

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-817

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA #: NDA 50-817 Supplement Type (e.g. SE5): NA Supplement Number: NA

Stamp Date: March 1, 2007 PDUFA Goal Date: January 1, 2008

HFD 520 Trade and generic names/dosage form: Cefepime Injection in GALAXY Container (PL 2040 Plastic)/ cefepime hydrochloride, USP/ 1g/50 mL container and 2g/100 mL container

Applicant: Baxter Healthcare Corporation Therapeutic Class: S3

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

Yes. Please proceed to the next question.

No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 5

Indication #1: Treatment of Pneumonia (moderate to severe) caused by *Streptococcus pneumoniae* including cases associated with concurrent bacteremia, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Enterobacter* species.

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. 2 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

X **Other:** This drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 2 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: This Drug product is appropriately labeled for use in ages 2 months up to 16 years for this indication. Therefore, no additional studies are needed in this age group.

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

DFS.

This page was completed by:

{See appended electronic signature page}

Kyong Hyon _____

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A

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

Indication #2: Empiric therapy for febrile neutropenic patients

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 0 yr. _____ Tanner Stage _____

Max _____ kg _____ mo. 2 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: This drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 2 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: This Drug product is appropriately labeled for use in ages 2 months up to 16 years for this indication. Therefore, no additional studies are needed in this age group.

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}

Kyong Hyon
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Indication #3: Treatment of uncomplicated and complicated urinary tract infections (including pyelonephritis)

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below):

Min _____	kg _____	mo. <u>0</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. <u>2</u>	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: This drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 2 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: This Drug product is appropriately labeled for use in ages 2 months up to 16 years for this indication. Therefore, no additional studies are needed in this age group.

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}

Kyong Hyon
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Indication #4: Treatment of Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin-

susceptible strains only) or *Streptococcus pyogenes*

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below)::

Min _____	kg _____	mo. <u>0</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. <u>2</u>	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: This drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 2 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: This Drug product is appropriately labeled for use in ages 2 months up to 16 years for this indication. Therefore, no additional studies are needed in this age group.

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}

Kyong Hyon

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Indication #5: Complicated intra-abdominal infections (used in combination with metronidazole) caused by *Escherichia coli, viridans*

group streptococci, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species, or Bacteroides fragilis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below)::

Min _____	kg _____	mo. <u>0</u>	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. <u>2</u>	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: This drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

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 (fill in applicable criteria below)::

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 (fill in applicable criteria below):

Min _____ kg _____ mo. 2 yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: This Drug product is appropriately labeled for use in ages 2 months up to 16 years for this indication. Therefore, no additional studies are needed in this age group.

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}

Kyong Hyon
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Kyong Hyon
12/21/2007 04:34:47 PM
CSO

Kathrine Laessig
12/21/2007 04:37:09 PM
MEDICAL OFFICER

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 50-817 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cefepime Injection in Galaxy Container Established/Proper Name: Cefepime Hydrochloride, USP Dosage Form: IV- 1g/50 mL & 2g/100 mL		Applicant: Baxter Healthcare Corporation Agent for Applicant (if applicable):
RPM: Kyong Hyon		Division: DAIOP
<p>NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>MAXIPIME (NDA 50-679)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>The proposed products are "ready to use" premixed IV formulations of Reference Listed Drug, Maxipime (Cefepime Hydrochloride) for Injections (NDA 50-679, held by Bristol-Myers Squibb, approved on 01/18/96). MAXIPIME is for IV or IM use and must be reconstituted with a suitable diluent prior to use. Baxter's proposed 1g/50 mL and 2g/100 mL premixed products in flexible plastic containers are for IV use only and are stored frozen.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: August 4, 2008</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		01/01/2008-1 st Cycle 08/05/2008-2 nd Cycle
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

• Previous actions (<i>specify type and date for each action taken</i>)	<input type="checkbox"/> None AE - 12/21/2007-1 st Cycle
❖ 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>)	<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed Requested in 1 st Cycle AE letter

Application² Characteristics

Review priority: Standard Priority
 Chemical classification (new NDAs only):

- Fast Track
- Rolling Review
- Orphan drug designation

- Rx-to-OTC full switch
- Rx-to-OTC partial switch
- Direct-to-OTC

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC

Comments: 505(b)(2) Application

Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html

- Applicant is on the AIP

Yes No

- This application is on the AIP

Yes No

- If yes, exception for review granted (*file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews*)
- If yes, OC clearance for approval (*file communication in Administrative/Regulatory Documents section with Administrative Reviews*)

Yes

Yes Not an AP action

Date reviewed by PeRC (*required for approvals only*)

If PeRC review not necessary, explain:

12/14/2008

BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM (*approvals only*)

Yes, date

BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (*approvals only*)

Yes No

Public communications (*approvals only*)

- Office of Executive Programs (OEP) liaison has been notified of action
- Press Office notified of action

Yes No

Yes No

- Indicate what types (if any) of information dissemination are anticipated

- None
- HHS Press Release
- FDA Talk Paper
- CDER Q&As
- Other

questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	Not needed: Old Antibiotic
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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. 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-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.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: 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.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric 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.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs 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. 	<input type="checkbox"/> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<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 type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> 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?

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 the rest of the patent questions.

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 OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist³

Included

Officers/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

Included

Documentation of consent/nonconsent by officers/employees

Included

Action Letters

❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s)
AE Letter-12/21/2007
AP Letter-August 05, 2008

Labeling

❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)

08/04/2008 - Labeling agreed between DAIOP & Baxter- This was sent to Baxter with AP Letter

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)

02/01/2008 with resubmission

❖ Original applicant-proposed labeling

02/28/2007-1st cycle

❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable

07/13/2007-submitted after Information Request letter sent to Baxter on 06/27/2007

❖ Medication Guide/Patient Package Insert/Instructions for Use (*write submission/communication date at upper right of first page of each piece*)

Medication Guide
 Patient Package Insert

³ Fill in blanks with dates of reviews, letters, etc.
Version: 5/19/08

	<input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	Original submission 02/23/2007 Resubmission 02/01/2008
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	
❖ Labeling reviews (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> RPM 06/25/2007 <input checked="" type="checkbox"/> DMEDP 08/24/2007-1 st cycle <input checked="" type="checkbox"/> 03/10/2008-2 nd cycle <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews SEALD TEAM PI content review received by DAIOP on 12/12/2007, but DFS on 1/22/2008 by SEALD Team
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	RPM Filing Reviewe - 12/21/2007
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included – Not needed: Old Antibiotic
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If approval action, OC clearance for approval 	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included – 12/21/2007
❖ 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 (include certification)	<input type="checkbox"/> Verified, statement is acceptable : Not needed because no independent study was conducted
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> Outgoing communications (if located elsewhere in package, state where located) Incoming submissions/communications 	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	
Internal memoranda, telecons, etc.	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 5/19/08

❖ Minutes of Meetings	There was no NDA, but had T-con (04/24/2006) under PIND 73,452 for Pre-NDA discussion. Minutes: 05/19/2006
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg Had T-con under PIND 73,452 for Pre-NDA discussion (04/24/2006)
• EOP2 meeting (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None Deputy Director review - 12/21/2007 Deputy Director review memo for 2 nd cycle - 08/05/2008
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11/20/2007 & 07/22/2008
• Clinical review(s) (<i>indicate date for each review</i>)	11/20/2007 & 07/21/2008
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	After Clinical Review 1 st Cycle- 12/31/2007 2 nd Cycle- 07/21/2008 - included in 2 nd cycle clinical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Page 10 of clinical review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ REMS • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
• Clinical Studies	

⁵ Filing reviews should be filed with the discipline reviews.
Version: 5/19/08

• Bioequivalence Studies	
• Clinical Pharmacology Studies	
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/21/2007
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/21/2007
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/20/2007
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/20/2007
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 05/07/2007
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 04/20/2007
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 01/02/2008
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 11/19/2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/12/2007, 01/10/2008, & 04/10/2008
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 12/11/2007, 01/09/2008, & 04/09/2008
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	12/21/2007 & 02/26/2008 <input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	

<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	12/11/2007
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: See CMC review pages 65-67 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ➢ TBP-EER ➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Appendix A to Action Package Checklist

An 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 ADRA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-817

Baxter Healthcare Corporation
Attention: Vicki L. Drews
Director, Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, IL 60085

Dear Ms. Drews:

Please refer to your new drug application (NDA) submitted February 28, 2007, for Cefepime Injection in Galaxy Container (PL 2040 Plastic), 1g/50 mL and 2g/100 mL.

As required under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding cefepime that covers the period from your last safety report submission dated November 30, 2007 to present. The safety update should include data from all non-clinical and clinical studies of cefepime regardless of indication, dosage form, or dose level and should also include a review of the published literature regarding cefepime regardless of the indication, dosage form, or dose level.

Please submit this information as soon as possible.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at 301-796-0734.

Sincerely,

{See appended electronic signature page}

Katherine Laessig, M.D.
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Kathrine Laessig
4/29/2008 11:34:16 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 50-817

Baxter Healthcare Corporation
Attention: Vicki L. Drews
Associate Director, Global Regulatory Affairs
1620 Waukegan Road
McGaw Park, IL 60085

Dear Ms. Drews:

We acknowledge receipt on February 5, 2008 of your February 1, 2008 resubmission to your new drug application for Cefepime Injection in GALAXY Container (PL 2040 Plastic), 1g/50 mL and 2g/100 mL.

We consider this a complete, class 2 response to our December 21, 2007 action letter. Therefore, the goal date is August 5, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that this drug product is appropriately labeled for use in the pediatric population for ages 2 months to 16 years of age. We are waiving the pediatric study requirement for ages 0 to two months because this drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this age group.

If you have any question, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

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

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/s/

Frances LeSane
4/4/2008 02:20:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): Lynn Panholzer, Division of Drug Marketing, Advertising, and Communications (DDMAC), WO22, RM 1460/ 301-796-0616			FROM (Name, Office/Division, and Phone Number of Requestor): Kyong Hyon, Division of Anti-Infective and Ophthalmology Products, HFD-520/ 301-796-0734		
DATE March 21, 2008	IND NO.	NDA NO. 50-817	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT February 1, 2008	
NAME OF DRUG. Cefepime Injection in Galaxy container		PRIORITY CONSIDERATION See completion date	CLASSIFICATION OF DRUG Antibiotic	DESIRED COMPLETION DATE April 11, 2008	
NAME OF FIRM: Baxter Healthcare Corporation					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS					
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: Please provide a PI and _____ review of NDA 50-817. PI _____ have been submitted electronically and they are available in the EDR. PLR/SPL is also available in the EDR.					
This submission is a class 2 complete response to our December 21, 2007 AE action letter. The action goal date is August 5, 2008. However, we would like to take an action may be by beginning of May. Please let me know if you have any questions or need assistance.					
Thank you, Kyong Hyon					
SIGNATURE OF REQUESTOR Kyong Hyon			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

b(4)

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/s/

Sumathi Nambiar
3/25/2008 05:28:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Office/Division): Anne Crandell, Division of Medication Errors and Technical Support (DMETS), HFD-410, WO22, RM4465			FROM (Name, Office/Division, and Phone Number of Requestor): Kyong Hyon, Division of Anti-Infective and Ophthalmology Products, HFD-520, WO22, RM6345		
DATE February 22, 2008	IND NO.	NDA NO. 50-817	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT February 1, 2008	
NAME OF DRUG Cefepime Injection in Galaxy Container		PRIORITY CONSIDERATION See the completion date	CLASSIFICATION OF DRUG 4010900	DESIRED COMPLETION DATE March 10, 2008	
NAME OF FIRM: Baxter Healthcare Corporation					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS					
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG SAFETY					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
COMMENTS / SPECIAL INSTRUCTIONS: The _____ review was done by your team in August 2007. This NDA received an AE action on December 22, 2007 and was resubmitted on February 1, 2008; in this second submission, the Sponsor made the changes to _____ per DMET's recommendation. Please provide _____ review of submission on February 1, 2008. PI and _____ are available in the EDR. We have a filing meeting on March 13, 2008 and requesting your team to provide your review prior to the filing meeting so that we can determine if the Sponsor's second submission would be filable or not. Please let me know if you have any questions or need assistance. Thank you, Kyong Hyon					
SIGNATURE OF REQUESTOR Kyong Hyon			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

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/s/

Alma Davidson
2/22/2008 03:51:10 PM

*Email Correspondence
with Industry*

Hyon, Kyong

From: Hyon, Kyong
Sent: Friday, December 21, 2007 3:39 PM
To: 'stacey_thompson@baxter.com'
Subject: RE: NDA 50-817, Cefepime Injection - areas of concern with respect to FDA proposed labeling and request for teleconference to discuss

Attachments: Response to Labeling Proposal concerns 21Dec07.pdf

Hello Mr. Thompson,

The attached is the Division's responses to your concerns about the Agency's labeling proposal, sent on December 18, 2007.

Best regards,

Kyong Hyon

From: stacey_thompson@baxter.com [mailto:stacey_thompson@baxter.com]
Sent: Thursday, December 20, 2007 6:51 PM
To: Hyon, Kyong
Cc: vicki_drews@baxter.com
Subject: NDA 50-817, Cefepime Injection - areas of concern with respect to FDA proposed labeling and request for teleconference to discuss
Importance: High

Hello Ms. Hyon,

We are working on incorporating FDA's labeling proposal for the direction insert for NDA 50-817, Cefepime Injection in Galaxy Container that we received on 12/18/07. Overall, the proposed text is largely acceptable and we are likely to incorporate almost all of FDA's changes. However, there are a few areas of concern that we need to discuss with FDA, and we propose a short teleconference be set up as soon as possible to get some clarification on these areas. As I said in my voice message, if we can teleconference very early Friday morning, Dec. 21, that would be best for us in order to finalize the changes and meet the user fee goal date.

Areas of Concern:

Section 8.1 - Pregnancy: The first paragraph references ratios of doses (e.g., 1.6 times, 0.3 times, etc.) that are different from the current labeling of the Reference Listed Drug (Maxipime). We are unable to verify the accuracy of the new numbers and would like

to discuss with FDA the basis for this change.

Section 12.4 - Microbiology (subheading, _____) has been removed. Baxter would like to discuss why this isolate was removed, as it is still listed in the Reference Listed Drug (Maxipime) direct insert. b(4)

Section 12.4 - Microbiology (Table 9): There is a _____ that is found in the CLSI Performance Standard added as Reference 4 in Section 15, References. b(4)

_____ Baxter would like to _____

Section 13.1 - Carcinogenesis, Mutagenesis, Impairment of Fertility: The second half of this paragraph was revised by the FDA. The following revision was made, _____ b(4)

_____ Also, the subcutaneous ratio dose is now reported as "1.6 times," which is different from the previously reported, _____. We are unable to verify the accuracy of the new text and numbers as it is no longer consistent with the current direction insert of the Reference Listed Drug (Maxipime), so we would like to discuss with FDA the basis for this change.

Other proposals/recommendations:

Section 12.1 - Mechanism of Action: FDA has proposed a single sentence, _____ b(4)

We recommend that FDA consider that the sentence as currently proposed is not necessarily a "mechanism of action" sentence; it is really just a statement of the drug class. It does not tell "how" the drug works, which is what we believe a mechanism of action should describe. Thus, we would recommend that sentence be replaced by:

"Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. [See Microbiology (12.4)]."

OR

Return this section back to our original submission, which would involve taking the first paragraph from Section 12.4 - Microbiology and placing it back into Section 12.1 - Mechanism of Action as follows:

Section 12.3 - Pharmacokinetics (Table 6): Data in columns 1-3 of this table are missing and we assume this was an error. Baxter intends to re-insert the numbers in the columns to match those of the Reference Listed Drug (Maxipime). We would like FDA concurrence that this is appropriate.

Minor edits and formatting revisions - For completeness, we want you to be aware that

we will also be making minor edits and formatting revisions. However, we do not expect any of these minor edits and format revisions to meaningfully affect the content of the information or the prominence of its presentation as proposed by FDA,

If you have any difficulty reaching me, please also contact Vicki Drews, Director of Global Regulatory Affairs, at (847) 473-6296. I have also copied Ms. Drews on this e-mail as she intends to participate in any labeling teleconference with FDA.

Thank you and kind regards,

Stacey S. Thompson
Senior Manager
Baxter Healthcare Corporation
Regulatory Affairs & Pharmacovigilance
1620 Waukegan Road
McGaw Park, IL 60085 USA

~~~~~  
Phone: (847) 473-6370 (Tie Line 895+6370)

Fax: (847) 785-5107

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## FDA RESPONSE TO YOUR QUESTIONS

The following are the Division's responses to your concerns about the Agency's labeling proposal, sent on December 18, 2007, for NDA 50-817, Cefepime Injection in Galaxy Container Package Insert.

The original question is reproduced in italic below, followed by the Division's response.

### Areas of Concern:

*Section 8.1 - Pregnancy: The first paragraph references ratios of doses (e.g., 1.6 times, 0.3 times, etc.) that are different from the current labeling of the Reference Listed Drug (Maxipime). We are unable to verify the accuracy of the new numbers and would like to discuss with FDA the basis for this change.*

**Division's Response:** The dose multiple calculations for the original Maxipime label were based on a lower maximum recommended human daily dose than is the current standard (6 g/day). The dose multiples were recalculated based on the current maximum recommended human dose and the label was modified accordingly.

The rationale for the calculations are as follows:

The highest recommended clinical dose of cefepime is 2 g every 8 hours, for a total of 6 g per day. In a 60 kg person, this is a 100 mg/kg dose. Using a conversion factor of 37, this dose can be converted to 3700 mg/m<sup>2</sup>. It is appropriate to base dose comparisons for systemically distributed intravenous drug products using body surface area when there are not sufficient animal pharmacokinetic data available for comparison to human. The reproduction toxicity studies in rats, mice, and rabbits used doses up to \_\_\_\_\_ respectively. Using conversion factors for each species of 6 (rat), 3 (mouse), and 12 (rabbit), these doses convert to 6000 mg/m<sup>2</sup>, 3600 mg/m<sup>2</sup>, and 1200 mg/m<sup>2</sup>. In turn, the comparison of these doses to the maximum recommended human dose are: rat, 1.6X; mouse, approximately equal, and rabbit, 0.3X. b(4)

The innovator has also been requested to make these label modifications.

*Section 12.4 - Microbiology (subheading, Facultative Gram-Negative Microorganisms): A bacterial isolate \_\_\_\_\_ has been removed. Baxter would like to discuss why this isolate was removed, as it is still listed in the Reference Listed Drug (Maxipime) direct insert.* b(4)

**Division's Response:** \_\_\_\_\_ was removed because there is *Enterobacter* spp. in the first list which technically covers all the species of *Enterobacter*. Please add "spp." after *Enterobacter* in line 440. The line 440 should now read, "*Enterobacter* spp." b(4)

*Section 12.4 - Microbiology (Table 9): There is a \_\_\_\_\_ that is found in the CLSI Performance Standard added as Reference 4 in Section 15, References.*

b(4)

**Division's Response:** The \_\_\_\_\_ was removed because Disk diffusion testing of *S. pneumoniae* has been found to be unreliable. In fact under Table 8, it was stated that susceptibility to cefepime as determined by disk diffusion testing should be done with an oxacillin disk not with a \_\_\_\_\_

b(4)

b(4)

\_\_\_\_\_. Additionally, we have done some rearrangement and rewording which hopefully clarifies this in the label (see lines 506 - 507).

*Section 13.1 - Carcinogenesis, Mutagenesis, Impairment of Fertility: The second half of this paragraph was revised by the FDA. The following revision was made.*

b(4)

\_\_\_\_\_. Also, the subcutaneous ratio dose is now reported as "1.6 times," which is different from the previously reported \_\_\_\_\_. We are unable to verify the accuracy of the new text and numbers as it is no longer consistent with the current direction insert of the Reference Listed Drug (Maxipime), so we would like to discuss with FDA the basis for this change.

**Division's Response:** The Carcinogenesis, Mutagenesis, Impairment of Fertility Section has been edited to remove the \_\_\_\_\_. As discussed above, the dose multiple has been recalculated based on the current maximum recommended human dose. The innovator has also been requested to make these label modifications.

b(4)

Other proposals/recommendations:

*Section 12.1 - Mechanism of Action: FDA has proposed a single sentence, "Cefepime is an antibacterial drug. [See Clinical Pharmacology (12.4)]."*

*We recommend that FDA consider that the sentence as currently proposed is not necessarily a "mechanism of action" sentence; it is really just a statement of the drug class. It does not tell "how" the drug works, which is what we believe a mechanism of action should describe. Thus, we would recommend that sentence be replaced by:*

*"Cefepime is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. [See Microbiology (12.4)]."*

OR

*Return this section back to our original submission, which would involve taking the first paragraph from Section 12.4 - Microbiology and placing it back into Section 12.1 - Mechanism of Action as follows:*

**Division's Response:** The wording chosen for Section 12.1 is consistent with the new PLR format requirement used in recent antibacterial approved labels.

**Section 12.3 - Pharmacokinetics (Table 6):** Data in columns 1-3 of this table are missing and we assume this was an error. Baxter intends to re-insert the numbers in the columns to match those of the Reference Listed Drug (Maxipime). We would like FDA concurrence that this is appropriate.

**Division's Response:** Yes, this was an error. The table 6 should appear as below.

**Table 6: Average Plasma Concentrations in mcg/mL of Cefepime and Derived Pharmacokinetic Parameters ( $\pm$ SD), Intravenous Administration**

| Parameter                 | CEFEPIME   |              |              |
|---------------------------|------------|--------------|--------------|
|                           | 500 mg IV  | 1 g IV       | 2 g IV       |
| 0.5 h                     | 38.2       | 78.7         | 163.1        |
| 1 h                       | 21.6       | 44.5         | 85.8         |
| 2 h                       | 11.6       | 24.3         | 44.8         |
| 4 h                       | 5          | 10.5         | 19.2         |
| 8 h                       | 1.4        | 2.4          | 3.9          |
| 12 h                      | 0.2        | 0.6          | 1.1          |
| C <sub>max</sub> , mcg/mL | 39.1 (3.5) | 81.7 (5.1)   | 163.9 (25.3) |
| AUC, h*mcg/mL             | 70.8 (6.7) | 148.5 (15.1) | 284.8 (30.6) |
| Number of subjects (male) | 9          | 9            | 9            |

**Minor edits and formatting revisions -** For completeness, we want you to be aware that we will also be making minor edits and formatting revisions. However, we do not expect any of these minor edits and format revisions to meaningfully affect the content of the information or the prominence of its presentation as proposed by FDA,

**Division's Response:** Please create an itemized list of your revisions.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Kyong Hyon  
12/26/2007 10:29:05 AM  
CSO

Kathrine Laessig  
12/27/2007 10:44:05 AM  
MEDICAL OFFICER

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 50-817 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Cefepime Injection in GALAXY Container (PL 2040 Plastic)  
Established Name: Cefepime Injection  
Strengths: 1g/50 mL and 2g/100 mL

Applicant: Baxter Healthcare Corporation  
Agent for Applicant (if applicable): N/A

Date of Application: 02/28/2007

Date of Receipt: 03/01/2007

Date clock started after UN: N/A

Date of Filing Meeting: 04/18/2007

Filing Date: 4/30/2007

Action Goal Date (optional):

User Fee Goal Date: 01/01/2008

Indication(s) requested: Treatment of various infections caused by susceptible strains of microorganisms (same indications are proposed as MAXIPIME)

Type of Original NDA: (b)(1)  (b)(2) x  
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P   
Resubmission after withdrawal? NO Resubmission after refuse to file? NO  
Chemical Classification: (1,2,3 etc.) 3S  
Other (orphan, OTC, etc.) N/A

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

User Fee Status: Paid X Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO X  
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO X
- 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  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO X  
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO X
- Does the submission contain an accurate comprehensive index? YES X NO  
If no, explain:
- Was form 356h included with an authorized signature? YES X NO  
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES X NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA N/A YES
2. This application is an eNDA or combined paper + eNDA YES X  
This application is: All electronic  Combined paper + eNDA X  
This application is in: NDA format  CTD format X  
Combined NDA and CTD formats

Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) N/A X YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?  
The electronic submission is Labeling and it is in SPL format

Additional comments:

3. This application is an eCTD NDA. N/A X YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO X  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO X

*No independent study was done- 505(b)(2) application*

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes
- List referenced IND numbers: PIND 73, 452
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO X  
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) April 24, 2006 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO X  
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES X NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO X
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES  NO
- Risk Management Plan consulted to OSE/IO? N/A X YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? N/A X YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO X

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES X NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 18, 2007

NDA #: 50-817

DRUG NAMES: Cefepime Injection in GALAXY Container (PL 2040 Plastic)

APPLICANT: Baxter Healthcare Corporation

BACKGROUND: The proposed products are "ready to use" premixed IV formulations of the Reference Listed Drug, MAXIPIME (Cefepime Hydrochloride) for injection (NDA 50-679, held by Bristol-Myers Squibb, approved on 01/18/96). MAXIPIME is for IV and IM use and must be reconstituted with a suitable diluent prior to use. The proposed 1g/50 mL and 2g/100 mL premixed products in flexible plastic container are for IV use only and are stored frozen.

ATTENDEES: Janice Soreth, Sumathi Nambiar, Alma Davidson, Jefferey Tworzanski, Avery Goodwin, Scott Komo, Yan Wang, Zhou Chen, Amy Ellis, Rapti Madurawe, Milton Sloan, Nancy Boocker, Kyong Hyon

ASSIGNED REVIEWERS (including those not present at filing meeting):

| <u>Discipline/Organization</u>                            | <u>Reviewer</u>    |
|-----------------------------------------------------------|--------------------|
| Medical:                                                  | Alma Davidson      |
| Statistical:                                              | Yan Wang           |
| Pharmacology:                                             | Amy Ellis          |
| Statistical Pharmacology:                                 | N/A                |
| Chemistry:                                                | Milton Sloan       |
| Environmental Assessment (if needed):                     | N/A                |
| Biopharmaceutical:                                        | Jeffery Tworzanski |
| Microbiology, sterility:                                  | N/A                |
| Microbiology, clinical (for antimicrobial products only): | Avery Goodwin      |
| DSI:                                                      |                    |
| OPS:                                                      |                    |
| Regulatory Project Management:                            | Kyong Hyon         |
| Other Consults: 505(b)(2) Application                     | Nancy Boocker      |

Per reviewers, are all parts in English or English translation? YES X NO   
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO X  
If no, explain: No clinical trials are included in this submission
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

|                                                                       |     |                          |                                     |                                     |                          |                                     |                                        |
|-----------------------------------------------------------------------|-----|--------------------------|-------------------------------------|-------------------------------------|--------------------------|-------------------------------------|----------------------------------------|
|                                                                       |     | N/A                      | <input checked="" type="checkbox"/> | YES                                 | <input type="checkbox"/> | NO                                  | <input type="checkbox"/>               |
| CLINICAL MICROBIOLOGY                                                 | N/A | <input type="checkbox"/> | FILE                                | <input checked="" type="checkbox"/> | REFUSE TO FILE           | <input type="checkbox"/>            |                                        |
| STATISTICS                                                            | N/A | <input type="checkbox"/> | FILE                                | <input checked="" type="checkbox"/> | REFUSE TO FILE           | <input type="checkbox"/>            |                                        |
| BIOPHARMACEUTICS                                                      |     |                          | FILE                                | <input checked="" type="checkbox"/> | REFUSE TO FILE           | <input type="checkbox"/>            |                                        |
|                                                                       |     |                          |                                     |                                     | YES                      | <input type="checkbox"/>            | NO <input checked="" type="checkbox"/> |
| • Biopharm. study site audits(s) needed?                              |     |                          |                                     |                                     |                          |                                     |                                        |
| PHARMACOLOGY/TOX                                                      | N/A | <input type="checkbox"/> | FILE                                | <input checked="" type="checkbox"/> | REFUSE TO FILE           | <input type="checkbox"/>            |                                        |
|                                                                       |     |                          |                                     |                                     | YES                      | <input type="checkbox"/>            | NO <input checked="" type="checkbox"/> |
| • GLP audit needed?                                                   |     |                          |                                     |                                     |                          |                                     |                                        |
| CHEMISTRY                                                             |     |                          | FILE                                | <input checked="" type="checkbox"/> | REFUSE TO FILE           | <input type="checkbox"/>            |                                        |
|                                                                       |     |                          |                                     |                                     | YES                      | <input checked="" type="checkbox"/> | NO <input type="checkbox"/>            |
| • Establishment(s) ready for inspection?                              |     |                          |                                     |                                     | YES                      | <input checked="" type="checkbox"/> | NO <input type="checkbox"/>            |
| • Sterile product?                                                    |     |                          |                                     |                                     |                          |                                     |                                        |
| • If yes, was microbiology consulted for validation of sterilization? |     |                          |                                     |                                     | YES                      | <input checked="" type="checkbox"/> | NO <input type="checkbox"/>            |

**ELECTRONIC SUBMISSION:**

Any comments: The Labeling is in SPL format

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Kyong Hyon

Regulatory Project Manager, HFD-520, DAIOP

## Appendix A to NDA Regulatory Filing Review

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

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

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

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

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

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES X NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): MAXIPIME (Cefepime Hydrochloride) for Injection, IV or IM (NDA 50-679, held by Bristol-Myers Squibb, approved on 01/18/96)
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES X NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES  NO X

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) 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.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO X

(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))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

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

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO

*(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.)*

If "No," to (a) skip to question 7. Otherwise, answer part (b) and (c).

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

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

If "Yes," to (c), proceed to question 7.

**NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO X

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. 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").

*This application provides a change in dosage form and formulation composition, from reconstituted MAXIPIME for IV or IM use to premixed IV use only products*

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO X

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made YES  NO X

available to the site of action less than that of the reference listed drug (RLD)?  
(See 314.54(b)(1)). If yes, the application may be refused for filing under  
21 CFR 314.101(d)(9)).

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO  X
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO  X

*The Applicant submitted Paragraph I Patent Certification.*

13. 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.)

Not applicable (e.g., solely based on published literature. See question # 7)

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

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):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

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):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents. FORM FDA 3542a submitted

- 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):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  X NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug (MAXIPIME- NDA 50-679)*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  X NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  X YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO  X

If "Yes," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|-----------------|-------------|------------------|------------------------|
|                 |             |                  |                        |
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/s/  
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Kyong Hyon  
12/21/2007 04:43:24 PM  
CSO

Kyong Hyon  
12/21/2007 04:46:09 PM  
CSO

## MEMORANDUM OF TELECON

DATE: July 25, 2007

APPLICATION NUMBER: NDA 50-679 (Maxipime)

BETWEEN:

Name: Dr. Margo Heath- Chiozzi  
Phone: 203-677-3819  
Representing: Bristol Myers Squibb

AND

Division of Anti-Infective and Ophthalmology Products (DAIOP)

Name: Sumathi Nambiar, MD – Medical Team Leader  
Frances LeSane – Project Manager

SUBJECT: Publication entitled "Efficacy and safety of cefepime: a systematic review and meta-analysis" published in Lancet Infectious Disease Journal, May 2007, 7(5):338-48 (Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. ).

This call was made to the sponsor to see if they were aware of the publication. Dr. Heath-Chiozzi was aware of the publication and asks that we sent an email with our questions and she would get back to us after meeting with management. The following email/wording was sent.

Per our conversation earlier today, please note the following questions regarding the publication entitled "Efficacy and safety of cefepime: a systematic review and meta-analysis" published in Lancet Infectious Disease Journal, May 2007, 7(5):338-48 (Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. ).

1. Sponsor's interpretation and comments regarding the article.
2. Changes to the product label if any.

Please indicate your timeline for submission response. If you have any questions, please call or email me at the address below.

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/s/

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Frances LeSane  
10/30/2007 09:54:14 AM  
CSO

**From:** LeSane, Frances V  
**Sent:** Wednesday, July 25, 2007 6:22 PM  
**To:** 'margo.heath-chiozzi@bms.com'  
**Cc:** Hyon, Kyong; Nambiar, Sumathi  
**Subject:** Cefepime Metanalysis Paper

Dear Margo,

Per our conversation earlier today, please note the following questions regarding the publication entitled "Efficacy and safety of cefepime: a systematic review and meta-analysis" published in Lancet Infectious Disease Journal, May 2007, 7(5):338-48 ([Yahav D, Paul M, Fraser A, Sarid N, Leibovici L.](#)).

1. Sponsor's interpretation and comments regarding the article.
2. Changes to the product label if any.

Please indicate your timeline for submission response. If you have any questions, please call or email me at the address below.

Thanks,  
Fran

---

Frances V. LeSane  
Chief, Project Management Staff  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Phone: 301-796-0747  
Fax: 301-796-9881  
[frances.lesane@fda.hhs.gov](mailto:frances.lesane@fda.hhs.gov)

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/s/

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Frances LeSane  
10/30/2007 09:50:35 AM  
CSO



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-817

Baxter Healthcare Corporation  
Attention: Vicki L. Drews  
Associate Director, Global Regulatory Affairs  
1620 Waukegan Road  
McGraw Park, IL 60085

Dear Ms. Drews:

Please refer to your new drug application (NDA) Cefepime Injection in Galaxy Container (PL 2040 Plastic) (cefepime injection).

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding cefepime. The safety update should include data from all non-clinical and clinical studies of cefepime regardless of indication, dosage form, or dose level and should also include a review of the published literature regarding cefepime regardless of the indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile of cefepime.
2. Provide a summary of worldwide experience on the safety of cefepime.
3. Provide English translations of current approved foreign labeling for cefepime.

Please submit this information as soon as possible.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at 301-796-0734.

Sincerely,

*{See appended electronic signature page}*

Katherine Laessig, M.D.  
Deputy Director  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Kathrine Laessig  
10/25/2007 09:52:25 AM



NDA 50-817

DISCIPLINE REVIEW LETTER

Baxter Healthcare Corporation  
Attention: Vicki L. Drews  
Associate Director, Global Regulatory Affairs  
1620 Waukegan Road  
McGraw Park, IL 60085

Dear Ms. Drews:

Please refer to your February 28, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefepime Injection in Galaxy Container.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

**Container Label (1 G and 2 G bags):**

1. Delete the use of "Tall Man" lettering and use a standard upper/lower case presentation, e.g. Cefepime Injection.
2. Your Company name appears as prominently as the established name on the label. Decrease the font of your company name to increase the prominence of the established name.



3. The use of a white background behind your company name, Baxter, in black print and the established name and product strength in red print on several cephalosporins in the GALAXY™ Container product line. The use of the same color background increases the potential for confusion between cephalosporins in Galaxy™ Containers. We recommend the use of black print for the established name for both strengths of Cefepime for injection to better distinguish this product from the other cephalosporins in Galaxy™ Containers.

- The strengths of Cefepime are differentiated by the use of different color print, black for the 1 g bag and red for the 2 g bag. The 2 g bag will also be larger than the 1 g bag. However, the use of the same color background increases the potential for the strengths to be confused. We recommend continued use of black and red to distinguish the strengths (1 g vs. 2 g) as well as using an additional means such as bolding, boxing, or some other means of differentiating the strength to decrease the potential of confusion between the strengths.

**1 g**

Leave the strengths as these distinguishing colors, but add another differentiating characteristic (e.g. boxing).

**2 g**

L  
L  
L  
L

L  
L

L

b(4)

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at 301-796-0734.

Sincerely,

*{See appended electronic signature page}*

Wiley Chambers, M.D.  
Acting Director  
Division of Anti-Infective and Ophthalmology Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Wiley Chambers  
10/25/2007 09:45:08 AM



NDA 50-817

INFORMATION REQUEST LETTER

Baxter Healthcare Corporation  
Attention: Vicki L. Drews  
Associate Director, Global Regulatory Affairs  
1620 Waukegan Road  
McGaw Park, IL 60085

Dear Ms. Drews:

Please refer to your February 28, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefepime Injection in GALAXY Container (PL 2040 Plastic), 1g/50 mL and 2g/100 mL.

We have reviewed your proposed labeling and have identified the following issues and/or deficiencies:

**Highlights**

- Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- Delete \_\_\_\_\_ above the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section.
- The \_\_\_\_\_ statement at the right upper corner of the Highlights page of the label should be deleted. This statement is not required for package insert labeling, only container labels and carton labeling.
- Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
- The drug name must be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)] Please revise to include route of administration.
- The following statement regarding antibiotic resistance should follow after the initial US approval date. [See 21 CFR 201.24]: "To reduce the development of drug-resistant bacteria and maintain the effectiveness of TRADENAME and other antibacterial drugs, TRADENAME should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria".
- In the table and under DOSAGE AND ADMINISTRATION, an asterisk (\*) should not be used to footnote information (an alternate symbol should be chosen) as the asterisk is used in the table of contents to footnote other information.
- Do not include the pregnancy category in Highlights. [See comment #34 Preamble]
- For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval.
- The trade name, "Cefepime Injection in Galaxy Container" in the highlights should not be italic.

b(4)

**Full Prescribing Information**

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Dosage and Administration (2) and Use in Specific Populations (8.4)] not [see Dosage and Administration (2) and Use in Specific Populations (8), Pediatric Use (8.4)]. Please correct the cross-references throughout the labeling. [See PLR Implementation Guidance]
- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
- All text of new paragraphs should consistently be either left justified or indented throughout the labeling.
- The preferred presentation of subsection headings should not be imbedded in the content. For example, the

subsection heading "1.1 Pneumonia" should be above the content that it represents. Please correct the subsection headings throughout the labeling.

- Avoid Latin abbreviations because of the greater potential for medication errors should an abbreviation be misread (e.g., QD being misread as QID). For example, q12h should be changed to every 12 hours. Please change all Latin abbreviations throughout the labeling. Refer to the Institute for Safe Medication Practices (ISMP's) website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for list of error-prone abbreviations, symbols, and dose designations.
- Throughout the FULL PRESCRIBING INFORMATION text, the phrases such as "THAWING OF PLASTIC CONTAINER", "DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION", "CEFEPIME INJECTION SHOULD BE ADMINISTERED INTRAVENOUSLY OVER APPROXIMATELY 30 MINUTES", should not be bolded and should not use all capital letters. Use another method for emphasis such as italics or underline.
- The revision date at the end of the highlights replaces the "\_\_\_\_\_ date at the end of the labeling. The revision date should not appear in both places. b(4)
- Laboratory Tests and Drug/Laboratory interaction should be under 5 WARNINGS AND PRECAUTIONS section not under other labeling sections.
- The standard paragraph, "Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice." should be inserted under 6.1 Clinical Studies Experience.
- Regarding references, are these references necessary? Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
- At the end of the labeling, following changes should be made:
  - 1) Unbold the company name
  - 2) Add, "Manufactured by":, above company name, Baxter Healthcare Corporation.
  - 3) Delete everything starting. ' \_\_\_\_\_ ' to "Revised November 2006." b(4)

Please address the identified deficiencies/issues and re-submit labeling by July 13, 2007 This updated version of labeling will be used for further labeling discussions.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at 301-796-0734.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Frances LeSane

6/27/2007 12:11:20 PM

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|--|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                   | <b>REQUEST FOR CONSULTATION</b>    |                                                                                                                                                                                         |                                                    |  |
| TO (Division/Office):<br><b>Director, Division of Medication Errors and<br/>Technical Support (DMETS), HFD-420<br/>WO22, RM 4447</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                   |                                    | FROM: Kyong Hyon, RPM, Division of Anti-Infective and<br>Ophthalmology Products, WO22, RM6345                                                                                           |                                                    |  |
| DATE<br>5-22-07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | IND NO.<br>73,452 | NDA NO.<br>50-817                  | TYPE OF DOCUMENT<br>General Correspondence                                                                                                                                              | DATE OF DOCUMENT<br>February 28, 2007              |  |
| NAME OF DRUG<br>Cefepime Injection in<br>GALAXY Container                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                   | PRIORITY CONSIDERATION<br>standard | CLASSIFICATION OF DRUG<br>4010300                                                                                                                                                       | DESIRED COMPLETION DATE<br>July 31, 2007 or sooner |  |
| NAME OF FIRM: <b>Baxter Healthcare Corporation</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>Trade name review</b> |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                   |                                    | STATISTICAL APPLICATION BRANCH                                                                                                                                                          |                                                    |  |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                                    | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW):      |                                                    |  |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   |                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                            |                                                    |  |
| <b>IV. DRUG EXPERIENCE</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                   |                                    | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |                                                    |  |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |                                    | <input type="checkbox"/> PRECLINICAL                                                                                                                                                    |                                                    |  |
| COMMENTS/SPECIAL INSTRUCTIONS: <b>Baxter Healthcare Corporation has submitted a b2 application. Please provide review of the trade name and labeling. Thank you! The labeling submission is located in the EDR.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| <b>PDUFA DATE: January 1, 2008</b><br><b>ATTACHMENTS: Draft Package Insert, Container and Carton Labels</b><br><b>CC: Archival IND/NDA 50-817</b><br><b>HFD-520/Division File</b><br><b>HFD-520/RPM</b><br><b>HFD-520/Reviewers and Team Leaders</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                   |                                    |                                                                                                                                                                                         |                                                    |  |
| NAME AND PHONE NUMBER OF REQUESTER<br><b>Kyong Hyon, 301-796-0734</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   |                                    | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND                                              |                                                    |  |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                   |                                    | SIGNATURE OF DELIVERER                                                                                                                                                                  |                                                    |  |

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/s/

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Frances LeSane  
6/4/2007 12:12:11 PM

## REQUEST FOR CONSULTATION

TO (Office/Division): **Dr. David Hussong/OPS/NDMS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Linda Athey/ONDQA 301-796-2096**

DATE  
**5-17-07**

IND NO.

NDA NO.  
**50-817**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**March 2, 2007**

NAME OF DRUG  
**Cefepime Injection,  
1g/50mL and 2g/100mL**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
**June 22, 2007**

NAME OF FIRM: **Baxter Healthcare Corporation**

### REASON FOR REQUEST

#### I. GENERAL

- |                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### II. BIOMETRICS

- |                                                                                                                                                                                                                                                 |                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### III. BIOPHARMACEUTICS

- |                                                                                                                                      |                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### IV. DRUG SAFETY

- |                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: **Quality Micro consult requested for NDA 50-817 and their supporting DMF 6344. \\CDSESUB1\NONECTD\N22133\N\_000\2007-02-28.**

This is a 505(b)(2) application and we had a Pre-NDA meeting on April 24, 2006 with Baxter under PIND 73, 452. Baxter is planning to formulate "premixed" cefepime Injection (1g/50 mL and 2g/100 mL) by mixing cefepime injection with 50 mL and 100 mL of \_\_\_\_\_ in Galaxy flexible plastic containers.

Under PIND 73, 452, Jeff Tworzanski did the clinical pharmacology review; Yan Wang did the statistical review; Jim Blank did the clinical review; Amy Ellis did the PharmTox Review; Avery Goodwin did the Micro review; and Milton Sloan did the CMC review.

SIGNATURE OF REQUESTOR  
**Linda Athey**

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Linda D Mullins-Athey  
5/17/2007 11:44:13 AM



**FILING COMMUNICATION**

NDA 50-817

Baxter Healthcare Corporation  
Attention: Vicki L. Drews  
Associate Director, Global Regulatory Affairs  
1620 Waukegan Road  
McGaw Park, IL 60085

Dear Ms. Drews:

Please refer to your February 28, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cefepime Injection in GALAXY Container (PL 2040 Plastic), 1g/50 mL and 2g/100 mL.

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)(2) of the Act on April 30, 2007 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 Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Frances LeSane  
5/15/2007 04:14:08 PM

## NDA FILEABILITY CHECKLIST

**NDA Number:** 50-817

**Applicant:** Baxter

**Stamp Date (Electronic Submission):** 01-March-2007

**Drug Name:** Cefepime Injection in GALAXY Container (PL2040 Plastic)

**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.

|    | <b>Parameter</b>                                                                                                                       | <b>Yes</b>            | <b>No</b>             | <b>Comment</b>                                                      |
|----|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-----------------------|---------------------------------------------------------------------|
| 1  | On its face, is the section organized adequately?                                                                                      | <input type="radio"/> |                       | The CMC section of the NDA is organized in the standard CTD format. |
| 2  | Is the section indexed and paginated adequately?                                                                                       | <input type="radio"/> |                       |                                                                     |
| 3  | On its face, is the section legible?                                                                                                   | <input type="radio"/> |                       |                                                                     |
| 4  | Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs? | <input type="radio"/> |                       |                                                                     |
| 5  | Is a statement provided that all facilities are ready for GMP inspection?                                                              | <input type="radio"/> |                       |                                                                     |
| 6  | Has an environmental assessment report or categorical exclusion been provided?                                                         | <input type="radio"/> |                       | A claim for categorical exclusion has been made.                    |
| 7  | Does the section contain controls for the drug substance (s)?                                                                          | <input type="radio"/> |                       | The drug substance is referenced in a DMF and has a USP monograph.  |
| 8  | Does the section contain controls for the drug product?                                                                                | <input type="radio"/> |                       |                                                                     |
| 9  | Has stability data and analysis been provided to support the requested expiration date?                                                | <input type="radio"/> |                       |                                                                     |
| 10 | Has all information requested during the IND phase, and at the pre-NDA meetings been included?                                         | <input type="radio"/> |                       |                                                                     |
| 11 | Have draft container labels been provided?                                                                                             | <input type="radio"/> |                       |                                                                     |
| 12 | Has the draft package insert been provided?                                                                                            | <input type="radio"/> |                       |                                                                     |
| 13 | Has an investigational formulations section been provided?                                                                             |                       | <input type="radio"/> | N/A                                                                 |
| 14 | Is there a Methods Validation package?                                                                                                 | <input type="radio"/> |                       |                                                                     |
| 15 | Is a separate microbiological section included?                                                                                        | <input type="radio"/> |                       | Included in DMF. Request for quality micro consult should be made.  |

**Have all DMF References been identified?**



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/s/

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Milton Sloan  
4/18/2007 04:32:13 PM  
CHEMIST  
No issues identified

Norman Schmuff  
4/19/2007 03:14:11 PM  
CHEMIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 50-817

**NDA ACKNOWLEDGMENT**

Baxter Healthcare Corporation  
Attention: Vicki L. Drews  
Associate Director, Global Regulatory Affairs  
1620 Waukegan Road  
McGaw Park, IL 60085

Dear Ms. Drews:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Cefepime Injection in GALAXY Container (PL 2040 Plastic), 1g/50 mL  
and 2g/100 mL

Review Priority Classification: Standard (S)

Date of Application: February 28, 2007

Date of Receipt: March 1, 2007

Our Reference Number: NDA 50-817

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 30, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 1, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 50-817

Page 2

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective and Ophthalmology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Frances LeSane  
3/15/2007 05:28:31 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 73, 452

Baxter Healthcare Corporation  
Attention: Stacey S. Thompson,  
Senior Manager, Global Regulatory Affairs  
1620 Waukegan Road  
McGaw Park, IL 60085

Dear Mr. Thompson:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Cefepime Injection 1 g/50 mL and 2 g/100 mL for IV administration.

We also refer to the teleconference between representatives of your firm and the FDA on April 24, 2006. The purpose of the meeting was to address the proposed content of the 505(b)(2) application for premixed formulation of Cefepime Injection and obtain Division's input on development of your study strategy.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure

# MEMORANDUM OF TELECON

**DATE:** April 24, 2006

**APPLICATION NUMBER:** PIND 73,452

**DRUG:** Cefepime Injection 1 g/50mL and 2 g/100mL

**BETWEEN:**

**Name:** Representatives from Baxter Healthcare Corporation

Dr. Mohsen Arghavani, PhD, Manager, Product Development  
Dr. Andrew Brugger, MD, Medical Director, Clinical Affairs  
Dr. Jon Cammack, PhD, DABT, Vice President, Technology Resources  
Ms. Vicki Drews, Associate Director, Regulatory Affairs  
Ms. Amy Giertych, Senior Director, Regulatory Affairs  
Mr. Jim Gorski, Associate Director, Stability Operations

Mr. William Hayward, Associate Research Scientist, Stability Operations

b(4)

Mr. Jeff McKee, Research Scientist, Technology Resources  
Dr. Neervalur Raghavan, PhD, Vice President, Product Development  
Mr. Stacey Thompson, Senior Manager, Regulatory Affairs

**Phone:** 1-866-248-0558

**AND**

**Name:** Representatives from Division of Anti-Infective and Ophthalmology Products (DAIOP) HFD-520

Lillian Gavrilovich, MD, Deputy Director  
Sumathi Nambiar, MD, MPH, Medical Team Leader  
James Blank, PhD, Clinical Reviewer  
Terry Peters, DVM, Acting Pharmacology/Toxicology Team Leader  
Jeffery Tworzanski, PhD, Biopharmaceutical Reviewer  
Yan Wang, PhD, Statistical Reviewer  
Norman Schmuff, PhD, Chemistry Team Leader  
Milton Sloan, PhD, Chemistry Reviewer  
Kyong Hyon, RN, MA, Regulatory Project Manager

**BACKGROUND:** This meeting was requested by the Sponsor on February 10, 2006. The Sponsor submitted questions for the meeting discussion in their meeting package on March 22, 2006 to which the Division had responded on April 21, 2006.

**MEETING OBJECTIVES:** The overall objective of the requested meeting was for the Sponsor to obtain Agency concurrence on the proposed content of the 505(b)(2) application for the Baxter premixed formulation of Cefepime Injection.

**DISCUSSION POINTS:** The following is a summary of the minutes of the teleconference held on April 24, 2006, including prior communication. The Sponsor's initial questions are in bold followed by responses from the Division and the points discussed during the teleconference.

**Clinical Question: Baxter intends to reference the clinical studies described in NDA 50-679 for MAXIPIME as the sole source of clinical data to support its premixed presentations of Cefepime Injection. Does the Agency agree that no additional clinical studies will be required to support approval of Baxter's 505(b)(2) application?**

Agency Response (per April 21, 2006 via e-mail): Yes. Additional clinical studies will not be necessary to support your 505(b)(2) application. However, you will not be able to directly refer to the clinical studies described in NDA 50-679. Instead, you will be relying upon the Agency's previous finding of safety and effectiveness to support the approval of your proposed drug product.

Discussion at the April 24, 2006 teleconference: No further discussion was needed.

**Pharmacokinetics Question: Baxter intends to reference the pharmacokinetic (PK) studies described in NDA 50-679 for MAXIPIME as the sole source of PK data to support its premixed presentations of Cefepime Injection. Does the Agency agree that no additional PK studies will be required to support approval of Baxter's 505(b)(2) application?**

Agency Response (per April 21, 2006 via e-mail): Yes. Additional pharmacokinetic (PK) studies will not be necessary to support your 505(b)(2) application. As noted above, you will not be able to directly refer to the pharmacokinetic (PK) studies described in NDA 50-679. Instead, you will be relying upon the Agency's previous finding of safety and effectiveness to support the approval of your proposed drug product.

Discussion at the April 24, 2006 teleconference: No further discussion was needed.

**Preclinical Questions: Baxter intends to reference the preclinical studies described in NDA 50-679 for MAXIPIME to support its premixed presentations of Cefepime Injection. Additionally, safety studies are proposed to qualify levels of certain impurities.**

**Does the Agency agree that impurity levels that exceed both the ICH qualification threshold and levels observed in the innovator product (MAXIPIME) can be qualified through the conduct of the proposed safety studies?**

Agency Response (per April 21, 2006 via e-mail): Your plan to qualify impurity and degradation product levels is acceptable from the nonclinical toxicology standpoint. We would, however, like to know which genotoxicity tests you plan to perform. Our assumption is that you would perform a standard battery, including *in vitro* tests covering both mutation and clastogenesis along with an *in vivo* rodent micronucleus test.

Discussion at the April 24, 2006 teleconference: The Sponsor stated that in ICH guidance on impurities consist of genotoxicity studies of point mutation, gene mutation, chromosomal aberrations, mouse lymphoma assay and human lymphocyte assay. The Sponsor inquired which

genotoxicity studies they should perform and requested Agency's rationale for recommending to perform the *in vivo* assay. The Agency stated that they believe in a comprehensive assay battery and the micronucleus assay test should be performed in addition to ICH impurity guidance because \_\_\_\_\_ has potential for genotoxicity. The Agency also responded that they are complying with the ICH guideline in that *in vivo* assay is also recommended as well as *in vitro* assays. b(4)

In summary, the Sponsor plans to perform following genotoxicity studies both in *in vitro* and *in vivo*: point of mutation, gene mutation, chromosomal aberrations, mouse lymphoma assay and human lymphocyte assay.

**Does the agency agree that no additional preclinical studies will be required to support approval of Baxter's 505(b)(2) application?**

Agency Response (per April 21, 2006 via e-mail): Additional nonclinical testing (beyond what you have proposed) will not be necessary to support your 505(b)(2) application.

**Chemistry Questions: Does the Agency agree that the proposed stability data package provides support for filing the proposed 505(b)(2) application and allows approval of at least \_\_\_\_\_ frozen expiration period? (Refer to Section 10, CMC Information)**

Agency Response(per April 21, 2006 via e-mail): No. We consider the proposed stability data inadequate to support the proposed expiry of \_\_\_\_\_ at -20°C. For \_\_\_\_\_ expiry, at -20°C, we expect to see at least 6 months of primary stability data at the proposed storage conditions; and appropriate supportive data from at least one lot of drug product stored at either 5°C or 25°C. b(4)

Discussion at the April 24, 2006 teleconference: The Sponsor plans to perform \_\_\_\_\_ for their stability study; the Sponsor inquired if it would be sufficient to obtain \_\_\_\_\_ frozen expiration period. The Agency responded that they are interested in seeing degradation profile. The Sponsor was asked how much degradation was anticipated, responded \_\_\_\_\_ expect \_\_\_\_\_. The Agency responded that they would expect to see approximately \_\_\_\_\_ degradation. [Post-teleconference note: The \_\_\_\_\_ figure is more in line with what would be expected in stress studies, which would be conducted independently. These levels might not necessarily be seen in accelerated studies.] b(4)

**Does the Agency agree that the proposed approach to setting specifications for related compounds and \_\_\_\_\_ is acceptable (i.e., that a higher limit, based on the levels qualified in the safety studies, may be applied to the product even though the actual values for related compounds and \_\_\_\_\_ generated on stability studies may be lower? (Refer to Section 10, CMC Information).** b(4)

Agency Response(per April 21, 2006 via e-mail):

No. Impurity acceptance criteria should be less than the level qualified. The acceptance criteria should be set based on manufacturing capability from the batches of the new drug product manufactured by the proposed commercial process, allowing sufficient latitude to deal with manufacturing and analytical variation.

Discussion at the April 24, 2006 teleconference: The Agency was asked to discuss their response sent to the Sponsor on April 21, 2006. The Agency indicated that in line with ICH Q3 Impurity Guidance, the consideration would be given to the manufacturing

capability and the expected variability of normal manufacture and analytical procedures. The Sponsor inquired about drug substance variability, and the Agency responded that all sources of variability would be considered. The Sponsor stated that they understood the Agency's position and perhaps their question was misleading in that it implied setting the acceptance criteria at the qualified level.

Additional Comments (per April 21, 2006 via e-mail): The Sponsor should include a manufacturing portion of the application with a separate section on sterility assurance.

Discussion at the April 24, 2006 teleconference: The Sponsor inquired if the additional comment on sterility assurance was related to impurities. The Agency responded that it was not, and it is simply related to having a separate package or section for Agency's sterile assurance to review. It was mentioned by the Agency that some applicants have submitted applications that do not adequately allow for separate review of the sterile assurance section.

The Sponsor proposed to perform stability studies on 2 lots of each package configuration (50 mL and 100 mL) instead of 3 lots and they would like to obtain Agency's concurrence. The Agency responded that they prefer not to address the questions in teleconference that have not been received in writing prior to the teleconference. However, the Agency will commit to responding to this proposal within 2 weeks of receipt, and requested that the Sponsor notifies the Project Manager of the Agency in writing when the submission is made.

In summary, the Sponsor plans to submit 6 months of long-term frozen (-20°C) stability data plus short-term thawed test for \_\_\_\_\_

b(4)

**General/Administrative Question:**

**Does the Agency agree that a 505(b)(2) application is a suitable regulatory mechanism to support registration of Baxter's premixed presentations of Cefepime Injection?**

Agency Response(per April 21, 2006 via e-mail):

Yes. As proposed, your application would be considered as a 505(b)(2) application.

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Kyong Hyon  
Regulatory Project Manager

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/s/

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Frances LeSane  
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