CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-796

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA#: 50-796 **Supplement Type: N/A** **Supplement Number: N/A**

Stamp Date: June 21, 2004 **Action Date: April 21, 2005**

HFD 520 **Trade and generic names/dosage form: Ceftriaxone for Injection and Dextrose Injection in the Duplex Container**

Applicant: B. Braun Medical, Inc. **Therapeutic Class: 4010300 (Cephalosporins, Systemic)**

Number of Indications for this application: 1

Indication #1: To treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

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

√ 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:**_____

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. Rocephin®, the reference listed drug is labeled for use in children and ceftriaxone sodium in the 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 2 grams). Hence, ceftriaxone for injection and dextrose injection in the Duplex container is not expected to be used in children weighing less than 20 kg.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Sumathi Nambiar, MD, MPH

{See appended electronic signature page}
J. Christopher Davi
Regulatory Project Manager

cc: NDA 50-796
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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.

ction 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.

ion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 50-796
HFD-960/ Grace Carmouze

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

(revised 10-14-03)

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 3, 2005

To: Susan Olinger	**From:** J. Christopher Davi
Company: B. Braun Medical, Inc.	Division of Anti-Infective Drug Products
Fax number: (610) 596-2502	**Fax number:** (301) 827-2325
Phone number: 610-596-2517	**Phone number:** (301) 827-2125

Subject: List of CMC deficiencies and comments for NDA 50-796.

Total no. of pages including cover: 2

Comments: Susan, per our phone conversation today, please see attached information.

Document to be mailed: • YES ☑ NO

List of CMC deficiencies and Comments for NDA 50-796

1. Under Section 4, Specification and method for drug substance, Dextrose USP specification and methods were not found.

The reviewer noted that there is a result table submitted on page 758, under batch analysis data for Dextrose anhydrous USP, and the specifications and methods are listed in this result table. Please confirm that these are proposed specifications and regulatory methods for Dextrose anhydrous USP.

2. The proposed Osmolality of Ceftriaxone for Injection (activated) was 240-340 mOsmol/kg (Table 4.43, page 764). Please justify the wide range and tighten if necessary.

3. The proposed total related compounds (TRC) specification of the drug product, Ceftriaxone for Injection (activated), was NMT [redacted] (Table 4.43, page 764). This acceptance criteria is much greater than that present in the drug substance (NMT [redacted]). Please justify the wide range and tighten if necessary. Please identify if any of these related compounds [redacted] are degradation products and report if their levels increase during storage.

4 [redacted]

5. The analytical method proposed in #4 is not yet laboratory validated by FDA during the review cycle. Will the sponsor agree to make necessary method modifications if warranted?

6. You proposed a shelf life of [redacted] for *Ceftriaxone/Dextrose for Injection.* However, there are no statistical regression analyses performed to justify a projection of [redacted]. The latest stability update provided data for [redacted] for 3 stability batches. Will you be providing a regression analysis to justify the [redacted] shelf life?

7. CMC deficiencies continue to be outstanding in DMFs [redacted] after responses were reviewed on 1/23/05. Failure to respond to the deficiencies will affect the CMC review and the subsequent approval of NDA 50-796 from B. Braun. The DMF holders have been notified by the Agency.
Microbiology DMF [redacted] is also deficient but will be reviewed by Quality Microbiology since it involves only microbiology issues. However, these DMF deficiencies also need to be corrected prior to NDA approval.

8. The proposed fill weight specification for ceftriaxone in the NDA was: "target [redacted], with lower limit at [redacted] and upper limit at [redacted] (Table 4.4, page 51 from e-file).

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.

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/s/

Christopher Davi
3/3/05 01:52:06 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 18, 2005

To: Susan Olinger	**From:** J. Christopher Davi
Company: B. Braun Medical, Inc.	Division of Anti-Infective Drug Products
Fax number: (610) 596-2502	**Fax number:** (301) 827-2325
Phone number: 610-596-2517	**Phone number:** (301) 827-2125

Subject: NDA 50-796 Review

Total no. of pages including cover: 2

Comments: Susan, Please see attached comments regarding the status of NDA 50-796 review.

Document to be mailed: ☐ YES ☑ NO

The Division met on January 13, 2005 to discuss the status of NDA 50-796 (Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container). The Division has the following information to convey to the Sponsor at this stage in the review process:

1. Drug Master File (DMF) # [redacted] is deficient, and theses deficiencies will need to be addressed by the DMF holder prior to completion of the review.

2. The Division contacted the Sponsor on January 7, 2005 to inform them that the following comparability protocols (submitted with NDA 50-796) will not be reviewed as part of the NDA 50-796 review:

   - NDA 50-779 (Cefazolin)
   - NDA 50-780 (Cefuroxime)
   - NDA 50-792 (Cefotaxime)

   Comparability protocols associated with the above listed NDAs would have to be submitted as separate supplements. The Sponsor is referred to the 2004 Post Approval Changes Guidance for additional information. The Sponsor is requested to provide a statement, through general correspondence, indicating that the above referenced comparability protocols are not expected to be reviewed as part of NDA 50-796, and request that the Division disregard these protocols.

3. The Sponsor is advised that stability information provided to date is insufficient, as it totals only [redacted] The Division is awaiting an additional [redacted] stability data. Without additional stability data, the approval of this NDA is jeopardized.

If you have questions regarding this correspondence, contact J. Christopher Davi, Regulatory Project Manager at (301) 827-2217.

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/s/

Christopher Davi
1/18/05 10:31:14 AM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 15, 2004

To: Susan Olinger	**From:** J. Christopher Davi
Company: B. Braun Medical Inc.	Division of Anti-Infective Drug Products
Fax number: (610) 596-2502	**Fax number:** (301) 827-2325
Phone number: (610) 596-2517	**Phone number:** (301) 827-2217

Subject: CMC Comments

Total no. of pages including cover: 2

Comments: Susan,

Please see attached comments from the chemistry review team relative to NDA 50-796. Let me know if you have questions.

Chris Davi

Document to be mailed: • YES ☑ NO

Regarding the "Comparability Protocol – Change of Container: Duplex [redacted] (Vol. 14/P3436, Attachment 40, e-page 543"), in page 3452, other NDAs were involved other than NDA 50-796 requesting approval of a comparability protocol proposing "reduced reporting requirements" upon its approval.

The reviewer recommends that the protocol involving other drugs ***[NDA 50-779 (Cefazolin), 50-780(Cefuroxime), and 50-792(Cefotaxime)]*** *be submitted separately, since the stability protocol involves separate drugs with different stability. A common document describing the container may be shared if it involves the same Duplex container change. Please provide a table comparing the current and the proposed " reduced reporting requirements" for each of the products in the comparability protocol. This change would not affect NDA 50-796.*

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/s/

Christopher Davi
12/15/04 04:19:45 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-796

B. Braun Medical, Inc.
Attention: Richard K. Bourne, PhD
Corporate Vice President, Regulatory Affairs
2525 McGaw Avenue
Irvine, CA 92614-5895

Dear Dr. Bourne:

Please refer to your June 18, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container, in 1g ceftriaxone and 2g ceftriaxone strengths.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 17, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

If you have any questions, call J. Christopher Davi, Regulatory Project Manager, at (301) 827-2217.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Judit Milstein
8/27/04 03:03:46 PM
Judit Milstein for F. LeSane

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: Pre-IND 67,794

Total no. of pages including cover: 3

Comments: Please call me if you have any questions.

Document to be mailed: • YES ☑ NO

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 Pre-IND 67,794

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

SUBJECT: Pre-IND 67,794 (received April 16, 2004) Chemistry Reviewer's Comments. In preparation for our meeting on May 13, 2004, this fax addresses CMC comments and information requested. Please be prepared to address each question. In addition, a list of FDA attendees is enclosed.

1. Is our approach on the container closure system evaluation, data collection and submission acceptable to the Agency?

The general approach for evaluation and brief description of fabrication of the container system is reasonable at this stage from a CMC view point. Data collection should include extractable with the new container and ensure compatibility with the new drug. More CCS test details will be required in Table 3. Microbiology will address the sterilization and container closure integrity issues separately.

2. Does the Agency have any comments on our approach to fill weight specification establishment?

FDA does not have any specific comments on the fill weight of Ceftriaxone for Injection since not many details is available for this drug. In general, overage should be justified and not used to compensate for instability. Reasonable manufacturing loss may be compensated. The fill weight range presented) is wide and the range may be reduced based on preliminary

examination. However, the precise filling range cannot be recommended at this point without more details on stability and information on the batches.

3. Does the Agency have any comments on our approach to implementation of our higher capacity manufacturing Line 2 based on the proposed filing strategy?

The new fill line facility should be validated and inspected. Details of the high capacity manufacturing line should be described and equipment differences should be compared. How many batches have been tested on the high capacity fill line? Quality microbiology will address separately on issues with [redacted] and sterilization validation.

4. Other CMC Comments:

a) Please provide specifications for both drug substance and drug product.
b) Please provide complete name, addresses, and contact names of all manufacturing facilities.
c) Please provide additional information on impurity and method of manufacture on the manufacture of the API made by [redacted] Does [redacted] have a Type II DMF on file with the Agency?

5. FDA Attendees:

Janice Soreth, M.D., Division Director
Lillian Gavrilovich, M.D., Deputy Director
Sumathi Nambiar, M.D., M.P.H., Acting Medical Team Leader
Alma Davidson, M.D., Medical Officer
James Vidra, Ph.D., Chemistry Team Leader
Andrew Yu, Ph.D., Chemistry Reviewer
Vinayak Pawar, Ph.D., Microbiology Sterility Reviewer
Connie Mahon, M.S., Acting Microbiology Team Leader
Robert Osterberg, Ph.D., Pharmacology Team Leader
Terry Peters, D.V.M., Pharmacology Reviewer
Venkateswar Jarugula, Ph.D., Clinical Pharmacology Team Leader
Charles Bonapace, Pharm.D., Clinical Pharmacology Reviewer
Thamban Valappil, Ph.D., Acting Statistical Team Leader
Frances LeSane, Chief, Project Management Staff
Raquel Peat, M.S., M.P.H., Regulatory Health Project Manager

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

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/s/

Raquel Peat
5/14/04 10:57:54 AM
CSO
Fax sent on May 6, 2004

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

MEMORANDUM OF MEETING MINUTES

Meeting Date:	May 13, 2004
Pre- IND:	67, 794
Location:	S-300
Time:	11:30 a.m. – 1:00 p.m.
Drug:	Ceftriaxone for Injection USP and Dextrose Injection in the Duplex® Container
Sponsor:	B. Braun Medical Inc.
Type of Meeting:	Pre-NDA (Type B)
Meeting Chair:	Dr. Janice Soreth, Division Director
Meeting Recorder:	LT Raquel Peat, Regulatory Health Project Manager

FDA Attendees:

Janice Soreth, M.D., Division Director
Lillian Gavrilovich, M.D., Deputy Director
Sumathi Nambiar, M.D., M.P.H., Acting Medical Team Leader
Alma Davidson, M.D., Medical Officer
James Vidra, Ph.D., Chemistry Team Leader
Andrew Yu, Ph.D., Acting Chemistry Team Leader
Vinayak Pawar, Ph.D., Product Quality Microbiology Reviewers, OPS
Connie Mahon, M.S., Acting Microbiology Team Leader
Robert Osterberg, Ph.D., Pharmacology Team Leader
Thamban Valappil, Ph.D., Acting Statistical Team Leader
Sue Bell, Ph.D., Statistical Reviewer
Jeffrey Tworzyanski, Pharm. D., Clinical Pharmacology Reviewer
Frances LeSane, Chief, Project Management Staff
Raquel Peat, M.S., M.P.H., Regulatory Health Project Manager

B. Braun Medical Inc. Attendees

Richard Bourne, Ph.D., Corporate VP, Regulatory Affairs
Marcus Schabacker, M.D., Ph.D., Corporate VP, Research and Development
David Schuck, Ph.D., Director, Pharmaceutical Development
Wendy Ricapito, Director, Quality Assurance
Walter York, Manager, Process Engineering

SUBJECT: The sponsor is planning to submit a 505 (b) (2) new drug application (NDA) for Ceftriaxone for Injection USP and Dextrose Injection in the Duplex® Container in June 2004. This meeting is to discuss their overall Duplex program, specifically relating to the filing of the Ceftriaxone NDA.

BACKGROUND: B. Braun presented a Pre-IND plan for Ceftriaxone for Injection USP and Dextrose Injection in the duplex container. The duplex container was demonstrated and proposed modifications were discussed. B. Braun intends to submit several NDAs for different cephalosporins for injection drug products in the duplex container. A list of CMC questions and comments raised in B. Braun's meeting package was sent to the sponsor on May 6, 2004 prior to the meeting. The present proposed CMC plan for Ceftriaxone for Injection/Dextrose Injection in Duplex container was discussed. The general approach was considered feasible from a CMC viewpoint. Details of CMC questions raised are listed below and answers to the questions follow. Comments from Quality Microbiology on Pre-IND #67,794 (if any) will be sent to the sponsor at a later date.

DISCUSSION AND RECOMMENDATIONS: A summary of discussions and conclusions reached at the meeting are listed below:

1. *Container closure system evaluation:* The general approach for evaluation and brief description of fabrication of the container system is reasonable at this stage from a CMC view point. Data collection should include extractables with the new container and ensure compatibility with the new drug. The Agency requested that the sponsor provide more container closure system test details as it relates to suitability in Table 3.

2. *Fill weight specification establishment:* FDA does not have any specific comments on the fill weight of Ceftriaxone for Injection since not many details are available for this drug. In general, overage should be justified and not used to compensate for instability. Reasonable manufacturing loss may be compensated. The fill weight range presented [redacted] is wide and the range may be reduced based on preliminary examination. However, the precise filling range cannot be recommended at this point without more details on stability and information on the batches. Hence, the fill weight should be explained and justified in the NDA submission.

3. *Implementation of their higher capacity manufacturing [redacted] based on the proposed filing strategy:* The new fill line facility should be validated and inspected. The Agency requested that the latest [redacted] media fill and environmental monitoring data be included in the submission along with the original validation data. Details of the high capacity manufacturing line should be described and equipment differences should be compared. Quality microbiology will address separately on issues with [redacted]

4. *Drug Substance:* B. Braun indicated that the preparation method is similar to that of the Reference-listed drug (RLD) and this information is contained in the Drug Master Files. Additionally, the sponsor indicated that the impurity profile is similar to the RLD and details of the comparability impurity profile will be submitted in the NDA.

5. *Stability:* The Agency noted that per ICH guidelines, a NDA submission should have [redacted] stability data and it does not accept statistical extrapolation for a [redacted] expiration date. After much discussion, the Agency will allow the sponsor to file their

[redacted]

6. *Pre-clinical considerations:* Based on the information provided in the briefing package, no additional pre-clinical studies are necessary.

7. *Clinical consideration:* The clinical reviewer requested that an executive summary of the literature on safety of ceftriaxone be included in the proposed NDA submission.

8. [redacted]

9. *E-submission:* Based on the guidance to industry the Agency will accept paper or electronic NDA submissions.

ADDITIONAL POINTS FOR DISCUSSION: None

ISSUES REQUIRING FURTHER DISCUSSION: None

ACTION ITEMS:

- Ceftriaxone for Injection USP and Dextrose Injection in the Duplex® Container NDA will be submitted in June 2004.

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

Janice Soreth, M.D.
Division Director

ATTACHMENTS: meeting sign in sheet and presentation slides.

29 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Janice Soreth
7/29/04 03:02:31 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 50-796	Efficacy Supplement Type: N/A	Supplement Number: N/A	
Drug: Ceftriaxone for Injection and Dextrose Injection in the DUPLEX® Container		Applicant: B. Braun Medical, Inc.	
RPM: J. Christopher Davi, MS		HFD-520	Phone #: (301) 827-2217
Application Type: ( ) 505(b)(1) **(X)** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **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 (including patent certification information) that is no longer correct.** **(X)** Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): ROCEPHIN® for Injection, NDA 50-585 (approved 12/21/84)	

❖ Application Classifications:	
• Review priority	**(X)** Standard ( ) Priority
• Chem class (NDAs only)	Ceftriaxone Sodium (broad spectrum cephalosporin) Class 3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	April 21, 2005
❖ 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 4765
• 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	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) 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.	(X) Verified
❖ Patent – N/A: Old Antibiotic (Prerepeal Antibiotic Drug)	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. N/A	( ) Verified
• 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. N/A	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [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).	
• [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 box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [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? (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)? *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 box below (Exclusivity).* *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 ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).* *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.*	( ) Yes ( ) No
❖ 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.)	No – This is a prerepeal antibiotic.
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *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.*	( ) Yes, Application #_____ **(X)** No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	None

Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) 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)	See AP Letter
• Most recent applicant-proposed labeling	April 19, 2005
• Original applicant-proposed labeling	Yes (enclosed)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	See discipline reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Yes (enclosed)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	No Change Requested
• Applicant proposed	Enclosed
• Reviews	See Chemistry Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	• Filing Communication (8/27/04) • Pre-IND CMC Fax (5/6/04) • CMC Comments (12/15/04) • DMF/Comparability protocol comments (1/18/05) • CMC deficiencies/comments (3/3/05)
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	Pre-NDA (5/13/04)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting - None	
• 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) *(indicate date for each review)*	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	April 19, 2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	April 18, 2005
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Enclosed
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	April 14, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	April 18, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	April 18, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	April 18, 2005
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	March 29, 2005
❖ Facilities inspection (provide EER report): N/A	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation: N/A	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 2, 2004
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A