andy

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/s/

Jim Vidra
6/28/04 09:42:09 AM

6/24/04

**NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)**

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): NDA 50-792, Cefotaxime for Injection USP and Dextrose Injection in the Duplex[®] Container.

Applicant: B. Braun Medical, Inc.

Date of Application: September 29, 2003

Date of Receipt: September 30, 2003

Date of Filing Meeting: November 17, 2003

Filing Date: November 25, 2003

Indication(s) requested: Cefotaxime for Injection USP and Dextrose Injection is indicated for the treatment of patients with serious infections caused by susceptible strains of the designated microorganisms.

Type of Application: Full NDA Supplement _____
(b)(1) _____ (b)(2)
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S P _____
Resubmission after a withdrawal or refuse to file N/A
Chemical Classification: (1,2,3 etc.) _____
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NOx

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NOx

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Waived _____ Waived (e.g., small business, public health) _____

Exempt (orphan, government) no

Form 3397 (User Fee Cover Sheet) submitted: YES NO _____

User Fee ID# 4607

Clinical data? YES _____ NO Referenced to NDA# 50-547

Date clock started after UN _____

User Fee Goal date: July 30, 2004

Action Goal Date (optional) July 30, 2004

- Does the submission contain an accurate comprehensive index? YESx NO
- Form 356h included with authorized signature? YESx NO

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YESx NO
 If no, explain:
- If electronic NDA, does it follow the Guidance? YES NO NAx
If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Technical Document, does it follow the guidance? YES NO NAx
- Patent information included with authorized signature? YES • NO
- Exclusivity requested? YES; If yes, _____ years NOx
 Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.
- Correctly worded Debarment Certification included with authorized signature? YESx NO
If foreign applicant, the U.S. Agent must countersign.

Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, "To the best of my knowledge,"

- Financial Disclosure included with authorized signature? YESx NO
 (Forms 3454 and/or 3455)
If foreign applicant, the U.S. Agent must countersign.
- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO NAx
 If no, for what ages and/or indications was a waiver and/or deferral requested:
- Field Copy Certification (that it is a true copy of the CMC technical section)? YESx NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YESx NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND 67,178

End-of-Phase 2 Meeting? Date_ _____ NOx
 If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s)_ August 19, 2003
 If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO NA_x

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
 YES NO NA_x

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
 YES NO NA_x

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
 YES NO NA_x

Advisory Committee Meeting needed? YES, date if known _____ NO_x

Clinical

• If a controlled substance, has a consult been sent to the Controlled Substance Staff?
 YES NO_x

Chemistry

• Did sponsor request categorical exclusion for environmental assessment? YES_x NO
 If no, did sponsor submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) package submitted? YES_x NO

• Parenteral Applications Consulted to Sterile Products (HFD-805)? YES_x NO

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in 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 capsules to solution").

Name of listed drug(s) and NDA/ANDA #: **NDA 50-547, Claforan[®]**

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
 (Normally, FDA will refuse-to-file such applications.)
 YES NO_x

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
 If yes, the application must be refused for filing under 314.54(b)(1) YES NO_x

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
 If yes, the application must be refused for filing under 314.54(b)(2) YES NO_x

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

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

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

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

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.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for 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.

21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
YESx NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES • NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YESx NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 17, 2003

BACKGROUND:

NDA 50-779 (Cefazolin for Injection USP and Dextrose Injection USP in the DUPLEX Container) was approved on 07/2/00. NDA 50-780 (Cefuroxime for Injection USP and Dextrose Injection USP in the DUPLEX Container) was approved on 02/21/01. In the current submission, NDA 50-792, the Sponsor is seeking approval of Cefotaxime in 1.0 and 2.0 g strengths in the DUPLEX container. The DUPLEX container is a patented drug delivery system consisting of a dual chamber, PVC-free, DEHP-free, and latex-free IV container. The diluent chamber contains 50 mL of the sterile diluent and the drug chamber contains either 1.0g or 2.0 g of the sterile API powder. The Sponsor is requesting right of reference in accordance with the provisions of the 505 (b) (2) provisions to clinical and pre-clinical studies performed by Aventis Pharmaceuticals in support of their NDA submission (50-547) for Claforan (Cefotaxime) approved 01/01/82.

ATTENDEES: Janice Soreth, David Ross, James Blank, Venkateswa Jarugula, Terry Peters, Robert Osterberg, James Vidra, Andrew Yu, Albert Sheldon, Connie Mahon and Raquel Peat

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	James Blank
Secondary Medical:	David Ross
Statistical:	Daphne Lin
Pharmacology:	Terry Peters
Statistical Pharmacology:	N/A
Chemist:	Andrew Yu
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Paul Buehlar
Microbiology, sterility:	Peter Cooney
Microbiology, clinical (for antimicrobial products only):	Connie Mahon
DSI:	Ni Aye Khin and Brenda Friend
Project Manager:	Raquel Peat
Other Consults:	

Per reviewers, all parts in English, or English translation? YES NO

CLINICAL – File Refuse to file

• Clinical site inspection needed: YES NO

MICROBIOLOGY CLINICAL – File Refuse to file

STATISTICAL – File Refuse to file

BIOPHARMACEUTICS – File Refuse to file

• Biopharm. inspection Needed: YES NO

PHARMACOLOGY – File X Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES X NO _____ File X Refuse to file _____

ADDITIONAL REVIEWER COMMENTS:

Chemistry, Manufacturing, and Controls

1. sources of sodium cefotaxime were used to manufacture this drug product. Demonstration of equivalence between these sources in stability, impurity and quality in the referenced DMF is crucial for approval of this product.
2. Control of manufacturing and instability loss will be an important issue in determining the specification for overage or overfill of the product.
3. Microbiological issues associated with sterility and are potential issues that will be addressed by the Quality Microbiology reviewer.
4. The analytical methods for related drug substance and Cefotaxime/Dextrose injection were submitted to the FDA laboratory for method validation. Approval of this NDA is dependent on a successful completion of the method validation.

REGULATORY CONCLUSIONS/DEFICIENCIES:

We request that the sponsor submit the following information:

Clinical

1. The addition of to the **ADVERSE REACTIONS** section is not supported by any documentation in the submission. Submit additional data, e.g., references from the literature, adverse reaction reports, etc., which show a close association between cefotaxime therapy and those adverse events.
2. Submit whatever additional information is available to support the statement under **CONTRAINDICATIONS** that reads: "Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products." The Division is aware of the statement's existence in the labeling for other products, including Baxter's Dextrose and Sodium Chloride Injection, USP.

Clinical Pharmacology

3. Submit data (if any) regarding pharmacokinetic changes in renally impaired patients compared to patients with normal renal function, data regarding the CYP450 isozymes responsible for the metabolism of Cefotaxime and data regarding the effect of Cefotaxime on the activity of various CYP450 isozymes.

Chemistry, Manufacturing, and Controls

4. The NDA was filed with limited stability data (3-9 months). The remaining stability data is to be submitted later by agreement. It is crucial that the remaining stability data be submitted by the 6th month of the NDA review in time to allow complete data analysis to support the proposed shelf life.

Animal Pharmacology

5. Conduct a genetic toxicology study to make your proposed label compliant with current standards prior to the final label being written. The Agency recommends you conduct a mouse lymphoma assay, however, either an *in vitro* test with cytogenetic evaluation of chromosomal damage in mammalian cells or an *in vitro* mouse micronucleus assay.

Comments above will be sent in the 74-day filing letter.

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

The application is unsuitable for filing. Explain why:

45- day filing meeting minutes recorded by:
LT Raquel Peat, M.S., M.P.H.
Regulatory Health Project Manager, HFD-520

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/s/

Raquel Peat
6/24/04 04:44:23 PM

MEMORANDUM

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

Date: June 1, 2004

To: LT Raquel Peat, M.S., M.P.H., USPHS
Regulatory Health Project Manager

From: Daphne Lin, Ph.D.
Statistical Team Leader, Division of Biometrics III

Subject: NDA 50-792, Cefotaxime for Injection USP and Dextrose Injection in the
DUPLEX Container

This memorandum is in response to your consultation request on review of NDA 50-792, Cefotaxime for Injection USP and Dextrose Injection in the DUPLEX Container.

I have reviewed this submission and discussed with the review team members. Our conclusion is that there is no need to perform statistical analysis on this application.

Should any changes be requested in the future, statistical analysis will be performed on the information and the data available at that time.

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/s/

Raquel Peat
6/10/04 11:18:21 AM
CSO
Statistical Review

Daphne Lin
6/10/04 11:50:44 AM
BIOMETRICS



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 6, 2004

To: Richard Bourne, PhD	From: LT Raquel Peat
Company: B. Braun Medical Inc.	Division of Division of Anti-Infective Drug Products
Fax number: (949) 660-2200	Fax number: (301) 827-2325
Phone number: (949) 660-2176	Phone number: (301) 827-2125
Subject: NDA 50-792	

Total no. of pages including cover: 4

Comments: Please call me if you have any questions.

Document to be mailed: • YES NO

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MEMORANDUM

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

DATE: May 6, 2004

TO: Richard Bourne, Ph.D.
Corporate Vice President, Regulatory Affairs
B. Braun Medical Inc.
2525 McGaw Avenue
P.O. Box 19791
Irvine, CA 92623-9761
Phone: (949) 660-2176
Fax: (949) 660-2200

THROUGH: Review Team for NDA 50-792

FROM: Raquel Peat, LT
Regulatory Health Project Manager
Division of Anti-Infective Drug Products
301-827-2125
301-827-2325 (Fax)

SUBJECT: NDA 50-792 (received September 30, 2003) Chemistry Reviewer's Comments.

List of CMC deficiencies and comments:

1. The primary and alternate test was proposed in the specification table for Sterile Sodium cefotaxime USP (4.A.I-3, Page 80), please clarify if the HPLC method (coded 2710 under specification 4.A.I-3) proposed is the alternate method and the USP method is still the primary regulatory method? FDA recommends the USP method be the regularly method for Sterile Sodium cefotaxime USP.
2. From p3178 –3179 Table I, the summary for various method validation (MV) result were provided. It was stated that the result are for: Bulk raw material, Drug powder packaged in Duplex container system and constituted product. No method code reference was stated. Please clarify.
3. It was unclear to the reviewer whether the summary result in #2 above were performed with the proposed method for the drug substance, drug product, or the reconstituted drug product. Please state the method code or # for each method validated. Was HPLC Method (coded 2710 under specification 4.A.I-3) validated?

4. If an alternate method is proposed besides the USP method, please provide a table comparing the accuracy and resolution of the alternate method to the USP method for assay of the drug substance and the drug product. Was USP reference standard used?
5. Please identify (preferably with page reference) the HPLC method (with method Code or number) proposed for 1) routine batch release, and 2) stability studies and impurity determination in the drug product.
6. Is [redacted] present as a process impurity in the drug substance produced by process A or B? If this impurity is formed, please set specification and explain how the new impurity is qualified.
7. On page 82/Volume 1, [redacted] was set at NMT [redacted] but the same impurity was set at NMT [redacted] in the table below. Please clarify.
8. In Table 4A.II.A-10, please explain why the HPLC method proposed is the non-USP method. If the method is improved for stability samples, the sponsor may consider proposing that to USP.
9. Please tighten or justify the shelf life specification for individual and total impurity [redacted] in table 4A.II.A-10 for the Cefotaxime/Dextrose injection in Duplex container. [redacted] was set at [redacted] and [redacted]. Are the specification consistent with currently Cefotaxime USP for injection?
10. On page 80/Volume 1, under specification Table 4.A.I-3, please list the method number or reference instead of "COA" for Cefotaxime Sodium.
11. On page 106/Volume 1, under specification Table 4.A.I-12, please list the method number or reference instead of "COA" for Dextrose.
12. Please tighten the specifications for [redacted] impurities of the constituted solution since the specification are much wider than the level present in the API (P151, Table 4.A.II.A-11). What are the levels of these impurities at the end of shelf life in the stability batches?
13. The fill weight specification proposed in the NDA is much higher than the label claim. Justification on overage was partly based on [redacted] loss due to degradation within [redacted] after reconstitution.

Target - [redacted]
Lower limit - [redacted]
Upper limit - [redacted]

Please reduce the level of the target and tighten the range. Overage should not be used to compensate for drug decomposition. Please justify the overage based on manufacturing

and analytical information of the batches, a tentative interim specification may be proposed with a commitment to finalize the data from more batches if necessary.

If you have any questions, please call me at the above number.

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/s/

Raquel Peat
5/24/04 12:03:28 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 8, 2004

To: Qansy Salako	From: LT Raquel Peat
Company: B. Braun Medical Inc.	Division of Division of Anti-Infective Drug Products
Fax number: (949) 660-3292/2370	Fax number: (301) 827-2325
Phone number: (949) 660-2401	Phone number: (301) 827-2125
Subject: NDA 50-792	

Total no. of pages including cover: 2

Comments: Please call me if you have any questions.

Document to be mailed: • YES NO

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MEMORANDUM

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

DATE: April 8, 2004

TO: Qansy Salako, Ph.D.
Director, Regulatory Affairs
B. Braun Medical Inc.
2525 McGaw Avenue
P.O. Box 19791
Irvine, CA 92623-9761
Phone: (949) 660-2444
Fax: (949) 660-3292

THROUGH: Review Team for NDA 50-792

FROM: Raquel Peat, LT
Regulatory Health Project Manager
Division of Anti-Infective Drug Products
301-827-2125
301-827-2325 (Fax)

SUBJECT: NDA 50-792 (received September 30, 2003) Clinical Reviewer's Comments.

1. Submit the patent number for cefotaxime, the date the drug was patented, and the date that the patent expired.
2. In addition, there are a number of differences in the proposed label from the Claforan label. Submit a copy of B. Braun's label for the duplex product containing cefotaxime with justifications for the differences. It is necessary for the completion of the review.

If you have any questions, please call me at the above number.

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/s/

Raquel Peat
4/8/04 04:04:45 PM
CSO
Fax sent on 4/5/04

NDA ACTION PACKAGE CHECKLIST

Application Information		
NDA 50-792	Efficacy Supplement Type: N/A	Supplement Number: N/A
Drug: CefOTaxime for Injection USP and Dextrose Injection in the Duplex® Container		Applicant: B. Braun Medical
RPM: J. Christopher Davi		HFD-520 Phone # (301) 827-2217
<p>Application Type: () 505(b)(1) (x) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review, if completed for this application. If not completed, or you otherwise have questions about whether an application is a 505(b)(1) or 505(b)(2) NDA, see Appendix A.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information that is no longer correct.</p> <p>(x) Confirmed and/or corrected</p>		Reference Listed Drug (NDA #, Drug name): Claforan (Cefotaxime for Injection) NDA 50-547
❖ Application Classifications:		
• Review priority		(x) Standard () Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		
		July 30, 2004
❖ Special programs (indicate all that apply)		
		(x) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
• User Fee		(x) Paid UF ID number 4607
• User Fee waiver - N/A		() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception – N/A		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input type="checkbox"/> Verified N/A (no new clinical data was submitted, only CMC data was reviewed)
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	<input checked="" type="checkbox"/> Verified No patents apply (old anti-biotic).
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug in the Orange Book and identify the type of certification submitted for each patent. – N/A	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be granted effective approval (but may be tentatively approved if it is otherwise ready for approval) until the date that the patent to which the certification pertains expires.	N/A
• [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 (certification of notification and documentation of receipt of notice). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity))	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there remaining 3 year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	N/A (old anti-biotic)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	June 26, 2004
General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	

• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A (label printed on container)
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	June 22, 2004 Meeting Minutes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	June 28, 2004
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (<i>indicate date for each review</i>)	N/A
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	July 29, 2004 (Filing review in DFS)
❖ Microbiology (efficacy) review(s) (<i>indicate date for each review</i>)	June 14, 2004/July 27, 2004/ Nov. 24, 2003
❖ Safety Update review(s) (<i>indicate date or location if incorporated in another review</i>)	N/A
❖ Risk Management Plan review(s) (<i>indicate date/location if incorporated in another rev</i>)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	August 12, 2004
❖ Demographic Worksheet (<i>NME approvals only</i>)	N/A
❖ Statistical review(s) (<i>indicate date for each review</i>)	June 10, 2004
❖ Biopharmaceutical review(s) (<i>indicate date for each review</i>)	October 17, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date for each review</i>)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A

CMC Information

CMC Information	
❖ CMC review(s) (<i>indicate date for each review</i>)	July 22, 2004 and November 20, 2003
❖ Environmental Assessment	
• Categorical Exclusion (<i>indicate review date</i>)	Included in chemistry review (pg.51)
• Review & FONSI (<i>indicate date of review</i>)	N/A
• Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (<i>indicate date for each review</i>)	July 6, 2004
❖ Facilities inspection (provide EER report)	Date completed: Oct. 22, 2003 (x) Acceptable () Withhold recommendation
❖ Methods validation	(x) Completed (pg. 60 CMC rev.) () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	February 18, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	N/A

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Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval, publicly available FDA reviews, or labeling of another drug sponsor's drug product to meet any of the approval requirements (unless application includes written right of reference to data in another sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to supply data that are normally required 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 published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought.

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), because a sponsor often owns or has a right of reference for one of the drugs in the combination but not the other.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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NDA 50-792

INFORMATION REQUEST LETTER

B. Braun Medical Inc.
Attention: Qansy Salako, Ph.D.
Director, Regulatory Affairs
2525 McGaw Avenue
Irvine, CA 92614-5895

12-10-03

Dear Dr. Salako:

Please refer to your September 29, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cefotaxime for Injection USP and Dextrose Injection in the Duplex® Container.

We are reviewing your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide the full toxicology study reports for the guinea pig maximization test, and the subacute toxicity in mice test.

If you have any questions, call LT Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

Terry Peters, D.V.M.
Pharmacology Reviewer
Division of Anti-Infective Drug Products, HFD-520
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Terry Peters
12/10/03 09:28:49 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-792

11-25-03

B. Braun Medical Inc.
Attention: Qansy Salako, Ph.D.
Director, Regulatory Affairs
2525 McGaw Avenue
Irvine, CA 92614-5895

Dear Dr. Salako:

Please refer to your September 29, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cefotaxime for Injection USP and Dextrose Injection in the Duplex® Container.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on November 28, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing, and Controls

1. — sources of sodium cefotaxime were used to manufacture this drug product. Demonstration of equivalence between these — sources in stability, impurity and quality in the referenced DMF is crucial for approval of this product.
2. Control of manufacturing and instability loss will be an important issue in determining the specification for overage or overfill of the product.
3. Microbiological issues associated with sterility and ^c are potential issues that will be addressed by the Quality Microbiology reviewer.
4. The analytical methods for related drug substance and Cefotaxime/Dextrose injection were submitted to the FDA laboratory for method validation. Approval of this NDA is dependent on a successful completion of the method validation.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical

1. The addition of ' [] to the **ADVERSE REACTIONS** section is not supported by any documentation in the submission. Submit additional data, e.g., references from the literature, adverse reaction reports, etc., which show a close association between cefotaxime therapy and those adverse events.
2. Submit whatever additional information is available to support the statement under **CONTRAINDICATIONS** that reads: "Solutions containing dextrose may be contraindicated in patients with hypersensitivity to corn products." The Division is aware of the statement's existence in the labeling for other products, including Baxter's Dextrose and Sodium Chloride Injection, USP.

Clinical Pharmacology

3. Submit data (if any) regarding pharmacokinetic changes in renally impaired patients compared to patients with normal renal function, data regarding the CYP450 isozymes responsible for the metabolism of Cefotaxime and data regarding the effect of Cefotaxime on the activity of various CYP450 isozymes.

Chemistry, Manufacturing, and Controls

4. The NDA was filed with limited stability data [] The remaining stability data is to be submitted later by agreement. It is crucial that the remaining stability data be submitted by the 6th month of the NDA review in time to allow complete data analysis to support the proposed shelf life.

Animal Pharmacology

5. Conduct a genetic toxicology study to make your proposed label compliant with current standards prior to the final label being written. The Agency recommends you conduct a mouse lymphoma assay, however, either an *in vitro* test with cytogenetic evaluation of chromosomal damage in mammalian cells or an *in vitro* mouse micronucleus assay.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NDA 50-792
Page 3

If you have any questions, call LT Raquel Peat, Regulatory Health Project Manager, at (301) 827-2125.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Janice Soreth
11/25/03 05:16:25 PM

11/24/03

NDA 50792
Cefotaxime for Injection
B. Braun Medical Inc

1 of 2

45 DAY MEETING CHECKLIST

MICROBIOLOGY FILEABILITY

On initial overview of the NDA application:

YES/NO

1. Is the microbiologic section of the NDA organized in a manner to allow substantive review to begin? Yes
2. Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes
3. Is the microbiology section and other microbiologically pertinent sections of the NDA legible so that substantive review can begin? Yes

HAS THE APPLICANT SUBMITTED:

4. *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on the submitted draft labeling? N/A
5. any required animal model studies necessary for approvability of the product based on the submitted draft labeling? N/A
6. draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin? N/A
7. all special studies/data requested by the Division during pre-submission discussions? N/A
8. draft labeling consistent with 201.56 and 201.57, current Divisional policy, and the design of the development package? No

NDA 50792
Cefotaxime for Injection
B. Braun Medical Inc

2 of 2

YES/NO

9. FROM A MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.

Yes

B Braun seeks approval for the same indications as Cefotaxime finished product as Claforan, an approved Reference Listed Drug (RLD) for cefotaxime injection. The labeling will be identical to the reference product, except for inclusion of information on the B. Braun DUPLEX® Container / Closure system.

The Microbiology subsection of the package insert (PI) for Cefotaxime, USP for injection and dextrose injection in the Duplex will be reviewed to determine if the information in the most recent PI are consistent with the most recent guidelines and published literature. Changes in format, other updates on the emergence of resistance, quality control ranges and interpretive criteria, if any, will be recommended where appropriate.

Connie R. Mahon, MS, CLS (NCA)

Reviewing Microbiology Officer

MicroTL/ATSheldon

Final signed 11/24/03 ATS

Supervisory Microbiology Officer

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this page is the manifestation of the electronic signature.**

/s/

Connie Mahon
11/24/03 09:13:01 AM
MICROBIOLOGIST

Albert Sheldon
11/24/03 09:18:04 AM
MICROBIOLOGIST

DATE: November 19, 2003
TO: Requel Peat, Project Manager
FROM: Andy Yu, Review Chemist
SUBJ: NDA 50-792 – NDA Filing checklist

NDA FILEABILITY CHECKLIST

NDA Number: 50-792 **Applicant:** B Braun Medical Inc. **Stamp Date:** 30-Sep-2003

Drug Name: Cefazolin for injection and Dextrose injection in the Duplex™ container.

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	✓		The CMC section of the NDA is organized in a manner to allow substantive
2	Is the section indexed and paginated adequately?	✓		
3	On its face, is the section legible?	✓		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	✓		Establishment information was clarified and confirmed with Sponsor
5	Is a statement provided that all facilities are ready for GMP inspection?	✓		They are all ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	✓		A claim for categorical exclusion has been made.
7	Does the section contain controls for the drug substance?	✓		Reference is made to DMF 13219.
8	Does the section contain controls for the drug product?	✓		
9	Has stability data and analysis been provided to support the requested expiration date?	✓		⌈ ⌋ stability data has been provided with additional stability data to follow by Pre-NDA agreement.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		
11	Have draft container labels been provided?	✓		
12	Has the draft package insert been	✓		

Cefazolin for injection and Dextrose injection in the Duplex™ container

	provided?			
13	Has an investigational formulations section been provided?	✓		Vol. 1.10 was listed but does not contain formulations for clinical, only for experiments.
14	Is there a Methods Validation package?	✓		Two copies were provided.
15	Is a separate microbiological section included?	✓		Vol. 1.6 & 1.9 are for Microbiology & sterilization

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist:

Date:

Team Leader:

Date:

cc:
Original NDA 50-792
HFD-520/Division File
HFD-520/Chem/Yu
HFD-520/PM/Peat
HFD-830/DivDir/Chen

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/s/

Andy Yu
11/19/03 05:24:39 PM
CHEMIST

Jim Vidra
11/20/03 08:51:51 AM
CHEMIST