

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-797**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA: 50-797

Stamp Date: August 12, 2004

Action Date: June 10, 2005

HFD-520

Trade and generic names/dosage form: Zmax™ (azithromycin extended-release) for oral suspension, 2 g

Applicant: Pfizer, Inc. Therapeutic Class: 4010400

Indication(s) previously approved: none

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

Number of indications for this application(s): 2

Indication #1: Community Acquired Pneumonia

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

- Yes: Please proceed to Section A.
- No: Please check all that apply:  Partial Waiver  Deferred  Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ < 6 months \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

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

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ 6 months yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ 18 years 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): December 31, 2005

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

Indication #2: Acute Bacterial Sinusitis

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

- Yes: Please proceed to Section A.
- No: Please check all that apply: X Partial Waiver X Deferred \_\_\_\_\_ Completed

NOTE: More than one may apply

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

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

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

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

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ < 6 months \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

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

### Section C: Deferred Studies

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ 6 months \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ 18 years \_\_\_\_\_ 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): December 31, 2005

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*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: Judit Milstein

*{See appended electronic signature page}*

Regulatory Project Manager

cc: NDA 50-797  
HFD-960/ Grace Carmouze

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

(revised 10-14-03)

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**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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Judit Milstein  
6/10/05 01:13:49 PM

John Alexander  
6/10/05 02:27:32 PM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

## Application Information

NDA 50-797	Efficacy Supplement Type SE-	Supplement Number
Drug: Zmax (azithromycin extended release) for oral suspension		Applicant: Pfizer, Inc
RPM: Judit Milstein		HFD-520      Phone # 301-827-2207
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)          (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><b>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</b></p> <p><input type="checkbox"/> Confirmed</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
User Fee Goal Dates		June 10, 2005
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid   UF ID number 4774
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<ul style="list-style-type: none"> <li>• This application is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Exception for review (Center Director's memo)</li> </ul>	
<ul style="list-style-type: none"> <li>• OC clearance for approval</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</li> </ul>	<input checked="" type="checkbox"/> Verified
<ul style="list-style-type: none"> <li>❖ Patent</li> </ul>	
<ul style="list-style-type: none"> <li>• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. <b>This NDA provides for a new dosage form for an "Old Antibiotic". No requirements for patent information</b></li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p>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)</p>
<ul style="list-style-type: none"> <li>• [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).</li> </ul>	
<ul style="list-style-type: none"> <li>• [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i></li> <li>• [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.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification)  <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes ( ) No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes ( ) No

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

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

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

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary: Exclusivity does not apply. This NDA provides for a new dosage form for an "Old antibiotic"</li> <li>• 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.)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	( ) Yes, Application # _____ ( X ) No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
❖ PM filing review	May 25, 2005

General Information	
<b>Actions</b>	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	(X) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only) through DFS</li> </ul>	(X) Yes ( ) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	X
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	X
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	DDMAC-12-22-04, 6-8-05 ODS 5-13-05
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	X
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	
❖ Post-marketing commitments	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
	X
❖ Memoranda and Telecons	
	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	October 4, 2002 October 21, 2002 (CMC)
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	June 10, 2003 (CMC) December 3, 2003
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Other</li> </ul>	
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> <li>Date of Meeting</li> </ul>	N/A
<ul style="list-style-type: none"> <li>48-hour alert</li> </ul>	N/A
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
	N/A

### Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )	6-10-05
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	6-10-05
❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )	6-8-05, 9-30-04
❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )	In MO review
❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet ( <i>NME approvals only</i> )	N/A
❖ Statistical review(s) ( <i>indicate date for each review</i> ) (2)	6-10-05 and 6-10-05
❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )	6-10-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6-10-05
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	10-12-04, 6-10-05
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> ) See CMC review, page 46	X
• Review & FONSI ( <i>indicate date of review</i> )	
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Microbiology (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	N/A
❖ Facilities inspection (provide EER report). See CMC review, page 68	Date completed: 6-10-05 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	9-3-04, 6-1-05 and 6-9-05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	N/A
❖ CAC/ECAC report	N/A

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**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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Judit Milstein  
6/23/05 03:38:26 PM

**MEMORANDUM**

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

**CLINICAL INSPECTIONS' SUMMARY**

**DATE:** June 8, 2005

**TO:** Judit Milstein, Regulatory Project Manager  
Frances LeSane, Regulatory Project Manager  
John Alexander, M.D., Clinical Review Team-Leader  
Nasim Moledina, M.D., Clinical Reviewer  
Janice Soreth, M.D., Director, HFD-520  
Division of Anti-Infective Drug Products, HFD-520

**THROUGH:** Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II/HFD-47  
Division of Scientific Investigations (DSI)

**FROM:** Mathew T. Thomas, M.D.  
Reviewer  
Good Clinical Practice Branch II

**SUBJECT:** Summary of Clinical Investigator Site Inspections and Sponsor Inspection.

**NDA:** #50-797  
**APPLICANT:** Pfizer, Inc.  
**DRUG:** Zmax (azithromycin) 2 gm Tablet

**CHEMICAL CLASSIFICATION:** 3

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATIONS:**

Acute Bacterial Sinusitis (ABS)  
Community Acquired Pneumonia (CAP)

**SUBMISSION DATE:** August 12, 2004  
**CONSULTATION REQUEST DATE:** October 14, 2004  
**ACTION GOAL DATE:** June 10, 2005  
**PDUFA DATE:** July 8, 2005



**B. Dr. Marco A. Camere**

Clinica San Pablo-Sede San Gabriel  
Consultorios externos de Neumologia  
Av. La Marina 2955  
San Miguel de Lima, Peru

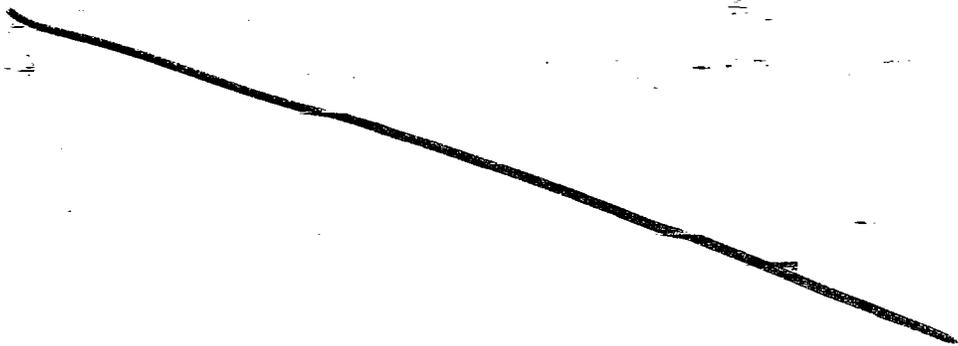
1. What was inspected?

The records of 29 subjects enrolled in protocol #A0661103 for CAP were reviewed. Twenty-eight subjects reportedly completed the study. The inspection included a review of 100% of the consent forms, and a comprehensive review of the study records for all 28 subjects.

2. Limitations of the Inspection: The inspection required the assistance of a translator.

3. General observations:

At the conclusion of the inspection a form FDA 483 was issued to the clinical investigator. The items listed pertained to:

- a. For all 29 subjects randomized in the study the clinical investigator did not maintain a copy of the CRF sent to the sponsor.
  - b. Case histories provided for all 28 subjects who received study treatment did not document a telephone number or other contact information for the subjects (Source Documents were limited).
  - c. Case histories for 98 subjects who were screened but not randomized to treatment were not available for review.
  - d. Change history page in the electronic CRF showed that certain information (concomitant antibiotic treatment and non-drug treatment procedures at end of study visit) was recorded prior to the actual visit.
  - e. Clinical signs (which required a physical examination) for subjects (e.g. #1004 thru 1009) at visit 3 telephone interview were reportedly elicited over the telephone.
- 

**C. Dr. Fabian Galleguillos**

Clinica Miguel de Servet  
Almirante Pasetene #150  
Providencia  
Santiago, Chile

1. What was inspected?

The records of 25 subjects enrolled in protocol #A0661103 for CAP were reviewed. The inspection included a review of 100% of the consent forms, and a comprehensive review of the study records for all 25 subjects.

2. Limitations of the Inspection: The inspection required the assistance of a translator.

3. General observations:

At the conclusion of the inspection a form FDA 483 was issued to the clinical investigator. The items listed pertained to:

- a. For all 25 subjects randomized in the study the clinical investigator did not maintain a copy of the CRF sent to the sponsor.
- b. Change history page in the electronic CRF showed that certain information (concomitant antibiotic treatment and non-drug treatment procedures at end of study visit) was recorded prior to the actual visit.
- c. Hospitalization records of a subject who experienced renal failure, while on study drug, was not available for inspection.

Observations/violations a. thru c. pertains to clinical investigator record keeping and items a. and b. are partially caused by the sponsor's investigational plan. These issues were discussed with the reviewing division during a meeting on May 26, 2005. In general, this study site maintained extensive case histories and DSI recommends that the data from this study site are acceptable.

**D. Dr. Maria Cristina DeSalvo**

Hospital General de Agudos Dr. E. Tornu  
Division of Neumotisiologia  
1° Piso  
Comatiente de Malvians 3002  
1427 Buenos Aires, Argentina

1. What was inspected?

The records of 30 subjects enrolled in protocol #A0661075 for CAP were reviewed.

2. Limitations of the Inspection: The inspection required the assistance of a translator.

3. General observations:

At the conclusion of the inspection a form FDA 483 was issued to the clinical investigator. The items listed pertained to:

- a. Case histories for subjects who were screened but not randomized to treatment were not available for review.
- b. Clinical signs (which required a physical examination) for subjects at visit 3 telephone interview were reportedly elicited over the telephone.

Regarding the violation addressed under item b., DSI has gathered information from other study sites and from the sponsor to support that the improper reporting of data pertaining to clinical signs (which require a direct physical examination) via a telephone call were not limited to this single study site. These issues were discussed with the reviewing division during a meeting on May 26, 2005. In general, the data collected from this study site are deemed acceptable.

### III. RESULTS OF THE SPONSOR INSPECTION:

#### **Rationale:**

Because of the inspectional observations noted during the clinical investigator inspections, that (1) the sponsor was providing clinical investigators a copy of all CRFs after cleaning and locking the data, [This is an acceptable practice, the issue is whether the CI maintained a copy of the information he/she sent to the sponsor.] and (2) data, which required a physical examination, were being captured and reported by study sites for a Visit that collected information through a telephone call, a sponsor inspection was initiated to determine the adequacy of site monitoring by the sponsor.

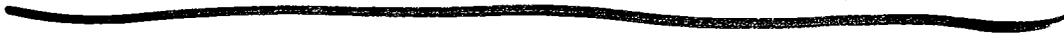
The S/M inspection at **PFIZER, Inc., Groton, Connecticut** mainly focused on the monitoring performed at the following clinical sites:

1. CAP Protocol #1103 - site #1056 (Dr. Camare, Lima, Peru)
2. CAP Protocol #1103 - site #1057 (Dr. Villaran, Lima, Peru)
3. CAP Protocol #1103 - site #1059 (Dr. Galleguillos, Santiago, Chile)

The inspection revealed several issues:

#### **ISSUE # I:**

PERTAINED TO THE CAPTURE OF EFFICACY DATA FOR ALL FOUR CLINICAL STUDIES IN THE NDA:

- a. There was a design related problem with the paper worksheets and/or electronic case report forms (eCRFs), which captured the data regarding signs and symptoms. Specifically, study site personnel were choosing the wrong evaluations because both forms (worksheets and eCRFs) contained a key at the top which lined up the wrong numerical choices below for each sign and symptom. This reportedly resulted in site personnel checking the wrong boxes. It is not possible to accurately determine the frequency with which this error occurred and how this issue was handled and/or fixed by individual clinical study sites and the sponsor. Sponsor personnel have acknowledged, and documentation supports, that that Pfizer was aware of this problem).
  
- b. Several sites were recording physical exam findings for telephone-call visits (such as assessments of tachypnea, auscultatory findings – rales, chest dullness to percussion, bronchial sounds, egophony, wheezing, ronchi, and decreased breath sounds). Telephone visit is when the subject is contacted by telephone and does not come to the study site for a physical exam. In response to this observation the sponsor did the following:
  - i. For protocol 1075 (CAP), queries were activated on 24 July 03 and between Oct 03 and January 04, a total of 73 data clarification forms (DCF) were created and sent to the sites.
  
  - ii. For protocol 1103 (CAP), queries were activated on 18 December 2003 and on 6 January 2004 a total of 305 DCFs were created. Because of this large and unexpected number of queries the sponsor decided to stop further queries during their meeting on 4 February 2004. The sponsor also determined that the telephone-call visit data was in addition to the cough, dyspnea, and rigors which the clinical team felt could be reliably assessed over the telephone. .
  
  - iii. For protocol 1078 (ABS), we are not sure what exactly was done about the data collected for this telephone visit.
  
- c. In addition, Pfizer correspondence showed that study sites were comparing a particular follow-up visit's signs and symptoms to the previous visit instead of the initial visit. The study team identified this problem in April/May 2003 and issued revised CRF completion guidelines in May 2003 and January 2004.

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Items a thru d listed above show that efficacy data collected for these studies may have been affected for a variety of reasons, but there are no specifics about which data were affected. For all studies the clinical signs data (which required a physical examination) reportedly collected through a telephone interview should not be used.

**ISSUE II:**

PERTAINED TO ELECTRONIC DATA CAPTURE (EDC) FOR ALL FOUR CLINICAL STUDIES:

The EDC system using I-Net (an application used for the completion, review and submission of clinical trial data) does not allow clinical investigators to retain a copy of the data they first submitted to the sponsor via an electronic case report form (eCRF). In the sites that FDA inspected we observed that the clinical investigators maintained at least worksheets which served as paper source documents. The sponsor sent .pdf images of the eCRFs on a compact disc (CD) to each respective clinical investigator after the data collected for all subjects from each site was locked and queried and clarified by the sponsor's clinical team.

Pfizer personnel stated that the clinical investigators were required to sign an EDC Study Sign-Off Record which states that the eCRFs on the CD supplied to the clinical investigator (by the sponsor) represent the CRF data collected at the investigator's site. Pfizer personnel stated that this Sign-Off Record is the documentation that the eCRFs on the CD are a true reflection of data collected at the site and that clinical investigators are to check the data on the CD for all subjects against eCRFs on I-Net prior to signing this document. After this verification is performed, Pfizer personnel stated the clinical investigator is to perform a "cleaning" (involves the deletion of study related records in the laptop computer on site) if they are not participating in other I Net studies/activities which removes the laptop's capability to connect to I Net. However, at the time of the start of FDA's sponsor inspection documentation shows that these EDC Sign-Off Records were not available as follows:

- i. for 16 out of 46 sites for Protocol A0661075
- ii. for 13 out of 43 sites for Protocol A0661078
- iv. for 28 out of 58 sites for Protocol A0661103

**ISSUE III:**

PERTAINED TO THE INADEQUATE MONITORING OF THE STUDY SITE IN LIMA PERU FOR PROTOCOL #1103 - CAP (Note: *The study monitoring for all sites*

*were performed by Pfizer personnel or individuals contracted to perform monitoring for Pfizer):*

Numerous examples pertaining to inadequate monitoring and/or inaccurate monitoring reports were revealed during FDA's sponsor monitor inspection leading Pfizer to launch an investigation and conclude that the monitoring reports for sites 1056 and 1057 (in Lima, Peru) in protocol #A0661003, which were monitored and supervised by personnel working for Pfizer in Lima, Peru, were backdated.

These issues were discussed with the reviewing division during a meeting on May 26, 2005. Pfizer was issued a Form FDA 483 summarizing the above mentioned issues. The review division requested Pfizer to provide additional information to support that the monitoring in general for all their study sites were adequate.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

DSI's recommendation regarding the validity of the data is stated above under the discussion of each inspection. In general, DSI inspections of some of the clinical investigator study sites, and Pfizer's monitoring of clinical studies revealed deficiencies and discrepancies that diminish the quality of data generated in support of NDA #50-797. However, there is insufficient evidence to invalidate the data submitted in support of the studies that were inspected and the data are deemed acceptable.

Signature  
Mathew T. Thomas, MD  
Division of Scientific Investigations

CONCURRENCE: Supervisory comments.

Leslie K. Ball, M.D.  
Branch Chief  
Good Clinical Practice Branch II/HFD-47  
Division of Scientific Investigations

#### **DISTRIBUTION:**

Division File: NDA #50,797  
HFD-45/Division File  
HFD-47/Program Management Staff (electronic copy)  
HFD-520/Project Manager/Milstein  
HFD-47/Thomas  
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O:\MTT\NDA50797sum5ac.doc  
Drafted: MTT: 6/8/05  
Reviewed: JPS: 6/10/05  
Reviewed: LKB: 6/10/05  
Revised: MTT: 6/10/05

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**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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Mathew Thomas  
6/10/05 04:27:51 PM  
MEDICAL OFFICER

Leslie Ball  
6/10/05 04:37:23 PM  
MEDICAL OFFICER



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 an approved (b)(1) or (b)(2) application? N/A  
**This is an "old antibiotic" and exclusivity does not apply**
- Does another drug have orphan drug exclusivity for the same indication? NO
- 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)]? NA  
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)? NO  
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? NA
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES  
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES

If no, explain:

- If an electronic NDA, does it follow the Guidance? YES  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?  
Modules 3, 2.5, 2.7, 5.3, and labeling

Additional comments: This is a hybrid submission with CTD structure and a traditional electronic submission format

- If in Common Technical Document format, does it follow the guidance? YES
- Is it an electronic CTD? NO  
**If an electronic CTD, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? N/A  
**No patent information required as per repeal of section 507**
- Exclusivity requested? NO  
**No exclusivity apply as this is a new formulation of an antibiotic pre-repeal of section 507**  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  
**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 . . . ."*
- Financial Disclosure forms included with authorized signature? YES  
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A  
**This submission contains Module 3 as an electronic submission**

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES
- List referenced IND numbers: I 66,194 and NDA 50-670
- End-of-Phase 2 Meeting(s)? Date(s) October 4, 2002  
October 21, 2002  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 3, 2003  
December 3, 2003  
~~May 19, 2004~~  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

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

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  
If no, did applicant submit a complete environmental assessment? N/A  
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

Appears This Way  
On Original



DSI:  
 Regulatory Project Management: Judit Milstein  
 Other Consults:

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

CLINICAL FILE: X REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES
- Advisory Committee Meeting needed? Not known at this time

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

CLINICAL MICROBIOLOGY FILE X

STATISTICS FILE X

BIOPHARMACEUTICS FILE X

- Biopharm. inspection needed: NO

PHARMACOLOGY FILE X

- GLP inspection needed: NO

CHEMISTRY FILE X

- Establishment(s) ready for inspection? YES
- Microbiology N/A

**ELECTRONIC SUBMISSION:**

Any comments: This submission is a hybrid NDA/CTD.

**MINUTES OF THE MEETING:**

Pfizer's request for priority review was discussed. The definition of a priority review product, as outlined in the MaPP 6020.3, was stated. It was noted that the product did not provide clear advantages in efficacy, safety or treatment of a new population. There was serious discussion of whether the increased compliance expected with the single dose azithromycin product represented a significant improvement in treatment, especially for community-acquired pneumonia. The decision on whether to grant a standard or priority review was tabled, until more detailed information about the CAP study results could be discussed.

Details of the results of the CAP studies were discussed during a meeting held on October 7, 2004, in the presence of J. Soreth, M. Imoisili, C. Cooper, J. Alexander; B. Osterberg, S. Pagay, P. Coderre, S. Komo, D. Lin, M. Goldberger, E. Cox, and Judit Milstein, and it was concluded that the product did not provide clear advantages in efficacy, safety or treatment of a new population to warrant a priority review; Therefore, this NDA will be reviewed under a standard timeframe.

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

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

  X   No filing issues have been identified. 74 day letter sent on October 8, 2004

\_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. 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.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Judit Milstein  
Regulatory Project Manager, HFD-520

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**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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Judit Milstein  
5/24/05 08:22:43 AM  
CSO

Frances LeSane  
5/25/05 11:12:31 AM  
CSO

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> January 21, 2005	<b>DESIRED COMPLETION DATE:</b> March 21, 2005	<b>ODS CONSULT #:</b> 05-0020
<b>DATE OF DOCUMENT:</b> January 13, 2005	<b>PDUFA DATE:</b> June 12, 2005	

**TO:** Janice Soreth, M.D.  
Director, Division of Anti-Infective Drug Products  
HFD-520

**THROUGH:** Judit Milstein  
Project Manager, Division of Anti-Infective Drug Products  
HFD-520

<b>PRODUCT NAME:</b> <b>Primary Name:</b> Zmax™ <b>Alternate Name:</b> _____ (Azithromycin for Extended-release Oral Suspension) 2 grams azithromycin (as azithromycin dihydrate)	<b>NDA SPONSOR:</b> Pfizer, Inc.
<b>NDA#:</b> 50-797	

**SAFETY EVALUATOR:** Charlie Hoppes, R.Ph., M.P.H.

- RECOMMENDATIONS:**
1. DMETS does not recommend the use of the proprietary names, Zmax \_\_\_\_\_
  2. DMETS recommends that the sponsor use the modifier, ER, conveying the extended-release characteristics of this product with the existing name, Zithromax.
  3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.
  4. DDMAC finds the proprietary name Zmax acceptable from a promotional perspective.
  5. The CDER Labeling and Nomenclature Committee has made recommendations regarding the proper designation of the established name for this product. See section III of this review.

Denise Toyer, Pharm. D. Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Fax: (301) 443-9664	Carol Holquist, R.Ph. Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242	Fax: (301) 443-9664
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**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** February 15, 2005

**NDA#** 50-797

**NAME OF DRUG:** Zmax™ [REDACTED]  
(Azithromycin for Extended-release Oral Suspension)  
2 grams azithromycin (as azithromycin dihydrate)

**NDA HOLDER:** Pfizer, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Infective Drug Products (HFD-520), for assessment of the proprietary names, "Zmax" [REDACTED] regarding potential name confusion with other proprietary or established drug names. Container labels, carton labeling, patient and professional package insert labeling were provided for review and comment.

This is the second time that the sponsor has proposed a proprietary name for this product. In a Memo dated December 16, 2004 (ODS Consult # 04-0341), DMETS communicated comments from DDMAC to the review division regarding the promotional nature of the proposed name, Zmax

[REDACTED]

[REDACTED]

[REDACTED] At this time, the sponsor proposes to market the product as "Zmax" [REDACTED]

**PRODUCT INFORMATION**

Zmax™ [REDACTED] is azithromycin for extended-release oral suspension, indicated for [REDACTED] sinus infections, and pneumonias, due to susceptible strains of bacteria. The usual adult dosage is 2 grams as a single dose. Zmax [REDACTED] is supplied in bottles containing 2 grams azithromycin (as azithromycin dihydrate). The dry powder should be stored at or below 30°C (86°F). After reconstitution, the resulting suspension may be stored at controlled room temperature and should be consumed within 12 hours of reconstitution.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Zmax to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Zmax. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Zmax acceptable from a promotional perspective.
2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Zmax. Additionally, the Panel identified "Amox" as an abbreviation for amoxicillin as also having potential for confusion with Zmax. Upon further review, the name "Zomig" also identified as having potential for confusion. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage. EPD panelists commented that the proposed name, Zmax, sounds like the terms C-max, V-max, T-max. Also panelists commented that Z-max could be mistaken as the abbreviation for Zithromax, rather than recognized as a distinct drug product with limited indications. Other panelists commented that Zmax is also the name of an engine additive and that phentolamine is marketed in Mexico as Z-max.

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<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Zimax or ██████████	Azithromycin for Extended-release Oral Suspension, 2 g (azithromycin)	Take one 2 g dose	
Xanax Xanax XR	Alprazolam Tablets, 0.25 mg, 0.5 mg, 1 mg, and 2 mg Alprazolam Extended-release Tablets, 0.5 mg, 1 mg, 2 mg, and 3 mg	Immediate-release: Take 0.25 mg to 0.5 mg three times daily. Extended-release: Take 3 mg to 6 mg daily in the morning. Xanax doses may be increased, 1 mg/day, to reach 6 mg to 10 mg per day.	LA/SA
Zithromax (commonly written as Z-Pak)	Azithromycin Tablets, 250 mg (6's) Azithromycin also available as: Azithromycin Tablets, 500 mg, 600 mg Azithromycin for Injection, 500 mg Azithromycin for Oral Suspension, 300 mg, 600 mg, 1200 mg, 1 g (100 or 200 mg/mL) when reconstituted	Oral: 500 mg/day for 3 days, Some indications – single 1 g or 2 g dose. IV: 500 mg/day for 2 days	LA/SA
Bumex	Bumetanide Tablets, 0.5 mg, 1 mg, 2 mg Bumetanide also available in injection: Bumetanide Injection, 0.25 mg/mL 2 mL, 4 mL and 10 mL	Oral: 0.5 mg to 2 mg every day Injection: 0.5 mg to 1 mg IV or IM. May give second and third dose at 4 to 5 hour intervals.	LA
Cedax	Ceftibuten Dihydrate Capsules, 400 mg Ceftibuten Dihydrate for Oral Suspension, 540 mg, 1080 mg, 1620 mg, and 2160 mg (18 mg/mL in 30 mL, 60 mL, 90 mL and 120 mL bottles)	Take 400 mg daily.	SA
Zovirax	Acyclovir Tablets, 400 mg and 800 mg Acyclovir Capsules, 200 mg Acyclovir Suspension, 200 mg/5 mL Acyclovir Ointment, 5% Acyclovir Cream, 5% Acyclovir Sodium for Injection, 500 mg and 1000 mg	Oral: 200 mg to 800 mg every 4 hours (2, 3, or 5 times a day)  Topically: Cover lesions every 3 hours up to six times daily.  Injection: 5 to 10 mg/kg	LA
Zyvox	Linezolid for Oral Suspension, 3 grams (will yield 150 mL of 100 mg/mL) Linezolid Injection, 200 mg/100 mL bag Linezolid Tablets, 400 mg and 600 mg	600 mg every 12 hours	LA
“Amox” (abbrev. for amoxicillin)	Amoxicillin for Oral Suspension USP 50 mg/5 mL, 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL Amoxicillin Capsules USP, 250 mg, 500 mg Amoxicillin Tablets USP, 125 mg, 200 mg, 250 mg, 400 mg, 500 mg, 875 mg	Take 750 mg to 1500 mg in two or three divided doses.	LA
Zomig	Zolmitriptan Tablet, 2.5 mg and 5 mg Zolmitriptan Nasal Spray, 5 mg/spray	Inhale 5 mg nasally or 2.5 mg to 5 mg orally at onset of headache. May repeat one time after 2 hour not to exceed 10 mg in 24 hours.	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PJ

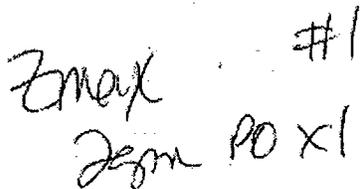
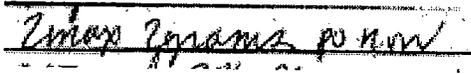
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All

names considered to have significant phonetic or orthographic similarities to Zmax were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Zmax with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zmax (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>Zmax by mouth, 2 g Give One.</p>
<p>Inpatient RX:</p> 	

2. Results:

One respondent interpreted the proposed name as V-max. V-max is a currently used medical abbreviation for a parameter of pulmonary function. Two participants of the inpatient study responded “Zimox”, the proprietary name for amoxicillin marketed in Italy. Additionally, four participants of the verbal study, one participant of the inpatient study, and two participants of the outpatient study spelled Z-max with a hyphen, even when no hyphen was written in the study sample (see images in table above). Z-max (hyphenated) is marketed as an anti-impotence drug in Mexico. See Appendix A for the complete listing of interpretations from the verbal and written studies. Study participants also provided the following insightful comments:

- Name is similar to Z-Pack which has a good chance of being misdispensed (sic) for Zmax.
- V-max 2 gm, which could be interpreted as an abbreviation for Vira-max (a "dietary supplement" for the enhancement of male sexual performance.) This also sounded like Zmax, which could be interpreted as an abbreviation for Zithromax.

#### D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Zmax, the primary concerns related to look-alike and sound-alike confusion with Xanax/Xanax XR, Zithromax (commonly written as Z-Pak), Bumex, Cedax, Zovirax, Zyvox, "Amox" (abbreviation for amoxicillin), and Vmax, an abbreviation for maximum expiratory volumes. We have also identified a foreign product with the name Zmax. DMETS has similar concerns with the name [REDACTED] as addressed in item 4 of this section. DMETS is also concerned with the possibility of Zmax being confused for Zithromax. Lastly, DMETS is concerned with the use of a new name for this extended release product. Upon further review of the names gathered from EPD and after independent review, the names Bumex and Zomig were not reviewed further due to a lack of convincing sound-alike and look-alike similarities with Zmax in addition to differentiating product characteristics such as the product strength, dosage form, and indication for use.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. These studies did not confirm confusion with the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Although there was no confirmation that the proposed name could be confused with any of the aforementioned names or the names of any products marketed in this country, it was confused with Zimox, an amoxicillin product marketed in Italy, and Z-max, an anti-impotence product marketed in Mexico. Zmax was also misinterpreted as V-max, which has meaning in the healthcare arena as a pulmonary function parameter. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Zmax.

##### 1. New proprietary name versus use of a modifier with the existing name, Zithromax

The addition of new products with extended-release characteristics to an existing product line have traditionally followed the naming convention of the addition of a modifier to the existing proprietary name, e.g., Flagyl and Flagyl ER. Rather than adopting this naming convention, the sponsor has proposed to use a new proprietary name for the product line extension. DMETS notes that before the addition of this product, the sponsor has already expanded their product line with the addition of new dosage forms all of which use the Zithromax name. The newly proposed product should follow this convention. Although there is some potential for the omission of a modifier from a prescription order, DMETS believes that the alternative, introduction of a new name into the marketplace is the worse option for two main reasons. First, the proposed name, Zmax, does not convey the extended-release properties of this product compared to Zithromax. This is further complicated by the fact Zithromax is already available in an immediate-release oral suspension and without conveying this product is extended release, health care practitioners may believe this is just merely a higher strength of the currently marketed oral suspension. Secondly, dual tradenames for the same active ingredient introduces the possibility that a patient may be taking both products without realizing that they have the same active ingredient or may be

allergic to the active ingredient and take Zmax inadvertently not knowing it contains the same active ingredient. For these reasons, DMETS recommends the use of an appropriate modifier with the Zithromax name rather than Zmax or any other new proprietary name.

2. Potential misinterpretation of “Zmax” for Zithromax

Zithromax is Pfizer’s proprietary name for azithromycin products (see table below).

Zithromax (Pfizer)	Tablets : 250 mg (as dihydrate)	Lactose. ( PFIZER 306 ). Pink, capsule shape. Film coated. In 30s, UD 50s, and Z-Pak 6s.
	500 mg (as dihydrate)	Lactose. ( PFIZER ZTM500 ). Pink, capsule shape. Film coated. In 30s, UD 50s, and TRI-PAK 3s.
	600 mg (as dihydrate)	Lactose. ( PFIZER 308 ). White, oval. Film coated. In 30s.
	Powder for injection, lyophilized : 500 mg	In 10 mL vials and 10 mL vials with 1 Vial-Mate adaptor.
	Powder for oral suspension : 100mg per 5mL (as dihydrate) when reconstituted	Sucrose. In 300 mg bottles.
	200 mg per 5 mL (as dihydrate) when reconstituted	Sucrose. In 600, 900, and 1,200 mg bottles.
	1 g/packet (as dihydrate)	Sucrose. In single-dose packets of 3s and 10s.

Although Zmax is a unique product with extended-release characteristics and is not bioequivalent to Zithromax, the proposed name may be viewed as a contraction of the drug *Zithromax*. Also, as stated in Section II.1. of this review, the proposed name, Zmax does not convey the extended-release properties of this product or any kinetic differences compared to Zithromax. Since a 2 g dose can be obtained with Zithromax (4 X 500 mg), it is possible for an order for Zmax, 2-g in one dose, to be filled with Zithromax. Zmax is formulated to release azithromycin slowly in the GI tract. Zmax has a single dose regimen for indicated infections where immediate-release products have three or five day courses of treatment. If an order for “Zmax” is filled with the immediate-release Zithromax in error the patient may not receive the expected kinetic performance, resulting in a higher peak but shorter duration. This type of error might result in treatment failure as a result of a shortened duration of action and patients might be at risk of increased side effects resulting from a higher than intended azithromycin peak. Conversely, if “Zmax” is used to fill an order for Zithromax, intended peak concentrations might not be reached since the bioavailability of Zmax relative to azithromycin for oral suspension is only 83%. Overall, because “Zmax” appears as though it could be an abbreviation for Zithromax, DMETS is concerned about the possibility of substitution of Zmax for immediate-release Zithromax products or vice-versa.

3. Sound-alike and or look-alike concerns

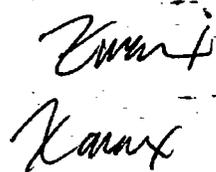
- a. Z-Pak may sound and look similar to Zmax. Z-Pak is Pfizer’s packaging configuration of six Zithromax (azithromycin) 250 mg tablets in a five day course. Z-Pak is indicated for treatment of azithromycin sensitive bacterial infections where a five day course will suffice, including upper respiratory tract infections, acute bacterial exacerbations of chronic bronchitis, and mild community acquired lower respiratory tract infections due to susceptible bacterial strains. Z-Pak and Zmax owe phonetic similarities to the initial “Z” sound and similar-sounding ending “ak” vs. “ax”, respectively. Z-Pak and Zmax also have orthographic similarities

including similar word lengths, shared letters, "Z" and "a". The "x" in Zmax may also look like the "k" in Z-Pak as seen in the writing sample (below).



In addition to orthographic similarities, Z-Pak and Zmax have numerous product similarities including; route of administration, indications of use (to treat bacterial infections), and overlapping patient and provider populations. Although Z-Pak and Zmax have differences including dosage form (tablet vs. for oral suspension), dose (250 mg vs. 2 gram), and dosing regimen (once daily for five days vs. one time dose), DMETS does not believe these differences will prevent confusion if orders are written for the Z-Pak or Zmax to be taken "as directed". Since both products have self contained directions of use, if an error is made, the patient will follow the directions which accompany the product. DMETS believes that either product may be written without reference to strength since they are only available in one strength. Overall, DMETS believes that sound-alike/look-alike properties along with strong product characteristic overlap contribute to increase the risk that these products will be confused.

- b. Xanax/Xanax XR may sound and look similar to Zmax. Xanax is the anxiolytic agent, alprazolam, indicated for the management of various stress-related symptoms including generalized anxiety disorder, panic attack, and the anxiety resulting from depression. The usual adult alprazolam dose is 0.25 mg to 0.5 mg three times daily for the immediate-release tablet or 3 mg to 6 mg once in the morning for the extended-release tablet (Xanax XR). Xanax and Zmax owe phonetic similarities to the shared "z" sound at the beginning of each two-syllable name and the "ax" ending. The "n" vs. "m" sounds in middle of Xanax and Zmax are also virtually indistinguishable. Look-alike properties may be attributed to endings, "max" vs. "nax", which look very much alike especially when scripted in cursive (see sample below).



Along with some sound-alike and look-alike properties, Xanax and Zmax share some product characteristics including; route of administration, and numerical similarity in strength (2 mg vs. 2 g), respectively. Additionally, DMETS is aware through postmarketing surveillance of confusion between the units "mg" and "g". Xanax/Xanax XR and Zmax also have differences including dosage form (tablet vs. for oral suspension), and indications of use (for anxiety vs. for infection), respectively. Since Xanax may be ordered as a one time dose, it is possible that a written inpatient order for "Zmax 2 g now" could be confused for "Xanax 2 mg now". If a patient takes Xanax rather than Zmax, they may suffer sedative side effects and have the infection go untreated. Overall, DMETS believes that sound-

alike/look-alike properties along with strong product characteristic overlap contribute to increase the risk that these products will be confused.

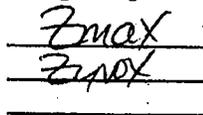
- c. Cedax may sound similar to Zmax when spoken. Cedax is ceftibuten dihydrate indicated for treatment of mild-to-moderate infections caused by susceptible strains of microorganisms, including acute exacerbations of chronic bronchitis, acute bacterial otitis media, pharyngitis, and tonsillitis. The recommended adult dose of ceftibuten is 400 mg daily for ten days. Cedax and Zmax owe phonetic similarities to similar sounding name beginnings, ("See" vs. "Zee" sounds) and shared "ax" ending. However, the strong "d" sound in Cedax may serve to differentiate the product names phonetically. Cedax and Zmax have many product similarities including; route of administration (oral), dosage form (for oral suspension), indications of use, as well as overlapping patient and provider populations. However, Cedax and Zmax differ in dose and dosing duration (400 mg daily for ten days vs. 2 g in a one-time dose), respectively. Although dosing directions for Zmax may be scripted as "UD", (as directed), most likely the specific instructions of use will be included with Cedax since it is not available in "Pak" packaging. Overall, DMETS believes that these differences as well as lack of convincing sound-alike similarities will minimize the potential for error.
- d. Zovirax may look similar to Zmax when written. Zovirax is acyclovir, an antiviral product available in a variety of dosage forms and by various routes of administration for the treatment of viral infections or amelioration of viral infection symptoms (see Table on page 4 describing available products and usual adult dosages). Zovirax is also available as a suspension containing 200 mg acyclovir per teaspoonful (5 mL). Zovirax and Zmax owe orthographic similarities to the shared "Z" beginning each name as well as the "ax" ending. Also, the "vi" in Zovirax, when written in cursive, may look like the "m" in Zovirax. However, Zmax has less letters, and is relatively shorter in length when scripted (see hand writing sample below).



Zovirax and Zmax also have overlapping product characteristics including; route of administration (oral), dosage form (suspension/for suspension), and share similar indications (both are anti-infectives). However, Zovirax and Zmax differ in dose and dosing duration (200 mg to 800 mg every 4 hours, 5 times daily vs. 2 g in a one-time dose), respectively. Although dosing directions for Zmax may be scripted as "UD", (as directed), most likely the specific instructions of use will be included with Zovirax due to variations in dosing with different indications. Overall, DMETS believes that these differences as well as lack of convincing look-alike similarities will minimize the potential for error.

- e. Zyvox may look similar to Zmax when written. Zyvox is linezolid, an antibiotic indicated for treatment of infections resulting from susceptible strains of bacteria, including certain vancomycin-resistant infections, nosocomial and community acquired pneumonia, and skin and skin structure infections. The usual adult dose is

600 mg every 12 hours. Zyvox is available in tablets, injection, and powder for oral suspension. Look-alike similarities between Zyvox and Zmax may be attributed to the shared letters "Z" and "x" at the beginning and end of each name and orthographic similarities in the lower case "o" vs "a". However, the downstroke of the "y" in Zyvox may serve to differentiate the names orthographically except when written on a lined order form where the downstroke lacks prominence (see writing sample below).



Zyvox and Zmax also have many product similarities including route of administration (oral), dosage form (for oral suspension), indication (treatment of respiratory tract infections), as well as overlapping patient and provider populations. However, Zyvox and Zmax differ in dose and dosing duration (600 mg to 800 mg every 12 hours vs. 2 g in a one-time dose), respectively. Although dosing directions for Zmax may be scripted as "UD", (as directed), most likely the specific instructions of use will be included with Zyvox since it is not available in "Pak" packaging. Overall, DMETS believes that these differences as well as lack of convincing look-alike similarities will minimize the potential for error.

- f. "Amox" (an abbreviation for amoxicillin) may look similar to Zmax when written. Entering "amox" in the search engine, Medilexicon<sup>6</sup> for medical abbreviations resulted in the identification of amoxicillin. Amox® is also a branded amoxicillin product, marketed in Canada<sup>7</sup>, which may cause confusion in the event that the prescription is ordered over the internet. Amoxicillin is a broad spectrum antibiotic indicated in the treatment of infections due to sensitive bacterial strains. Although the usual adult dosage is 750 mg to 1500 mg in two to three divided doses, amoxicillin may be given in single large doses, e.g., 2 grams prior to a dental procedure as recommended by the American Heart Association<sup>8</sup>. Amoxicillin is available in tablets, capsules, and powder for oral suspension. Amox and Zmax owe orthographic similarity to similar word lengths, shared letters "m" and "x", and similarities in the lower case "o" vs. "a". The "A" in "Amox" may also look like the "Z" in Zmax, especially if it is crossed (see writing sample below).



In addition to orthographic similarities, Amox and Zmax have numerous product similarities including route of administration, dosage form (for oral suspension), indication for use (to treat bacterial infections), dose and dosing regimen (a single 2 gram dose), and patient and provider populations. DMETS considers the misinterpretation of an order for Zmax 2 gram to be a distinct possibility. If

<sup>6</sup> Web Reference for MediLexicon: <http://www.pharma-lexicon.com/>

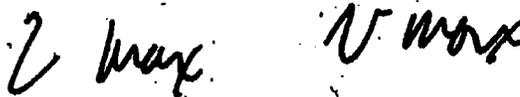
<sup>7</sup> Web Reference: <http://www.lung.ca/drugs/pages/303.html>

<sup>8</sup> Web Reference: <http://www.qualitydentistry.com/dental/information/abiotic.html>

amoxicillin was dispensed rather than azithromycin, the patient might not receive adequate coverage to treat the infection and might experience treatment failure. Overall, DMETS believes that look-alike properties along with strong product characteristic overlap contribute to increased risk that these products will be confused.

4. Potential confusion of "Zmax" with medical abbreviations

DMETS has concerns related to look-alike and sound-alike confusion of Zmax with the medical abbreviations,  $T_{max}$ , and  $C_{max}$ , used to describe pharmacokinetics and the abbreviation,  $V_{max}$ , a term used to describe the maximum expiratory volume in patients with bronchial asthma. Although it is difficult to imagine a scenario in actual practice where kinetic terminology references  $T_{max}$ , or  $C_{max}$ , would be confused with this drug product, DMETS believes there may be a possibility for confusion between  $V_{max}$  and Zmax, especially considering that Zmax may be used to treat bronchitis and pneumonia.  $V_{max}$  and Zmax owe their sound-alike properties to the combination of similar sounding fricatives, "v" and "z" beginning each name with the phonemes "max" at the end. In fact, one participant of the verbal prescription study responded "V-max" to the verbal order for Zmax.  $V_{max}$  and Zmax may also look similar when scripted due to similarities in the cursive "z" and "v" (see writing sample below).

The image shows two handwritten cursive samples. The first sample is 'Z max' and the second is 'V max'. The letters 'z' and 'v' are written in a cursive style that makes them look very similar, especially when followed by 'max'.

Due to orthographic and phonetic similarities, DMETS is concerned with the possibilities for error, for example, a hospitalized patient's order for Zmax, e.g., "Zmax stat" to be confused with an order for assessment of breathing function, " $V_{max}$  stat", or vice versa. Such an error could result in the loss or delay of treatment with Zmax. However, inpatient orders will generally include a route of administration which will help differentiate the two names. Additionally,  $V_{max}$  is one component of Pulmonary Function Tests (PFTs). PFTs are generally ordered and not specific components such as  $V_{max}$ . Despite the orthographic similarities, DMETS believes that differences in ordering scenarios will minimize the potential for confusion.

5. DMETS nomenclature concerns with "Zmax" extend to \_\_\_\_\_

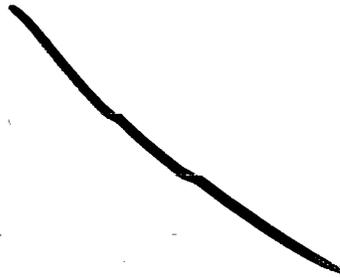
The additional words \_\_\_\_\_ following the proprietary name Zmax do little to allay the concerns expressed by DMETS regarding Zmax. Through post marketing experience DMETS is aware of the inadvertent omission of modifiers. Still more information implicating the omission of modifiers from the proprietary name in medication errors appears in drug safety literature<sup>9</sup>. DMETS believes that the modifier \_\_\_\_\_ has high potential of being omitted from verbal or written orders. Thus the potential exists for the prescription to be scripted as Zmax and ultimately misinterpreted as the names identified under the Zmax name review (Section D3). Since the product is only available in a single dose, inclusion of this modifier in the proprietary name may be viewed as extraneous or redundant by prescribers, especially

<sup>9</sup> Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

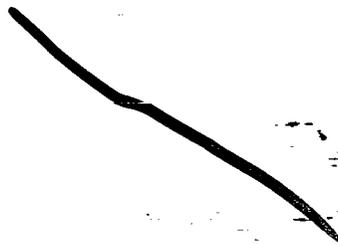
since the directions would be expected to have the same words, e.g., "Take the contents of the bottle in a single dose".

6. Domestic and foreign marketing of other "Z-max" and "Zmax" products

Through internet searches (Google), DMETS has become aware of marketing of Zmax products which have different active ingredients than the proposed product. Both of the OTC supplements pictured below state that these-zinc-containing products work to increase testosterone thereby increasing muscle strength<sup>10,11</sup>.



Both of these supplements can also be purchased on-line. Another product containing phenolamine, [fentolamina (Spanish)], is marketed as an anti-impotence drug in Mexico under the proprietary name, Z-Max<sup>12</sup> (see image below). A U.S. traveler in Mexico might experience surprising side-effects but worsening infection in attempting to cure a respiratory infection with the Z-Max (fentolamina).



DMETS is aware of references in drug safety literature of confusion and medication errors resulting from US brand names with different active ingredients abroad<sup>13,14</sup>. Although the articles implicate naïve travelers and drug-re-importation as contributing factors in errors resulting from international nomenclature discrepancies, DMETS is

<sup>10</sup> Web Reference for LA Muscle Zmax Compound: <http://www.fuelsport.co.uk/ProductPage.asp?pro=1201401>

<sup>11</sup> Web Reference for Zmax: <http://www.maxsportsmag.com/science/issue22/22sci2.htm>

<sup>12</sup> Web Reference for Z-Max: [http://news.bbc.co.uk/1/hi/special\\_report/1998/viagra/248168.stm](http://news.bbc.co.uk/1/hi/special_report/1998/viagra/248168.stm)

<sup>13</sup> Same name, different drug. *Medication Safety Alert!* January 13, 2005, 10(1), 2.

<sup>14</sup> New dangers in the drug re-importation process: Will we know what our patients are taking? *Medication Safety Alert!* January 27, 2005, 10(2), 1,2.

also concerned about the possibility of confusion resulting from on-line (www) availability or reference to these products. In one scenario, a patient may try to fill their Zmax prescription on-line and receive the wrong product. Perhaps a more likely scenario would see a patient research the "Zmax" prescribed by their doctor and find that it is for male sexual enhancement or muscle growth. In the latter scenario, a patient might be confused and result in calls to the doctor about the Zmax order, or worse, not have the prescription filled.

### III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary names Zmax or Zmax . Additionally, DMETS is concerned that use of a different name will not convey the extended-release properties of this product and that Zmax may be mistaken as an abbreviation for Zithromycin. In reviewing the proprietary name for look-alike and/or sound-alike confusion DMETS identified the following names of concern, Z-Pak, Xanax, and "Amox" (abbreviation for amoxicillin). DMETS was also concerned with the possibility of medication errors as a result of confusion between Zmax and other currently marketed Z-max or Zmax products.

#### A. New proprietary name versus use of a modifier with the existing name, Zithromax

The addition of new products with extended-release characteristics to an existing product line have traditionally followed the naming convention of the addition of a modifier to the existing proprietary name, e.g., Flagyl and Flagyl ER. Rather than adopting this naming convention, the sponsor has proposed to use a new proprietary name for the product line extension. DMETS notes that before the addition of this product, the sponsor has already expanded their product line with the addition of new dosage forms all of which use the Zithromax name. The newly proposed product should follow this convention. Although there is some potential for the omission of a modifier from a prescription order, DMETS believes that the alternative, introduction of a new name into the marketplace is the worse option for two main reasons. First, the proposed name, Zmax, does not convey the extended-release properties of this product compared to Zithromax. This is further complicated by the fact Zithromax is already available in an immediate-release oral suspension and without conveying this product is extended release, health care practitioners may believe this is just merely a higher strength of the currently marketed oral suspension. Secondly, dual tradenames for the same active ingredient introduces the possibility that a patient may be taking both products without realizing that they have the same active ingredient or may be allergic to the active ingredient and take Zmax inadvertently not knowing it contains the same active ingredient. For these reasons, DMETS recommends the use of an appropriate modifier with the Zithromax name rather than Zmax or any other new proprietary name.

B. Potential misinterpretation of “Zmax” for Zithromax

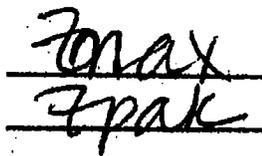
Zithromax is Pfizer’s proprietary name for azithromycin products (see table below).

Zithromax (Pfizer)	Tablets : 250 mg (as dihydrate)	Lactose. ( PFIZER 306 ). Pink, capsule shape. Film coated. In 30s, UD 50s, and Z-Pak 6s.
	500 mg (as dihydrate)	Lactose. ( PFIZER ZTM500 ). Pink, capsule shape. Film coated. In 30s, UD 50s, and TRI-PAK 3s.
	600 mg (as dihydrate)	Lactose. ( PFIZER 308 ). White, oval. Film coated. In 30s.
	Powder for injection, lyophilized : 500 mg	In 10 mL vials and 10 mL vials with 1 Vial-Mate adaptor.
	Powder for oral suspension : 100mg per 5mL (as dihydrate) when reconstituted	Sucrose. In 300 mg bottles.
	200 mg per 5 mL (as dihydrate) when reconstituted	Sucrose. In 600, 900, and 1,200 mg bottles.
	1 g/packet (as dihydrate)	Sucrose. In single-dose packets of 3s and 10s.

Although Zmax is a unique product with extended-release characteristics and is not bioequivalent to Zithromax, the proposed name may be viewed as a contraction of the drug Zithromax. Also, as stated in Section II.1. of this review, the proposed name, Zmax does not convey the extended-release properties of this product or any kinetic differences compared to Zithromax. Since a 2 g dose can be obtained with Zithromax (4 X 500 mg), it is possible for an order for Zmax, 2 g in one dose, to be filled with Zithromax. Zmax is formulated to release azithromycin slowly in the GI tract. Zmax has a single dose regimen for indicated infections where immediate-release products have three or five day courses of treatment. If an order for “Zmax” is filled with the immediate-release Zithromax in error the patient may not receive the expected kinetic performance, resulting in a higher peak but shorter duration. This type of error might result in treatment failure as a result of a shortened duration of action and patients might be at risk of increased side effects resulting from a higher than intended azithromycin peak. Conversely, if “Zmax” is used to fill an order for Zithromax, intended peak concentrations might not be reached since the bioavailability of Zmax relative to azithromycin for oral suspension is only 83%. Overall, because “Zmax” appears as though it could be an abbreviation for Zithromax, DMETS is concerned about the possibility of substitution of Zmax for immediate-release Zithromax products or vice-versa.

C. Sound-alike and or look-alike concerns

1. Z-Pak may sound and look similar to Zmax. Z-Pak is Pfizer’s packaging configuration of six Zithromax (azithromycin) 250 mg tablets in a five day course. Z-Pak is indicated for treatment of azithromycin sensitive bacterial infections where a five day course will suffice, including upper respiratory tract infections, acute bacterial exacerbations of chronic bronchitis, and mild community acquired lower respiratory tract infections due to susceptible bacterial strains. Z-Pak and Zmax owe phonetic similarities to the initial “Z” sound and similar-sounding ending “ak” vs. “ax”, respectively. Z-Pak and Zmax also have orthographic similarities including similar word lengths, shared letters, “Z” and “a”. The “x” in Zmax may also look like the “k” in Z-Pak as seen in the writing sample (below).


  
 The image shows the words "Zmax" and "Zpak" written in a cursive, handwritten style. The "Z" in both words is very similar, starting with a sharp hook. The "x" in "Zmax" and the "k" in "Zpak" are also written in a way that makes them look alike, with the "k" having a short, rounded tail that resembles the bottom of an "x".

In addition to orthographic similarities, Z-Pak and Zmax have numerous product similarities including; route of administration, indications of use (to treat bacterial infections), and overlapping patient and provider populations. Although Z-Pak and Zmax have differences including dosage form (tablet vs. for oral suspension), dose (250 mg vs. 2 gram), and dosing regimen (once daily for five days vs. one time dose), DMETS does not believe these differences will prevent confusion if orders are written for the Z-Pak or Zmax to be taken "as directed". Since both products have self contained directions of use, if an error is made, the patient will follow the directions which accompany the product. DMETS believes that either product may be written without reference to strength since they are only available in one strength. Overall, DMETS believes that sound-alike/look-alike properties along with strong product characteristic overlap contribute to increase the risk that these products will be confused.

2. Xanax/Xanax XR may sound and look similar to Zmax. Xanax is the anxiolytic agent, alprazolam, indicated for the management of various stress-related symptoms including generalized anxiety disorder, panic attack, and the anxiety resulting from depression. The usual adult alprazolam dose is 0.25 mg to 0.5 mg three times daily for the immediate-release tablet or 3 mg to 6 mg once in the morning for the extended-release tablet (Xanax XR). Xanax and Zmax owe phonetic similarities to the shared "z" sound at the beginning of each two-syllable name and the "ax" ending. The "n" vs. "m" sounds in middle of Xanax and Zmax are also virtually indistinguishable. Look-alike properties may be attributed to endings, "max" vs. "nax", which look very much alike especially when scripted in cursive (see sample below).

The image shows two lines of handwritten text in cursive. The top line is 'Zmax' and the bottom line is 'Xanax'. The letters are slanted and connected, illustrating the phonetic and orthographic similarities mentioned in the text.

Along with some sound-alike and look-alike properties, Xanax and Zmax share some product characteristics including; route of administration, and numerical similarity in strength (2 mg vs. 2 g), respectively. Additionally, DMETS is aware through postmarketing surveillance of confusion between the units "mg" and "g". Xanax/Xanax XR and Zmax also have differences including dosage form (tablet vs. for oral suspension), and indications of use (for anxiety vs. for infection), respectively. Since Xanax may be ordered as a one time dose, it is possible that a written inpatient order for "Zmax 2 g now" could be confused for "Xanax 2 mg now". If a patient takes Xanax rather than Zmax, they may suffer sedative side effects and have the infection go untreated. Overall, DMETS believes that sound-alike/look-alike properties along with strong product characteristic overlap contribute to increase the risk that these products will be confused.

3. "Amox" (an abbreviation for amoxicillin) may look similar to Zmax when written. Entering "amox" in the search engine, Medilexicon<sup>15</sup> for medical abbreviations resulted in the identification of amoxicillin. Amox® is also a branded amoxicillin product,

<sup>15</sup> Web Reference for MediLexicon: <http://www.pharma-lexicon.com/>

marketed in Canada<sup>16</sup>, which may cause confusion in the event that the prescription is ordered over the internet. Amoxicillin is a broad spectrum antibiotic indicated in the treatment of infections due to sensitive bacterial strains. Although the usual adult dosage is 750 mg to 1500 mg in two to three divided doses, amoxicillin may be given in single large doses, e.g., 2 grams prior to a dental procedure as recommended by the American Heart Association<sup>17</sup>. Amoxicillin is available in tablets, capsules, and powder for oral suspension. Amox and Zmax owe orthographic similarity to similar word lengths, shared letters “m” and “x”, and similarities in the lower case “o” vs. “a”. The “A” in “Amox” may also look like the “Z” in Zmax, especially if it is crossed (see writing sample below).



In addition to orthographic similarities, Amox and Zmax have numerous product similarities including route of administration, dosage-form (for oral suspension), indication for use (to treat bacterial infections), dose and dosing regimen (a single 2 gram dose), and patient and provider populations. DMETS considers the misinterpretation of an order for Zmax 2 gram to be a distinct possibility. If amoxicillin was dispensed rather than azithromycin, the patient might not receive adequate coverage to treat the infection and might experience treatment failure. Overall, DMETS believes that look-alike properties along with strong product characteristic overlap contribute to increased risk that these products will be confused.

D. DMETS nomenclature concerns with “Zmax” extend to \_\_\_\_\_

The additional words “\_\_\_\_\_” following the proprietary name Zmax do little to allay the concerns expressed by DMETS regarding Zmax. Through post marketing experience DMETS is aware of the inadvertent omission of modifiers. Still more information implicating the omission of modifiers from the proprietary name in medication errors appears in drug safety literature<sup>18</sup>. DMETS believes that the modifier “\_\_\_\_\_” has high potential of being omitted from verbal or written orders. Thus the potential exists for the prescription to be scripted as Zmax and ultimately misinterpreted as the names identified under the Zmax name review (Section C). Since the product is only available in a single dose, inclusion of this modifier in the proprietary name may be viewed as extraneous or redundant by prescribers, especially since the directions would be expected to have the same words, e.g., “Take the contents of the bottle in a single dose”.

E. Domestic and foreign marketing of other “Z-max” and “Zmax” products \_\_\_\_\_

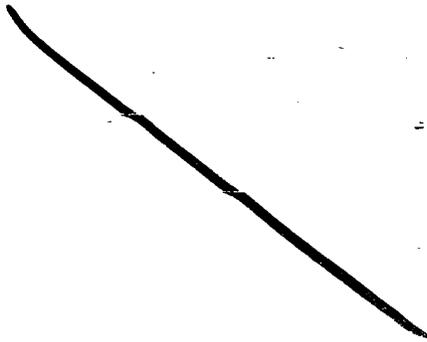
Through internet searches (Google), DMETS has become aware of marketing of Zmax products which have different active ingredients than the proposed product. Both of the OTC

<sup>16</sup> Web Reference: <http://www.lung.ca/drugs/pages/303.html>

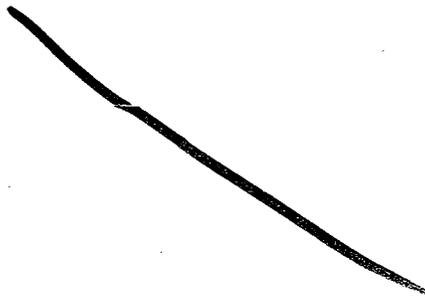
<sup>17</sup> Web Reference: <http://www.qualitydentistry.com/dental/information/abiotic.html>

<sup>18</sup> Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

supplements pictured below state that these zinc-containing products work to increase testosterone thereby increasing muscle strength<sup>19,20</sup>.



Both of these supplements can also be purchased on-line. Another product containing phentolamine, [fentolamina (Spanish)], is marketed as an anti-impotence drug in Mexico under the proprietary name, Z-Max<sup>21</sup> (see image below). A U.S. traveler in Mexico might experience surprising side-effects but worsening infection in attempting to cure a respiratory infection with the Z-Max (fentolamina).



DMETS is aware of references in drug safety literature of confusion and medication errors resulting from US brand names with different active ingredients abroad<sup>22,23</sup>. Although the articles implicate naïve travelers and drug re-importation as contributing factors in errors resulting from international nomenclature discrepancies, DMETS is also concerned about the possibility of confusion resulting from on-line (www) availability or reference to these products. In one scenario, a patient may try to fill their Zmax prescription on-line and receive the wrong product. Perhaps a more likely scenario would see a patient research the “Zmax” prescribed by their doctor and find that it is for male sexual enhancement or muscle growth. In the latter scenario, a patient might be confused and result in calls to the doctor about the Zmax order, or worse, not have the prescription filled.

<sup>19</sup> Web Reference for LA Muscle Zmax Compound: <http://www.fuelsport.co.uk/ProductPage.asp?pro=1201401>

<sup>20</sup> Web Reference for Zmax: <http://www.maxsportsmag.com/science/issue22/22sci2.htm>

<sup>21</sup> Web Reference for Z-Max: [http://news.bbc.co.uk/1/hi/special\\_report/1998/viagra/248168.stm](http://news.bbc.co.uk/1/hi/special_report/1998/viagra/248168.stm)

<sup>22</sup> Same name, different drug. *Medication Safety Alert!* January 13, 2005, 10(1), 2.

<sup>23</sup> New dangers in the drug re-importation process: Will we know what our patients are taking? *Medication Safety Alert!* January 27, 2005, 10(2), 1,2.

2 Page(s) Withheld

       Trade Secret / Confidential

✓ Draft Labeling

       Deliberative Process

#### IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary names Zmax or
- B. DMETS recommends that the sponsor use the modifier, ER, conveying the extended-release characteristics of this product with the existing name, Zithromax.
- C. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- D. DDMAC finds the proprietary name Zmax acceptable from a promotional perspective.
- E. The CDER Labeling and Nomenclature Committee has made recommendations regarding the proper designation of the established name for this product. See section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Scott Dallas, Project Manager, at 301-827-7849.

---

Charlie Hoppes, RPh, MPH  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Ajina Mahmud, RPh, MS  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A. Prescription Studies for Zmax

Verbal	Inpatient	Outpatient
Z-max	Zmax	Z-max
Zemax	Zmax	Zmax
V-max	Zmax	ZMax
Zemax	Zmax	Zmax
Zmax	Zmax	Zmax
Zeemax	Zmax	Zmax
Z Max	Zmax	Z max
Z-max	Zmax	Zmax
Zmax	Zimax	Zmax
Zmax	Zmax	Zmax
Zmax	Zmax	Zmax
Zimax	Z-max	Z-max
Z Max	Zimox	Zmax
Zmax	Zimox	Zmax
Z-max	Zmax	Zmax
Z-max	Zmax	Zmax
Z-Max	Zmax	

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/s/  
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Charles Hoppes  
5/13/05 03:24:30 PM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
5/13/05 03:30:08 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
5/13/05 03:34:46 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
5/13/05 04:20:26 PM  
DRUG SAFETY OFFICE REVIEWER

# Memo

**To:** Janice Soreth, M.D.  
Director, Division of Anti-Infective Drug Products  
HFD-520

**From:** Charlie Hoppes, R.Ph., M.P.H.  
Safety Evaluator, Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Through:** Alina Mahmud, R.Ph., M.S., Team Leader  
Carol Holquist, R.Ph., Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420

**Date:** December 16, 2004

**Re:** ODS Consult 04-0341; Zmax [REDACTED] (NDA 50-797); August 12, 2004 submission

---

This memorandum is in response to a November 13, 2004 request from your Division for a review of the proprietary name, Zmax [REDACTED] (NDA 50-797). Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) had the following promotional concerns with the proprietary name:

[REDACTED]

As per the e-mail from Judit Milstein of the Division of Anti-Infective Drug Products Project Manager, dated December 8, 2004, the Division concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, ZMax [REDACTED] since the Division supports DDMAC's

objection of the name based on promotional concerns. DMETS also acknowledges comments from the Division Project Manager (voicemail dated December 10, 2004), that the Division plans to notify the sponsor of the decision to reject the name based on the promotional concerns and request submission of an alternate proprietary name for NDA 50-797. Please forward the alternate name for DMETS review upon submission.

If you have any questions for DDMAC, please contact the Senior Regulatory Review Officer, Debi Tran. If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

cc: NDA 50-797

HFD-520: Division Files/Judit Milstein, Project Manager

HFD-520: Janice Soreth, Division Director

HFD-040: Debi Tran, Senior Regulatory Review Officer, DDMAC

HFD-120: Robert Kang, Project Manager, DDRE

HFD-420: Sammie Beam, Project Manager, DMETS

HFD-420: Denise Toyer, Deputy Director, DMETS

HFD-420: Alina Mahmud, Team Leader, DMETS

HFD-420: Charlie Hoppes, Safety Evaluator, DMETS

L:\ODS04\Hoppes\Premarketing Reviews\04-034. ~~XXXXXXXXXX~~

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/s/

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Charles Hoppes  
12/22/04 11:10:38 AM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
12/22/04 02:03:45 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
12/22/04 02:09:45 PM  
DRUG SAFETY OFFICE REVIEWER

**NDA FILEABILITY CHECKLIST**

NDA Number: 50-797

Drug Name: Zmax

(azithromycin)

Applicant: Pfizer

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

Yes X No

**Table 1**

The following parameters are necessary for initiating a full review, e.g. complete enough for review but may have deficiencies.

	PARAMETER	YES	NO	COMMENT
1	Is the NDA organized adequately for its CMC content?	x		
2	Are the CMC sections adequately indexed & paginated?	x		
3	Is the CMC sections legible?	x		
4	Are all facilities identified with full street addresses, contact names & CFN#s?	x		
5	Is there a statement that all facilities are prepared for GMP inspections?	x		Also, OC checks the status before their visit to a plant.
6	Has an environmental assessment or categorical exclusion been provided?		x	Did not find in EDR. Will request.
7	Does the drug substance section contain controls?	x		
8	Does the drug product section contain controls?	x		
9	Has stability data been submitted to justify the requested expiry date?	x		The reviewer will need to analyze the data
10	Has the applicant provided all requested data by the division during the IND & pre-NDA phases?	x		Based on cursory review
11	Have draft container labels been provided?	x		
12	Has a draft package insert been provided?	x		
13	Has an Investigational Formulations section been included?	x		Listed in the overall quality summary section
14	Are there three Methods Validation documents?	X		
15	Is a statistical consult required?		x	
16	Is there a separate microbiological section? Is a micro consult required?		x	No

EER REPORT ATTACHED

Table 2

Table 2

DMF INFORMATION

DMF #	DMF HOLDER	TYPE	LOA DATE	DATE OF LAST REVIEW
		III	4/2/04	Will review if needed
		III	4/8/04	"
		III	4/2/04	"
		III	3/30/04	"
		II	4/5/04	"
		IV	4/8/04	"

EXPLANATION WHY THIS NDA IS NOT FILEABLE: It is filable  
COMPLETION DATE: 3/31/05  
See DFS

Shrikant Pagay, Ph.D.

Review Chemist

James D. Vidra, Ph.D.  
Chemistry Team Leader

Attachment

Cc: Original NDA  
HFD-520/Division File  
HFD-520/Chm/  
HFD-520/ChmTL/Vidra  
HFD-520/ProjMgr/  
HFD-830/ActDivDir/Lin

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/s/

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Shrikant Pagay  
10/12/04 10:23:14 AM  
CHEMIST

Jim Vidra  
10/12/04 10:31:40 AM  
CHEMIST \*

45 DAY MEETING CHECKLIST FOR NDA 50-797

MICROBIOLOGY FILEABILITY

- On initial overview of the NDA application:
- |  | YES | NO |
|--|-----|----|
| 1. Is the microbiologic section of the NDA organized in a manner to allow substantive review to begin?                                 | √   |    |
| 2. Is the microbiologic section of the NDA indexed and paginated in a manner to allow substantive review to begin?                     | √   |    |
| 3. Is the microbiology section and other microbiologically pertinent sections of the NDA legible so that substantive review can begin? | √   |    |
- HAS THE APPLICANT SUBMITTED:
- |  |     |    |
|--|-----|----|
| 4. <i>In vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains and using necessary numbers of approved laboratories to meet current Divisional standards for approvability of the product based on the submitted draft labeling? |     | √* |
| 5. Any required animal model studies necessary for approvability of the product based on the submitted draft labeling?   | √   |    |
| 6. Draft breakpoints and interpretive criteria in a manner consistent with contemporary standards, in a manner which attempts to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?                    | √** |    |
| 7. All special studies/data requested by the Division during pre-submission discussions?   | √   |    |
| 8. Draft labeling consistent with 201.56 and 201.57, current Divisional policy, and the design of the development package?   |     |    |
| 9. FROM A MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.   | √   |    |

\*= On page 4, Section 5.3.5.4.1 (Clinical Microbiology) of the submission, the Applicant has stated that the information pertaining to the *in vitro* spectrum, mechanism of action, and activity of the drug in various animal models of infection may be found in the original application. However, the Applicant has failed to specifically identify these documents. The Reviewer asks the Applicant supply the exact identity of the submissions to which they refer.

\*\*= The Applicant has supplied MICs in tabular form for clinical isolates for each indication. However, the Applicant has not supplied scattergrams correlating MICs and zones of inhibition. The Reviewer asks the Applicant supply scattergrams correlating MICs and zones of inhibition for each organism identified in the indications. These data should include MICs and zones of

inhibition for both laboratory strains and clinical isolates of each organism.

Peter Coderre, PhD  
Reviewing Microbiology Officer  
and  
Supervisory Microbiology Officer

September 23, 2004

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/s/

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Peter Coderre  
9/30/04 08:31:01 AM  
MICROBIOLOGIST

Lillian Gavrilovich  
9/30/04 05:18:28 PM  
MEDICAL OFFICER

;



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 66,194

Pfizer, Inc  
Attention: Donald R. Jaffe, PhD  
Director, Worldwide Regulatory Affairs  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Jaffe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CP-62,993 (azithromycin).

We also refer to the meeting between representatives of your firm and the FDA on May 19, 2004. The purpose of the meeting was to discuss requirements for resistance claims, study conduct, labeling requirements and other issues related to the upcoming NDA submission.

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 Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Minutes of the meeting

3 Page(s) Withheld

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Draft Labeling

Deliberative Process

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/s/  
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Judit Milstein  
6/18/04 04:12:25 PM  
Judit Milstein for Frances LeSane

John Alexander  
6/18/04 04:16:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 66,194

Pfizer, Inc.  
Attention: Ashley Milton, PhD  
Senior Associate Director  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Milton:

Please refer to the meeting between representatives of your firm and FDA on December 3, 2003. The purpose of the meeting was to discuss and seek agreement on the Levofloxacin trial blinding proposal, to share examples of tables and data formats, and to share the CTD/NDA submission plans.

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 Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Minutes of the Meeting

## MEETING MINUTES

**MEETING DATE:** December 3, 2003

**TIME:** 12:00-1:00 p.m.

**LOCATION:** Teleconference

**APPLICATION:** IND 66,194 - Zithromax powder for oral suspension

**SPONSOR:** Pfizer Inc.

**TYPE OF MEETING:** pre-NDA

**MEETING CHAIR:** John Alexander, MD, MPH

### **FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

Janice M. Soreth, MD, Director, Division of Anti-Infective Drug Products

John Alexander, MD, MPH, Medical Team Leader

Nasim Moledina, MD, Medical Officer

Scott Komo, PhD, Statistical Reviewer

Venkat Jarugula, PhD, Biopharmaceutics Team Leader

Harold V. Silver, Microbiologist

Judit Milstein, Regulatory Project Manager

### **EXTERNAL CONSTITUENT ATTENDEES AND TITLES:**

Marie Ulrey - Development operations

Cindy Maclelland - Project management

Jean Breen - Clinical Team Leader

Daniel Jorgensen - Clinical Development

Fredrick Whaley - Bio statistics

David Douglas - Full Development Team Leader

Andrea Clark - Risk evaluation and documentation

Sandra Jacques - Submission Management Sciences

Ron Trust - Regulatory Affairs

Ashley Milton - Regulatory Affairs

### **BACKGROUND:**

Zithromax (azithromycin) is currently approved in the form of tablets, capsules, sachet, powder for oral suspension, and intravenous formulations. The recommended duration of therapy ranges from 1-5 days, depending on the infection being treated.

The current IND investigates a new SR formulation, which allows for single-dose therapy days, for a wide range of infections.

The questions posted by the sponsor are **bolded**. Discussions are in regular font.

**MEETING OBJECTIVES:** (as per sponsor's briefing package)

1. To discuss and seek agreement on the Levofloxacin blinding proposal
2. To share examples of tables and data formats
3. To share the CTD/NDA submission plans

**SUMMARY OF UNDERSTANDINGS**

1. Pfizer's proposal on bioequivalence of levofloxacin comparators is acceptable.
2. Review of the data will determine the adequacy of the laboratory safety data collected, and the nature of the information to be conveyed in the label.
3. Data on efficacy and safety of the trial for adult pharyngitis is necessary as supportive information if approval for treatment of pediatric pharyngitis is sought.
4. The Division does not grant claims for penicillin-intermediate strains.
5. Information on pediatric use obtained through efficacy studies may be listed in the INDICATIONS and USAGE sections of the labeling, depending on the study results. Information for pediatric patients extrapolated from adult trials will be conveyed in the PRECAUTIONS, Pediatric Use sections of the package insert.
6. The Sponsor confirmed that the following tables would be included in their submission:

Analysis of subgroups by age, gender and ethnicity.

Tables of ITT/MITT analyses, where missing or unknown observations are classified as failures.

**QUESTIONS AND ANSWERS**

**Clinical Pharmacology Issue**

**1. Bioequivalence of levofloxacin comparators**

*Based on pharmacokinetic and comparative dissolution rationale previously submitted (23<sup>rd</sup> Sept 2003), Pfizer has concluded that labeled pharmacokinetic parameters of the two commercial formulations, coupled with suitable comparative dissolution data demonstrate bioequivalence of these and their blinded counterparts, in order to pool data from different regions using the different sourced materials (see appendix E). Does the Division concur with Pfizer's conclusion?*

The Division agrees with Pfizer's conclusion. This concurrence was previously communicated to Pfizer on an e-mail dated November 20, 2003.

### Administrative Issues

#### CTD summaries and tables

2. **Currently conducting pediatric pharyngitis and AOM trials. For the pediatric pharyngitis study, the age range (2 to 12 years) is sufficiently different from that of the AOM study (3 months to 4 years). Should a claim be sought for pediatric pharyngitis, it is proposed that safety data from these two trials will be described separately in the Summary of Clinical Safety. Does the Division concur with this proposal?**

The Division would also like to see the combined safety data available for pediatric patients, in addition to the individual data from the pharyngitis and AOM trials.

3. **Safety labs will be collected in approximately 700/800 subjects in the comparative AOM study, A0661073. Will laboratory safety data in approximately 700 children, 3 mo. to 4 years of age, approximately 350 each treated with either azithromycin SR or Augmentin ES-600, comprise a suitable laboratory safety database for pediatric use?**

Review of the data will determine the adequacy of the laboratory safety data collected. Pfizer clarified that only the AOM trial is collecting laboratory safety data.

4. **Examples of some efficacy, safety and microbiology summary tables are provided in Appendix B of this briefing package. Does the Division find these tables to be suitable? Are there any additional tables that the Division would like to review in advance of the application?**

The Division confirmed with the Sponsor that the following additional tables would be included in their submission:

Analysis of subgroups by age, gender and ethnicity.

Tables of ITT/MITT analyses, where missing or unknown observations are classified as failures.

5. **Please review the draft NDA/CTD Table of Contents provided in Appendix C.**

**The full archival copy of the azithromycin SR CTD/NDA will be submitted in electronic format in accordance with the guidance titled "Providing Regulatory Submissions in Electronic Format - NDA (January 1999)", as directed in the draft guidance titled "Submitting Marketing Applications According to the ICH-CTD Format - General Considerations (August 2001)", Section V - Electronic Submission. Each Item of the eNDA will link to the appropriate 1999 guidance-specified folder. Each folder will contain a Table of Contents organized according to the CTD organizational structure, with CTD components linked as appropriate.**

*A mapping table (Table 1, Appendix B) is provided for reference. Is the proposal acceptable to the Division? Does the outline for the Clinical Overview/Clinical Summary for the CTD contain the relevant information expected by the Agency? CTD Guidances issued to date do not clearly describe the placement of Microbiology data within the dossier. Please advise where in the Application the Division prefers to have the non-clinical and clinical microbiology data (a draft Microbiology Table of Contents is included in the Overall NDA-TOC (Appendix B), in Item 5.3.5.4 (Other Studies), and is also provided in Appendix D).*

Pfizer's proposal is acceptable. In addition, comments on the Microbiology information were e-mailed to the sponsor on December 1, 2003. A copy of this e-mail is included at the end of these minutes.

Also, a copy of the "Draft Guidance for Industry- Microbiological Data for Antibacterial Drug Products- Development, Analysis, and Presentation" was faxed to Pfizer on December 3, 2003.

6. **There are no new toxicology studies that have been conducted for this application. Pfizer proposes cross-referencing NDA-50-670 for prior submissions of Pharmacology/Toxicology information. Does the Division concur with this proposal? Does the Division require desk copies of previously submitted toxicology reports from other NDAs?**

The Division concurs with Pfizer's proposal and does not require desk copies of previously submitted toxicology reports from other NDAs. A clear reference on the location of the information in other NDAs will suffice.

#### 7. Clinical Study Reports

In NDA Item 8, complete Clinical Study Reports will be provided for the following clinical trials (see appendix C for study titles):

- Pivotal Phase 3 trials (note this list excludes the Phase 3 pharyngitis studies): A0661073, A0661075, A0661078, [REDACTED] A0661103
- Pivotal Phase 1 trials: A0661084, A0661086, A0661107, A0661113 A0661114, A0661115, A0661124
- Other Phase 1 trials: A0661090, A0661096, A0661098, A0661099, A0661100

*Does the Division concur with this proposal?*

This proposal is acceptable. In addition, the data on efficacy and safety of the trial for adult pharyngitis is necessary as supportive information if approval for treatment of pediatric pharyngitis is sought. A second study in pediatric pharyngitis could substitute the information provided by the adult pharyngitis study.

#### 8. Case Report Tabulations: Electronic Data Sets

NDA Item 11 will be provided as electronic data components as follows:

- Full SAS datasets for the following pivotal Phase 3 studies and reports: A0661073, A0661075, A0661078, [REDACTED] A0661103, Summary of Clinical Safety (SCS), Summary of Clinical Efficacy (SCE).
- Partial SAS datasets for the following studies:

- Pharyngitis/tonsillitis Phase 3 studies A0661071 and A0661119 (safety data only)
- PK data from pivotal Phase 1 studies A0661084, A0661086, A0661107, A0661113, A0661114, A0661115, and A0661124 (adverse event data from A0661086 will also be included)
- Other Phase 1 studies: A0661090, A0661096, A0661098, A0661099, A0661100 will have Section 13 line listings in conjunction with a complete clinical study report.
- Electronic CRFs and tabulations for all completed studies for which a study report is provided.

The individual study datasets will be provided in guidance-compliant fashion (SAS transport files, definition document and annotated CRF for each study). To facilitate review, an annotated template of selected unique tables will be provided to indicate the datasets and variables used to produce the information displayed in the tables. Section 13 listings will not be provided for these studies. Datasets will be provided for the SCS and SCE in guidance-compliant SAS transport files and will be accompanied by a definition document. *Does the Division concur with this proposal?*

The Division concurs with this proposal. In addition, all available data on adult pharyngitis is needed as supportive documentation.

9. With a completely electronic submission, and under the assumption that all reviewers and district personnel will have network access, Pfizer proposes to exclude any paper archival, review or field copies, as per 21 CFR 314.50. *Does the Division concur with this proposal?*

A paper copy for the field is still needed. It should comply with requirements set forth in 21 CFR 314.50 (k) (3).

10. Our previous experience with applications to the Division suggests that certain supervisory personnel have requested desk copies of the Administrative and Summary documentation. *Can the Division advise if this is the current operating model?*

In the absence of electronic signatures, signed hard copies of the sections required to have a signature are needed (e.g., form 356h, cover letter, debarment certification, etc.). No desk copies of the Administrative and Summary documentation is requested.

**Labeling Issues (please refer to Targeted Product Information – preliminary labeling document contained in Enclosure 2 of this briefing package)**

**11. ADVERSE REACTIONS, CLINICAL STUDIES**

For description of the various treatment-related adverse reactions (mostly gastrointestinal), Pfizer intends to display the major AEs (those occurring with an incidence of  $\geq 1\%$ ) in the usual fashion. Pfizer will also propose to describe these AEs by day of onset and duration. *Does the Division concur with this proposal? Does the Division have any additional comments on the CTD or the Target Product information or any other concerns at this time?*

1. Information to be included in the labeling will depend on the review of the data, including information on onset and duration of the AEs.



**Additional questions and comments:**

Responding to a question by the Division on patients who vomit after dosing, Pfizer clarified that the protocols calls for:

Collecting blood samples for those patients who vomit within 30 minutes after dosing, for Zithromax and placebo groups.

Collecting blood samples in a subset of non-vomiters.

Analysis of outcome for those patients who vomit against patients who do not vomit.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 66,194

Pfizer Inc.  
Attention: Ronald Trust, Ph.D., MBA  
Senior Associate Director, U.S. Regulatory Strategy  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Trust:

Please refer to the meeting between representatives of your firm and FDA on June 10, 2003. The purpose of the meeting was to discuss Pfizer's approaches in preparation for the submission of the NDA for Azithromycin SR.

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 Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Minutes of the meeting



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Draft Labeling

Deliberative Process

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/s/

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Frances LeSane  
7/10/03 02:52:24 PM

Jim Vidra  
7/10/03 04:09:28 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 66,194

Pfizer, Inc.  
Attention: Ronald Trust, Ph.D., MBA  
Senior Associate Director, U.S. Regulatory Strategy  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Trust:

Please refer to the telecon between representatives of your firm and FDA on April 8, 2003. The purpose of the telecon was to discuss Pfizer's proposed protocols for upcoming clinical trials.

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

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Minutes of the telecon



CAP:

The Division indicated that a delta of 10% is acceptable, however a meta-analysis is not. Analysis of each study should stand by its own.

This indication would likely be presented at an Advisory Committee Meeting considering that these trials would support a single-dose treatment for CAP.

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/s/

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Maureen Dillon-Parker  
5/7/03 04:33:43 PM  
IND 66,194 - MDParker for FVLeSane

John Alexander  
5/9/03 10:19:11 AM

4 Page(s) Withheld

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Draft Labeling

Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public-Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 24,999

Pfizer Inc.  
Attention: Ronald Trust, Ph.D., and MBA  
Senior Associate Director  
Regulatory Strategy, Policy and Registration  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Trust:

Please refer to the meeting between representatives of your firm and FDA on October 21, 2002. The purpose of the meeting was to obtain the Division's concurrence on Pfizer's proposed development plan for the registration of azithromycin.

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 me at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

Judit Milstein  
Regulatory Project Manager  
Division of Anti-Infective Drug Products  
Office of Drug Evaluation-IV  
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

## MEETING MINUTES

**MEETING DATE:** October 21, 2002

**TIME:** 3:00-4:00 p.m.

**LOCATION:** Corporate Building, Conference Room S-300

**APPLICATION:** IND 24,999

**TYPE OF MEETING:** EOP2, CMC

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Shrikant Pagdy, Ph.D., Chemistry Reviewer  
Chi Wan Chen, Ph.D., Director, Division of New Drug Chemistry III  
Charles Bonapace, Pharm.D., Biopharmaceutics Reviewer  
Philip Colangelo, Pharm.D., Ph.D., Biopharmaceutics Acting Team Leader  
Judith Milstein, Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Scott Herbig, Director, Pharmaceutical Research and Development, Pfizer Inc.  
Chandra Sekhar, Ph.D., Assistant Director, Analytical Research and Development.  
Ronald Trust, Ph.D., MBA, Sr. Associate Director, Worldwide Regulatory Affairs  
Lucia Sokol, Project Leader, Regulatory CMC  
Roger Nosal, Director, Regulatory CMC

### BACKGROUND:

Pfizer is developing a sustained release oral powder for suspension dosage form of azithromycin                     , that would permit a complete course of antibiotic therapy as a single dose.

A separate pre-clinical/clinical EOP2 meeting was held October 2, 2002.

### MEETING OBJECTIVES:

To discuss the                      ' process described in the briefing package.  
To obtain the Division's concurrence on Pfizer's proposed plan for the registration of azithromycin                     

### SUMMARY OF UNDERSTANDINGS

1. Submission of the CMC section of the NDA in CTD format is acceptable
2. Approved azithromycin drug substance specifications limits are appropriate for the registration of Azithromycin
3. Revised azithromycin drug substance specification to include only tightened particle size acceptance criteria                      use ICH Q6A terminology wherever appropriate] necessary for azithromycin                      is acceptable.
4. Adjustments of fill weights to account for variability of azithromycin drug substance potency are acceptable.

5. Pfizer's proposed dissolution method (i.e., medium and speed) for evaluating azithromycin product performance is acceptable. Further discussion is needed to determine the appropriate time points and acceptance criteria.
6. The proposed stability protocol is acceptable for the drug product. Although the protocol does follow the ICH Q1A(R) recommendation, I would not refer to it as "ICH stability protocol."

**DISCUSSION:**

After introductions, the questions posted by the sponsor (**bolded text**) were addressed as follows.

**1. Does the Division concur with Pfizer's plans to submit the CMC Section of the NDA in CTD format?**

Yes, the Division concurs with Pfizer's proposal. Pfizer clarified that a discussion on the development of the product, including the process, will be included in the Pharmaceutical Development section.

**2.a Does the Division concur with Pfizer that the approved azithromycin drug substance specification limits are appropriate for registration of Azithromycin?**

Yes, the Division concurs with Pfizer's proposal. A copy of the most recent specification [use singular in this context] for the drug substance will be included in the submission.

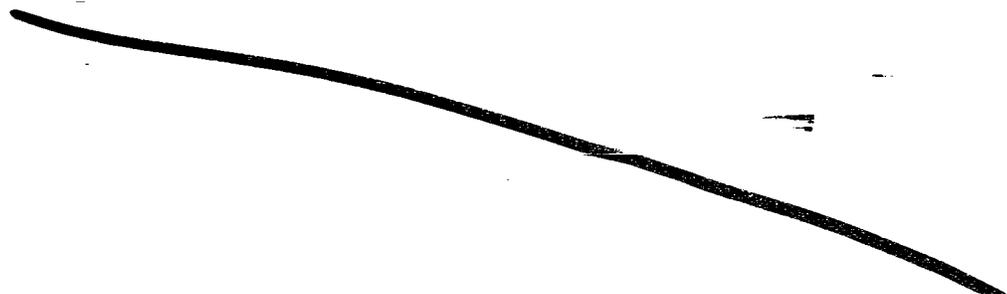
**2.b Does the Division concur with Pfizer's intention to submit a revised azithromycin drug substance specification to include only tightened particle size limits required for drug product manufacture?**

Yes, the Division concurs with Pfizer's proposal. The justification for the tightened particle size acceptance criteria will be included in the Pharmaceutical Development plan. However, at the request of the Division, Pfizer did agree to also include the rest of the drug substance specification in the new NDA.

**3.a Does the Division concur with Pfizer's plans to adjust fill weights to account for variability of azithromycin drug substance potency?**

Pfizer explained that the drug substance is a dihydrate of azithromycin, but the drug substance assay is based on contents of anhydrous azithromycin. The active microspheres are comprised of azithromycin dihydrate. Pfizer intends to adjust the microsphere fill weight based on drug substance assay of the microsphere to achieve potency of azithromycin in the drug product. This proposal is acceptable to the Division.

**2.b Does the Division concur with Pfizer's rationale for Azithromycin microspheres as a commercial step in the manufacturing process?**



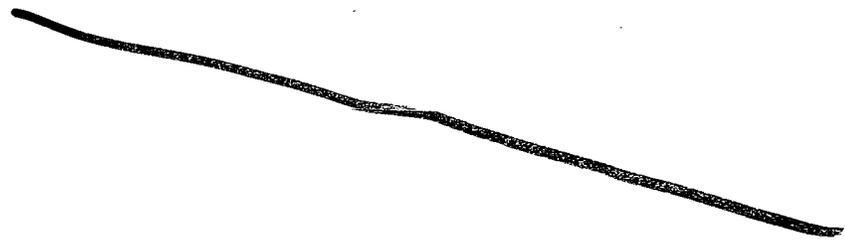
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**4. Does the Division concur with Pfizer's proposed dissolution method criteria for evaluating Azithromycin SR product performance and discriminating changes in the manufacturing process?**

The Division concurs with Pfizer's proposed dissolution method (USP Apparatus 2, 50 rpm, 900 mL, phosphate buffer pH 6.0). The inclusion of an additional time point to detect potential problems between batches was recommended by the Division.

Pfizer indicated that they currently perform full dissolution profiles and that they will submit this data to the Division.



**5. Does the Division concur with ICH stability protocols for drug product?**

Yes, the Division concurs with the proposed stability protocol for the drug product. Pfizer also confirmed that primary stability batches for the submission in the NDA meet the site specific stability study requirements.

Judit Milstein, October 23, 2002

Chi Wan Chen, Ph.D., Director, Office of New Drug Chemistry III, November 27, 2002

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/s/

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Judit Milstein  
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Chi Wan Chen  
12/2/02 07:01:39 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 24,999

Pfizer Inc.  
Attention: Ronald Trust, Ph.D., MBA  
Senior Associate Director, U.S. Regulatory Strategy  
50 Pequot Avenue  
New London, CT 06320

Dear Dr. Trust:

Please refer to the meeting between representatives of your firm and FDA on October 4, 2002. The purpose of the meeting was to review the Zithromax<sup>®</sup> [REDACTED] Release program and to discuss Pfizer's proposals for Phase 3 studies.

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 Judit Milstein, Regulatory Project Manager, at (301) 827-2207.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Minutes of the meeting

## MEETING MINUTES

**MEETING DATE:** October 4, 2002

**TIME:** 2:00-4:00 p.m.

**LOCATION:** Corporate Building, Conference Room S-300

**APPLICATION:** IND 24,999

**SPONSOR:** Pfizer, Inc.

**TYPE OF MEETING:** EOP2

**MEETING CHAIR:** John Alexander, M.D., M.P.H., Medical Team Leader

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Janice M. Soreth, M.D., Division Director  
John Alexander, M.D., M.P.H., Medical Team Leader  
Nasim Moledina, M.D., Medical Officer  
Albert Sheldon Jr., Ph.D., Microbiology Team Leader  
Philip Colangelo, Pharm. D., Ph.D., Biopharmaceutics Team Leader  
Joel Jiang, Ph.D., Statistics Reviewer  
Daphne Lin, Ph.D., Statistics Team Leader  
Amy Ellis, Ph.D., Pharmacology and Toxicology Reviewer  
Terry Peters, DVM, Pharmacology and Toxicology Acting Team Leader  
Jonca Bull, M.D., Director, Office of Drug Evaluation V  
Brenda Friend, R.Ph., J.D., Division of Scientific Investigations  
Antoine El-Hage, Ph.D., Associate Director, Division of Scientific Investigations  
Judit Milstein, Regulatory Project Manager

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Jeanne Breen, M.D.	Clinical Development – New London
Richa Chandra, M.D.	Clinical Sciences – New London
Daniel Jorgensen, M.D.	Clinical Development – New London
Paul Miller, Ph.D.	Discovery Microbiology - Groton
Ronald Trust, Ph.D.	Regulatory Affairs – New London
Rebecca Benner, Ph.D.	Clinical Biostatistics – New London
Ann Carey	Regulatory Affairs – New York
Michael Dunne, M.D.	Clinical Development-New London
Howard Mayer, M.D.	Clinical Development – New London
Linda Shurzinske, Ph.D.	Clinical Biostatistics – New London
Scott Herbig	Pharmaceutical R&D – Groton
Roger Nosal, Ph.D.	Pharmaceutical R&D – Groton
Susan Poirier	Project Management – New London
Mark Taisey	Regulatory Affairs – La Jolla
Melissa Tassinari, Ph.D.	Drug Safety Evaluation (Pharm/Tox) - Groton

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/s/

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Frances LeSane  
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John Alexander  
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