CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-821

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 21-821 SUPPL # HFD # 520

Trade Name Tygacil

Generic Name Tigecycline

Applicant Name Wyeth Pharmaceuticals, Inc.

Approval Date, If Known June 15, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ Explain:	NO ☐ Explain:

Investigation #2	
YES ☐ Explain:	NO ☐ Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Judit Milstein
Title: Regulatory Project Manager
Date: June 15, 2005

Name of Office/Division Director signing form: Janice M. Soreth, MD
Title: Director, Division of Anti-Infective and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Janice Soreth
6/15/05 05:24:30 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA: 21-821

Stamp Date: December 15, 2004 **Action Date: June 15, 2005**

HFD-520_ Trade and generic names/dosage form: Tygacil (tigecycline), IV

Applicant: Wyeth Pharmaceuticals, Inc. **Therapeutic Class: 1**

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: Complicated skin and skin structure infections

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_____	mo._____	yr < 8 years	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.= 8**	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.= 18**	**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): June 15, 2008

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.

Attachment A

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

Indication #2: Intra-Abdominal infections

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_____**	**mo._____**	**yr.< 8 years**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.= 8**	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr. = 18**	**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): June 15, 2008

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 520
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)

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

/s/

Judit Milstein
6/15/05 11:33:57 AM

John Alexander
6/15/05 01:03:21 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-821	Efficacy Supplement Type SE-	Supplement Number	
Drug: Tygacil (tigecycline), IV		Applicant: Wyeth Pharmaceuticals, Inc.	
RPM: Judit Milstein		HFD-520	Phone # 301-827-2207

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications: • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC)	( ) Standard (X) Priority 1
❖ User Fee Goal Dates	June 15, 2005
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information • User Fee • User Fee waiver • User Fee exception	(X) Paid UF ID number _4808__ ( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____ ( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP) • Applicant is on the AIP • This application is on the AIP	( ) Yes (X) No ( ) Yes (X) No

• Exception for review (Center Director's memo) • OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its	( ) Yes ( ) No

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)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	X , June 15, 2005
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	February 28, 2005

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (X) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	December 15, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS 6-6-05 DDMAC 6-14-05 DMETS 5-6-05, 8-13-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	December 15, 2004, May 10, 2005
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	N/A
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	7-3-2001 and 11-21-2002 (CMC)
• Pre-NDA meeting (indicate date)	2-18-2004, 5-24-2004 and 6-24-2004 (CMC)
• Pre-Approval Safety Conference (indicate date; approvals only)	May 18, 2005
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Team Leader 6-15-05 Office Dep.Director/Division Director 6-15-05
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	6-15-05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	6-15-05
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MO review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	6-6-05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	6-15-05
❖ Statistical review(s) *(indicate date for each review)*	6-14-05
❖ Biopharmaceutical review(s) *(indicate date for each review)*	6-15-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6-14-05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	6-15-05
❖ Environmental Assessment • Categorical Exclusion *(indicate review date)* • Review & FONSI *(indicate date of review)* • Review & Environmental Impact Statement *(indicate date of each review)*	See CMC review, page 71
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	March 24, 2005
❖ Facilities inspection (provide EER report) 3-8-05	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	6-15-05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

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

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/s/

Judit Milstein
6/23/05 03:42:24 PM

Deputy Office Director and Division Director Review Memo

Applicant: Wyeth Pharmaceuticals, Inc.

NDA #: NDA 21-821

Drug: tigecycline, for injection

Trade Name: Tygacil™

Indications: (1) Complicated skin and skin structure infections
(2) Complicated intra-abdominal infections

Date of submission: December 15, 2004

PDUFA goal date: June 15, 2005

Recommended Regulatory Action:

Approval for NDA 21-821

The pre-clinical and clinical reviewers have evaluated the issues in their disciplines in detail with regard to the safety and efficacy of Tygacil. For a comprehensive review by discipline, the reader is referred to these individual reviews. This memorandum will focus on selected findings and issues from the application.

The Chemistry for Tygacil™ is discussed in Dr. Pagay's review, and he has recommended approval. Tygacil™ (tigecycline) for injection is a sterile lyophilized powder for reconstitution and intravenous infusion. Dr. Riley's Product Quality Microbiology Review also recommends approval. The Applicant will use a limit for the acceptance criteria in accordance with the Inspections of the facilities have been completed and deemed acceptable.

The Pharmacology/Toxicology studies for tigecycline found bone marrow suppression (decreased erythrocytes, reticulocytes, leukocytes, and platelets) along with marrow hypocellularity at exposures 8 to 10 times human exposures. In short term dog studies with higher doses, vomiting was observed. In animal studies, tigecycline was noted to localize to bone. No effect was seen on QT in telemetrized dogs receiving doses up to 12 mg/kg. With regards to effects on liver, elevations of liver enzymes and histopathologic changes were not seen with the exception of occasional decrements in

total protein and fatty changes in the liver noted in the 2 week dog study at 20 mg/kg. Tigecycline was not found to exhibit phototoxicity in animal studies. Tygacil is labeled as Pregnancy Category D, consistent with the tetracycline class of antibiotic drugs. For additional details on Pharmacology/Toxicology, please see Dr. Wendelyn Schmidt's Review.

The Clinical Pharmacology of tigecycline is described in Dr. Jeff Tworzyanski's Clinical Pharmacology and Biopharmaceutics review. Analysis of protein binding showed that tigecycline was 71% to 89% protein bound. Tigecycline is not extensively metabolized and is excreted via biliary/fecal route and, to a lesser extent, via urinary excretion. In studies evaluating metabolism utilizing human liver microsomes *in vitro*, tigecycline did not inhibit metabolism mediated by the CYP P450 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4. The usual dose for tigecycline, 100 mg IV for the first dose, followed by 50 mg IV every twelve hours, requires adjustment in patients with severe hepatic impairment, to a regimen of 100 mg IV for the first dose, followed by 25 mg IV every twelve hours. Dose adjustment is not required for renal insufficiency. With concomitant administration of warfarin and tigecycline, decreased clearance of warfarin was noted. Coagulation studies should be monitored in patients receiving concomitant warfarin, as noted in the product label.

The microbiology of tigecycline is described in Dr. Fred Marsik's microbiology review . Tigecycline is a glycylcycline antibacterial agent. Its mechanism of action is inhibition of bacterial protein translation by binding to the 30S ribosomal subunit blocking tRNA molecules. Tigecycline can retain activity in the setting of efflux and ribosomal protection mechanisms of resistance for tetracyclines.

The results of the clinical trials have been thoroughly discussed in Dr. Charles Cooper's Medical Officer's review and Dr. Thamban Valappil's Statistical review. For a detailed analysis of the findings, the reader is referred to their reviews.

For the indication of complicated skin and skin structure infections (cSSSI), the applicant provided data from two pivotal randomized phase 3 trials of tigecycline compared to vancomycin and aztreonam (studies 300 and 305). The results from the FDA analysis for the Clinically Evaluable (CE) and Clinical Modified Intent-to-Treat (c-mITT) populations are summarized in Table 1. The FDA analysis limits the test of cure visit to at least 14 days and up to 35 days after the last dose of study drug.

Table 1. Clinical Cure Rates from Two Pivotal Studies in Complicated Skin and Skin Structure Infections after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Vancomycin/Aztreonam[b] n/N (%)	95% CI
Study 300			
CE	165/199 (82.9)	163/198 (82.3)	(-7.4, 8.6)
c-mITT	209/277 (75.5)	200/260 (76.9)	(-9.0, 6.1)
Study 305			
CE	200/223 (89.7)	201/213 (94.4)	(-10.2, 0.8)
c-mITT	220/261 (84.3)	225/259 (86.9)	(-9.0, 3.8)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Vancomycin (1 g IV every 12 hours)/Aztreonam (2 g IV every 12 hours)

The results of the studies support the non-inferiority of tigecycline to its vancomycin/aztreonam comparator for the treatment of complicated skin and skin structure infections. The clinical cure rates by infecting pathogen in the Microbiologically Evaluable Patients with cSSSI for tigecycline-treated patients with *Staphylococcus aureus* were 125/139 (89.9%) for methicillin-susceptible *Staphylococcus aureus* (MSSA) and 29/37 (78.4%) for patients with methicillin-resistant *Staphylococcus aureus* (MRSA); the corresponding results in the comparator arms for MSSA were 118/126 (93.7%) and for MRSA 26/34 (76.5%).

For the indication of complicated intra-abdominal infections, the applicant provided data from two pivotal randomized phase 3 trials of tigecycline compared to imipenem/cilastatin (studies 301 and 306). The results from the FDA analysis for the Microbiologically Evaluable (ME) and Microbiologic Modified Intent-to-Treat (m-mITT) populations are summarized in Table 2. The FDA analysis limits the test of cure visit to at least 14 days and up to 35 days after the last dose of study drug.

Table 2. Clinical Cure Rates from Two Pivotal Studies in Complicated Intra-abdominal Infections after 5 to 14 Days of Therapy

	TYGACIL[a] n/N (%)	Imipenem/Cilastatin[b] n/N (%)	95% CI
Study 301			
ME	199/247 (80.6)	210/255 (82.4)	(-9.0, 5.4)
m-mITT	227/309 (73.5)	244/312 (78.2)	(-11.8, 2.3)
Study 306			
ME	242/265 (91.3)	232/258 (89.9)	(-4.0, 6.8)
m-mITT	279/322 (86.6)	270/319 (84.6)	(-3.7, 7.7)

[a] 100 mg initially, followed by 50 mg every 12 hours
[b] Imipenem/Cilastatin (500 mg every 6 hours)

The results of the studies support the non-inferiority of tigecycline to its imipenem/cilastatin comparator for the treatment of complicated intra-abdominal infections.

Safety

Preclinical toxicology studies in rats and dogs showed that tigecycline, like tetracyclines, binds to bone and causes discoloration. Both species showed signs of histamine release, as well as decreases in red cells, white cells, and platelets. There was minor renal damage, but no observed effects on the liver. At higher doses, gastrointestinal side effects developed, notably vomiting. There were no Tygacil-related effects on EKGs, including QT interval, at any dosage in dogs.

Clinical data for approximately 1400 hospitalized adults in phase 3 studies comprise the safety database. Product labeling accurately reflects these safety findings. The most common treatment-emergent adverse events with Tygacil were nausea and vomiting.

There were a total of 32 deaths (2.3%) for patients treated with Tygacil contrasted with 22 deaths (1.5%) in patients treated with comparator drugs. Careful review of all deaths did not establish a relationship to study drug, and the difference in deaths between drugs was not statistically significant. Of note, there were no differences between Tygacil and comparators in median time to death, the distribution of days to death, or in the rates of infection-related death.

Trials of complicated intra-abdominal infections included a total of 1642 patients randomized 1:1 to Tygacil or comparator. In patients with clinically apparent intestinal perforations, 6 patients treated with Tygacil and 2 patients treated with comparator developed sepsis/septic shock. Due to differences in APACHE II scores, higher in Tygacil-treated patients, as well as small numbers, a relationship to drug could not be established. Prescribers are cautioned about the use of Tygacil as monotherapy in patients with complicated intra-abdominal infections secondary to intestinal perforation. A single patient on tigecycline developed pancreatitis, but the case was confounded by concomitant medication.

Review of laboratory data in phase 3 patients showed some elevations in liver-associated enzymes. The incidence (4-5%) was similar between Tygacil and comparators for treatment-emergent increases in SGOT and SGPT. However, patients on Tygacil were more likely to develop these liver enzyme abnormalities in the post-therapy period, in contrast to patients on comparator drugs. Whether or not this is related to Tygacil's longer half-life is unclear. No signals in clinical trials available to date were noted in blood counts.

Tygacil is a glycylcycline antibiotic, structurally similar to the tetracycline class. As such, product labeling includes warnings that Tygacil may cause fetal harm when administered to pregnant women and may cause permanent discoloration of teeth if given during tooth development.

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name Tygacil. The company's proposed Risk Management Program for Tygacil, which includes the approved product labeling, routine postmarketing surveillance and pharmacovigilance, and monitoring of tigecycline usage patterns, has been reviewed by ODS and is considered appropriate for Tygacil. The Division of Scientific Investigation conducted inspections of selected clinical study sites and recommended that data from two sites not be used to support the safety and efficacy of the application. Analyses conducted excluding these two sites did not change the overall conclusions

The pediatric studies required under PREA for the indications being approved in these NDAs are waived in pediatric patients under 8 years of age and deferred in pediatric patients 8 to 18 years of age. Other than the pediatric studies which are being deferred there are no phase 4 postmarketing commitments.

Further Development

There is a clear need for the development of new antibacterial therapy to treat patients with infectious diseases, in particular for patients with more serious illness and with important resistant pathogens. Tygacil, with its broad spectrum of activity, appears to be an important addition to the armamentarium. On-going studies in community- and [illegible] patients with vancomycin-resistant enterococci, and patients with [illegible] methicillin-resistant *Staphylococcus aureus* will provide important additional experience in the safety and efficacy of Tygacil.

Summary Recommendation

Approval for the indications of complicated skin and skin structure infections and complicated intra-abdominal infections.

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/s/

Janice Soreth
6/15/05 05:56:24 PM
MEDICAL OFFICER

Edward Cox
6/15/05 06:40:11 PM
MEDICAL OFFICER

14 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

MEMORANDUM

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

DATE: June 6, 2005

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

FROM: Claudia B. Karwoski, Pharm.D.,
Scientific Coordinator for Risk Management Programs (detail)
Office of Drug Safety, HFD-400

DRUG: Tygacil (tigecycline) for injection

NDA#: 21-821

APPLICANT: WYETH Pharmaceuticals, Inc.

SUBJECT: Review of Proposed Risk Management Program (RMP) submitted December 15, 2004

PID #: D050223

EXECUTIVE SUMMARY

The Office of Drug Safety (ODS) has reviewed the proposed Risk Management Program (RMP) for Tygacil, as submitted on December 15, 2004, and concludes that it does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance. The other measures proposed by the sponsor including good pharmacovigilance monitoring of tigecycline usage patterns to promote proper use of tigecycline, and surveillance of post-marketing (spontaneous) adverse event reports appear to be routine but seem reasonable and appropriate since there were no major safety issues identified during the clinical review.

BACKGROUND

Tygacil (tigecycline) is a novel glycylcycline antibiotic with expanded broad-spectrum antibacterial activity against gram-positive, gram-negative, atypical, and anaerobic bacteria,

including activity against multiple-resistant gram-positive and gram-negative bacteria. Tygacil has been developed for the treatment of serious hospital infections and the route of administration is IV. The proposed indications for this application are:

> Complicated skin and skin structure infections (cSSSI) caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible strains only), *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis.*
>
> Complicated intra-abdominal infections (cIAI) caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible strains only), *Staphylococcus aureus* (methicillin-susceptible strains only), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*

The safety database is comprised of 1415 tigecycline-treated subjects in phase 3 studies, 328 tigecycline-treated subjects in phase 2 studies, and 424 tigecycline-treated subjects in phase 1 studies. All studies were conducted in adult subjects. The results of integrated safety analyses support the conclusion that administration of 50 mg of tigecycline infused every 12 hours (after an initial loading dose of 100 mg) appears safe for subjects with cIAI and cSSSI. The most common adverse events (AEs) in the tigecycline group in all phase 3 studies were nausea and vomiting which were reported by 406 (28.7%) and 275 (19.4%) of subjects.[1]

The Sponsor has identified the following potential safety issues or risks in their risk management plan submission[2]:

- Nausea and vomiting
- Diarrhea
- Hypersensitivity
- Prothrombin time (PT)/Partial Thromboplastin Time (PTT) prolongation
- Hyperbilirubinemia
- Increased blood urea nitrogen
- Antimicrobial resistance
- Off-label use

Dr. Charles Cooper, MD, the medical officer assigned to the clinical review of this NDA, indicated in a discussion with the Office of Drug Safety on April 19, 2005 and again at the Pre-Approval Safety Conference (PSC) on May 18, 2005 that risk management measures beyond professional and patient labeling were not warranted. He verified that there are no major safety issues identified preapproval that would require an RMP other than the sponsor's submitted proposal. At the PSC, Dr. Cooper provided a thorough overview of the

[1] Tygacil™ (tigecycline) New Drug Application--Request for Priority Review; December 15, 2004.
[2] Tigecycline Risk Management Plan (NDA 21-821, December 15, 2004); Section 2.1-2.2· pgs 4-8.

clinical trial data, and he felt the important safety concerns were nausea, vomiting, and possible late onset of increased liver function tests all of which would be addressed in product labeling.

The proposed RMP consists of:

- Professional labeling
- Routine postmarketing surveillance and pharmacovigilance
- Monitoring of antibiotic usage

CONCLUSION

The sponsor's proposed Risk Management Plan for tygecycline, NDA 21-821, does not appear to differ substantially from a typical new product labeling and routine passive post-marketing safety surveillance. The other measures proposed by the sponsor including good pharmacovigilance monitoring of tigecycline usage patterns to promote proper use of tigecycline, and surveillance of post-marketing (spontaneous) adverse event reports appear to be routine but seem reasonable and appropriate since there were no major safety issues identified during the clinical review.

If the sponsor or the review division identifies a safety concern and determines that a Risk Minimization Action Plan (RiskMAP) is warranted or should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

/S/

Claudia B. Karwoski, Pharm.D., Scientific Coordinator (detail)
Office of Drug Safety, HFD-400

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/s/

Mary Dempsey
6/6/05 10:35:41 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
6/6/05 10:43:32 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: May 18, 2005

SUBJECT: **Safety Conference**
NDA 21-821, Tygacil (tigecycline), IV

Attendees: Mark Goldberger, ODE IV Director
Edward Cox, ODE IV Deputy Director
Janice Soreth, Division Director
Lillian Gavrilovich, Deputy Director
John Alexander, Medical Team Leader
Charles Cooper, Clinical Reviewer
Thamban Valappil, Statistical Reviewer
Wendelyn Schmidt, Pharmacology and Toxicology Reviewer
Jeff Tworzyanski, Clinical Pharmacology Reviewer
Venkat Jarugula, Clinical Pharmacology Team Leader
Suresh Pagay, Chemistry Reviewer
Fred Marsik, Microbiology Reviewer
Yanling Wang, Pharmacometrics Reviewer
Melissa Truffa, ODS Team Leader
Ron Wassell, ODS Reviewer (via audioconference)
Judit Milstein, Regulatory Project Manager

BACKGROUND:
Submission Date: December 15, 2004
Goal Date: June 15, 2005
Indications: Complicated Skin and Skin Structure Infections (CSSIs) and Complicated Intra-Abdominal Infections (cIAI)

DISCUSSION:
Treatment emergent Adverse Events (AEs) were discussed as follows:

Nausea and vomiting:
Tigecycline-treated patients at a higher rate of nausea in all phase 3 combined studies, 31.6% vs. 18.5%, and also for vomiting, 21.2% vs. 12.1%. The majority of this difference, however, is derived from the cSSSI studies where the rates nausea for tigecycline vs. comparator (vanco/aztreonam) were 35.3% vs. 9.3% and the rates of vomiting were 20.4% vs. 4.3%. In the cIAI studies, the rates of nausea and vomiting were more similar between tigecycline and the comparator (imipenem/cilastin). It is difficult from this information to know whether the differences in rates of nausea and vomiting by indication are related to differences between the comparators or the result of a disease interaction.

Deaths:
There were also differences in the death rates for tigecycline vs. comparator. Overall, the death rate for tigecycline in the 4 combined cIAI and cSSSI studies was 2.2% for tigecycline vs. 1.3% for comparator. Looking only at death rates by indication, the results are, for tigecycline vs. comparator, 2.9% (24/817) vs 2.1% (17/825) for cIAI, and 1.1% (6/566) vs. 0.2% (1/550) for CSSI. Detailed review of the deaths in the cSSSI studies revealed that they were unlikely to be related to study drug as they included such events as pulmonary embolism, cardiac failure, and myocardiac infection. Review of the deaths in the cIAI studies did not result in a clear explanation for the difference in the death rate.

Liver Function Tests (LFTs) abnormalities:
There is concern about the lack of follow up on patients who had elevated LFTs at the Test of Cure (TOC). However, none of the cases reviewed represent a clear, non-confounded instance of drug-related liver toxicity, and there are not cases in which there was severe hepatic failure without a non-drug related explanation.

QTc Prolongation
Studies in telemetrized dogs did not show tigecycline-related effects on ECG, including QT interval, at any dosage. Results from the pooled four Phase 3 studies, when normalized by the logarithmic linear method corrections did show a small increase in the QTc interval (3.3 msec), that is lower that the threshold for "increased risk" for development of Torsade de Pointe established by the current ICH draft guidance.

Prothrombin time (PT) and Partial Thromboplastin Time (PTT) prolongation
The sponsor identified this two AES in their Risk Management Program. These are common AEs in the tetracycline class of antibiotics, and are not specific to tigecycline.

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/s/

Judit Milstein
6/15/05 06:29:19 PM
CSO

John Alexander
6/15/05 06:35:32 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-821 Supplement # n/a Efficacy Supplement Type SE- /N/A

Trade Name: Tygacil™
Established Name: tigecycline
Strengths: 50 mg

Applicant: Wyeth Pharmaceuticals
Agent for Applicant: N/A

Date of Application: December 15, 2004
Date of Receipt: December 15, 2004
Date clock started after UN: N/A
Date of Filing Meeting: January 13, 2005
Filing Date: February 11, 2005
Action Goal Date (optional): User Fee Goal Date: June 15, 2005

Indication(s) requested: Complicated Skin and Skin Structure Infections
Complicated Intra-Abdominal Infections

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

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

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

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

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

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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? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ 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)]? YES ☐ NO ☐

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

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  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 ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 56,518

- End-of-Phase 2 Meeting(s)? Date(s) 9/30/01 and 11/21/02 CMC NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 5/24/04 and 6/24/04 CMC NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☐ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☐ YES ☒ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☐ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

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

Chemistry

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

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ATTACHMENT

MEMO OF FILING MEETING

DATE: January 13, 2005

BACKGROUND: Tigecycline is a novel glycylcycline antibiotic with expanded broad-specrum antibacterial activity against gram-positive, gram-negative, atypical and anaerobic bacteria, including activity against multiple-resistant gram-positive and gram-negative bacterial
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Janice Soreth, John Alexander, Charles Cooper, Suresh Pagay, Jim Vidra, Dapnhe Lin, Thamban Valappil, Venkat Jarugula, Jeff Tworrzyanski, Wendy Shcmidt, Bob Osterberg, Lillian Gavrilovich, Frances LeSane, Fred Marsik, George Rochester, Bryan Ryley (over the phone), Judit Milstein

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

Discipline	Reviewer
Medical:	Chuck Cooper
Secondary Medical:	
Statistical:	Thamban Valappil
Pharmacology:	Wendy Schmidt
Statistical Pharmacology:	
Chemistry:	Suresh Pagay
Environmental Assessment (if needed):	
Biopharmaceutical:	Jeff Tworzyanski
Microbiology, sterility:	Brian Riley
Microbiology, clinical (for antimicrobial products only):	Fred Marsik
DSI:	
Regulatory Project Management:	Judit Milsten
Other Consults:	DDMAC, ODS, DSI

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

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known Not known yet NO ☐
- 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 ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS		FILE ☐	REFUSE TO FILE ☐
• Biopharm. inspection needed?			YES ☐ NO ☐
PHARMACOLOGY	N/A ☐	FILE ☒	REFUSE TO FILE ☐
• GLP inspection needed?			YES ☐ NO ☐
CHEMISTRY		FILE ☒	REFUSE TO FILE ☐
• Establishment(s) ready for inspection?			YES ☒ NO ☐
• Microbiology			YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

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

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of 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.☒ Convey document filing issues/no filing issues to applicant by Day 74.

_____
Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

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

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

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

Appears This Way
On Original

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

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

   If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   If "No," skip to question 4. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

   If "Yes," skip to question 6. Otherwise, answer part (c).

   (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES ☐ NO ☐

   If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

   (***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

   If "No," skip to question 5. Otherwise, answer part (b).

   (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐
   (The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

   NOTE: *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

*If "**Yes**," skip to question 6. Otherwise, answer part (c).*

(c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES ☐ NO ☐

*If "**No**," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES ☐ NO ☐

*If "**No**," skip to question 6.*

*If "**Yes**," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

(b) Is the approved drug product cited as the listed drug? YES ☐ NO ☐

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

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

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☐

10. Are there certifications for each of the patents listed for the listed drug(s)? YES ☐ NO ☐

11. Which of the following patent certifications does the application contain? (Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)

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

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

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

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

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

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

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

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

  YES ☐ NO ☐

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES ☐ NO ☐

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

  N/A ☐ YES ☐ NO ☐

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

  N/A ☐ YES ☐ NO ☐

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

      YES ☐ NO ☐

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

      YES ☐ NO ☐

    - EITHER

      The number of the applicant's IND under which the studies essential to approval were conducted.

      IND# _____ NO ☐

      OR

      A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

      YES ☐ NO ☐

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

    YES ☐ NO ☐

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/s/

Judit Milstein
2/25/05 05:01:47 PM
CSO

Frances LeSane
2/28/05 03:43:07 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,518

Wyeth Pharmaceuticals
Attention: Randall B. Brenner
Associate Director
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your Investigational New Drug Application (IND submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline (GAR-936).

We also refer to the meeting between representatives of your firm and the FDA on September 14, 2004. The purpose of the meeting was to discuss to review the currently available data on the Phase 3 studies, and to obtain concurrence from the Division regarding the opportunity for priority review and rolling 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 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

MEETING MINUTES

MEETING DATE:	September 14, 2004
TIME:	2:00-3:00 p.m.
LOCATION:	Corporate Building, Conference Room S-300
APPLICATION:	IND 56,518
DRUG NAME:	Tigecycline (GAR-936)
TYPE OF MEETING:	Guidance

FDA ATTENDEES: (Title and Office/Division)
Mark J. Goldberger, MD, MPH, Director, Office of Drug Evaluation IV
Edward Cox, MD, Deputy Director, Office of Drug Evaluation IV
Janice M.Soreth, MD, Director, Division of Anti-Infective Drug Products
Charles Cooper, MD, Medical Reviewer
John Alexander, MD, MPH, Medical Team Leader
Frederic Marsik, PhD, Clinical Microbiology Reviewer
Peter Coderre, PhD, Acting Clinical Microbiology Team Leader
Thamban Valappil, PhD, Statistical Reviewer
Daphne Lin, PhD, Statistical Team Leader
Judit Milstein, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Patricia Bradford, PhD, Infectious Disease Discovery Research
Randall Brenner, Associate Director, Regulatory Affairs
Evelyn Ellis-Grosse, PhD, Director, Clinical Research and Development
Robert Herbertson, Associate Director, Clinical Biostatistics
Evan Loh, MD, Vice President, Clinical Research and Development
Christine Rosser, Senior Manager, Regulatory Affairs
Gilbert Rose, PhD, Senior Director, Clinical Research and Development

BACKGROUND:
The sponsor is planning to submit an NDA for tigecycline by the end of this year, in an electronic technical document format (eCTD), using the rolling submission mechanism. This original NDA will include clinical studies to support skin and skin structure infections (cSSI) and intra-abdominal infections (IAI) claims.

MEETING OBJECTIVES:
To present the Phase 3 data available to date from one IAI and two cSSI studies.
To obtain the Division's concurrence regarding the opportunity for priority review and proposed rolling submission schedule.

DISCUSSION POINTS:
The decision on the priority review will be made at the time of filing, and it will be based on the apparent benefit to certain population not currently covered such as patients with methicillin-resistant *Staphylococcus aureus* (MRSA), and multi-drug resistant Gram negative pathogens.

If review of the data indicates that the risk/benefit for tigecycline is similar to Wyeth's conclusion, the Division would not foresee the need for an Advisory Committee meeting. On the

other hand, if significant questions arise abut the efficacy and/or safety of the drug, an advisory committee meeting may be needed.

Review of the data will determine the need for Phase 4 commitments; therefore the need for such commitments could only be evaluated toward the end of the review cycle. The Division noted that pediatric studies are now listed under Phase 4 commitments. Provide in your NDA submission an outline of your proposed pediatric studies.

Submission of additional data from patients with resistant pathogens during the review cycle would be acceptable if the cases are very few and the sponsor is not relying on these data to support specific labeling claims. The Division noted that submission of large amount of clinical data later in the review cycle may constitute a major amendment.

The Division has no direct interactions with CDRH with regard the approval of in vitro susceptibility devices.

DECISIONS (AGREEMENTS) REACHED:

The Division concurs with Wyeth's proposed rolling review schedule.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Wyeth will set up a WebEx conference to obtain input from FDA clinical reviewers on navigation tools for the Case Report Forms (CRFs).

ATTACHMENTS/HANDOUTS:

None

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/s/

Judit Milstein
10/13/04 01:34:23 PM
Judit Milstein for Frances LeSane

MEMORANDUM OF TELECON

DATE: June 24, 2004

APPLICATION NUMBER: IND 56,518, Tigecycline

BETWEEN:

Name: Randall Brenner, Associate Director, Regulatory Affairs
Sherry Ku, PhD, Senior Director, Early Development Unit
Pat F. Mann, Director, Worldwide Regulatory Affairs
Jeffrey Medwid, PhD, Director, Stability
Norris Pyle, Senior Regulatory Specialist, CMC
Christine Rosser Senior Manager, Global Regulatory Affairs
Ken Schanbacher, Associate Director, Project Management
Jane Watts, Senior Principal Writer, Chemical and Pharmaceutical Development

Phone: 866-703-9405

Representing: Wyeth Pharmaceuticals, Inc.

AND

Name: Shrikant Pagay, PhD, Chemistry Reviewer
James D. Vidra, PhD, Chemistry Team Leader
Judit Milstein, Regulatory Project Manager
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: Discussion of CMC issues related to the upcoming NDA submission.

BACKGROUND:
Tigecycline, a glycylcycline related to the tetracycline antibiotics class is currently being developed as an IV formulation for the treatment of Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra-Abdominal Infections,

During the pre-NDA meeting held on May 24, 2004, a decision was made to have a separate CMC meeting to answer questions posted by the sponsor in their briefing package. Preliminary responses, as well as discuss additional questions generated by the Division were sent to the sponsor on June 23, 2004, via e-mail (see attachment # 1)

SUMMARY OF THE DISCUSSIONS:
Drug Substance:

If the NDA is granted priority review, additional stability data can be submitted no latter than 3 month after the original complete NDA submission.
If the NDA is granted standard review, additional stability data can be submitted no later than 6 months after the original complete NDA submission.

With a total of s stability data (at submission and additional , at a latter submission) for the , the Division could consider a expiration dating if review of the data supports it. Any further extension of the expiration dating will require a CBE-30 supplement.

Drug Product:

Same scheduling for additional submissions as for the Drug Substance

Change for EOP2

For the material used in the Phase 3 studies, the sponsor will provide comparative impurity profile data for the materials manufactured both at the Rouses Point, NY, facility and by

Y-site compatibility

Wyeth clarified that the tigecycline and the drug/diluent "X" would be in two separate bags, and that they will be physically mixed for this study. The sponsor plans to assay the samples at pre-determined time interval instead of assaying several samples in a time study. The Division agreed with Wyeth's proposal.

Comparability Protocol for projected changes for vial and/or stopper

The supplement for changes in size and/or shape of sterile product could be reviewed under a CBE-30 timeline, if only a change in size or shape is proposed. If in addition a new manufacturing site is proposed, the supplement will be a prior approval.

Addition of a new manufacturing site

For sterile drug products, the sterilization validation data needs to be reviewed by a microbiology consult as a prior approval supplement.

Additional questions from the Division

Wyeth indicated that based on a maximum clinical dose of 150 mg/day, the maximum level of , would be , well below the permitted daily exposure (PDE) of .

As per ICH guideline Q3A, every impurity peak above 0.1% will be identified in the NDA.

Wyeth stated that the three major impurities ( ) are controlled specifications.

For drug product, the " " refers only to the acceptance criteria for . Specification in the NDA will include other than

The NDA will include specifications for individual and total degradants following ICH guidelines.

Wyeth has not conducted a specific safety study at the limit for . The Division recommended to include in the NDA any supportive data, including literature searches. The Division will also discuss this topic with the Pharmacology and Toxicology Reviewers.

Wyeth indicated that in-process acceptance criteria for the drug substance currently outlined in DMF will be incorporated directly in the NDA instead of referencing the DMF. Drug product acceptance criteria includes . In-process acceptance criteria will be outlined in the NDA.

Wyeth clarified that the actual data referenced in the submission , is from the initial release data on the primary stability batches. Stability data showed a wider range.

FDA specified that only shelf life specifications are required for NDA filing (FDA does not require Wyeth to file release specifications), however FDA will review the release specifications, if included in the NDA.

Wyeth also clarified that the vial potency assay quantitates the whole vial content to achieve the tight precision of the HPLC assay. Although no manufacturing or stability overage is added to the vial, a 6% USP overfill excess is added to ensure withdrawal of the labeled dose. Thus the actual target content is 106% to which a range is added in the specification. The Agency asked that this be clearly identified in the NDA such as in the pharmaceutical development report, to which Wyeth agreed.

The District Office would be initiating the request for the method validation samples, as early as October, 2004.

The Division encouraged the submission of the Letters of Authorization (LOAs) for the DMFs as early as possible, even before the September initial submission.

The Division agreed to accept one executed batch record (from a primary stability batch which has been used in a pivotal Phase 3 study) and one unexecuted batch record for inclusion in the NDA; However the Division indicated that Wyeth can submit executed batch data for all three batches. Wyeth will also submit a summary of batch manufacturing deviations to facilitate the review.

Wyeth reinforced the fact that the NDA will be in eCTD format.

Attachment # 1:

Pre-NDA Meeting
6/24/04

For sponsor's questions, please refer to the 4/26/04 briefing document (4 questions starting from page 9) and e-mail June 9, 2004. The following information consists of CMC summary and FDA response.

IND NUMBER: I 56,518

Sponsor's questions

Q 1. NDA Stability Data:

Proposed Expiration Date: — for both the drug substance and the drug product.

Drug Substance:

Container /closure systems: — glass

Stability Data Submission with NDA (NDA submission date 12/04; pre-submission of CMC module date 9/04)

— real time data and — accelerated data on — batches stored in glass —
— real time data and — accelerated data on — batches stored in —

During Review (February 2005)

— real time data (long term) in — glass —
— real time data in — is.

Supporting data

— real time data on pilot scale batches stored in — glass —
Statistical analysis of the data to support the proposed expiration date.

FDA Response for Drug Substance: If the review cycle is 6 months (priority), the sponsor may consider submitting — as a supplemental application due to limited data available at the time of submission..
If the review cycle is 10 months, the sponsor may consider submission of additional stability data for the — by May 2005 for evaluation of the data.
The expiration date will depend on the review of actual data for each container type.

Drug product

Container/closure: glass vials.

Stability Data Submission with NDA (NDA submission date 12/04; pre-submission of CMC module date 9/04)

real time data and accelerated data on all batches manufactured at
parenteral production site I, one batch at parenteral production site III (actual production site for this drug product).

During Review

real time data

Supporting data

real time data and accelerated data on validation batches.

FDA Response for Drug Product Stability: The proposed drug product data will be adequate for the application for both 6 and 10 month review cycle; however, additional data will be reviewed if submitted by May 2005. The data will be reviewed to determine the shelf life.

Q 2. Change from EOP 2 plan

Delete Wyeth NY facility from NDA submission.

FDA response: If the clinical studies were performed from the drug substance manufactured at the Wyeth NY facility, please provide the impurity data in the NDA to show that the clinical and commercial material (manufactured by y) are same.

Q 3. Addition of new site for the drug product manufacturing post approval

FDA response : Acceptable.

Q 4. Y-site compatibility study

FDA response: The proposed plan is acceptable with the following comment: →
For chemical compatibility study, please provide kinetic data (change in potency of the 2 components, i.e., tigecycline and diluent or another drug as a function of time under a given set of infusion mixture to determine the stability of the infusion mixture as a function of time).

The following questions were submitted by the sponsor in a recent e-mail (date June 9, 04)

Q 5. Comparability protocol for projected changes for vial and/or stopper

FDA response: The changes guidance (1999 Guidance to an Approved NDA or ANDA) requires that
"Changes in the size and and/or shape of a sterile drug product requires a PA supplement". If a comparability protocol is submitted in the NDA, appropriate recommendation will be provided based on the information.

Q 6. Addition of a new manufacturing site for the drug product.

FDA response: The new facility may meet the profile class requirements from PAI consideration; however for sterile drug product, the sterilization validation data needs to be reviewed under a PA supplement, unless all aspects are identical (equipment, container closure, — etc.). A PA supplement is required.

Other Issues to be discussed (questions from FDA)

- *— specifications (acceptance criteria) for the drug substance is — and for the drug product — . Does processing during manufacturing of the drug product achieves — Does — . limit also meets the criteria under ICH?*
- *Acceptance criteria for the largest single impurity in the drug substance is — No impurities above 0.1% have been identified other than — What program is in place to identify any unknowns above 0.1%?*
- *Are all process impurities controlled at the drug substance level?*
- *For drug product, acceptance criteria is listed under " — ". Does it include — other related compounds?*
- *There are no specifications for individual impurities in the drug product. Please explain.*
- *Is there a safety study data on — for the proposed limit at —*
- *There are no in-process acceptance criteria set in manufacturing the drug substance and the drug product. Please explain.*
- *Target label claim of the drug product acceptance criteria is — with the actual data between — Could the acceptance criteria be tightened?*
- *Is the lyophilization process appropriate — for better product control and some future regulatory relief. Is there such a consideration?*

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/s/

Judit Milstein
7/23/04 04:52:43 PM
CSO

Jim Vidra
7/23/04 05:03:22 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,518

Wyeth Pharmaceuticals, Inc
Attention: Randall B. Brenner
Associate Director
Worldwide Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for GAR-936.

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2004. The purpose of the meeting was to discuss the content and format for the upcoming NDA submission and present a review of the Phase 3 data currently available from the complicated skin and skin structure infection study.

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

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 24, 2004
TIME: 12:00-1:30 p.m.
LOCATION: Corporate Building, Conference Room S-300
APPLICATION: IND 56,518
DRUG NAME: GAR-936
TYPE OF MEETING: pre-NDA

MEETING CHAIR: Janice M. Soreth, MD, Division Director

FDA ATTENDEES: (Title and Office/Division)
Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV
Janice M. Soreth, MD, Director, Division of Anti-Infective Drug Products
Lillian Gavrilovich, MD, Deputy Director
Charles Cooper, MD, Medical Officer
John Alexander, MD, MPH, Medical Team Leader
Wendelyn Schimdt, PhD, Pharmacology and Toxicology Reviewer
Robert Osterberg, PhD, Pharmacology and Toxicology Team Leader
Frederic Marsik, PhD, Microbiology Reviewer
Shrikant Pagay, PhD, Chemistry Reviewer
Charles Bonapace, PhD, Clinical Pharmacology Reviewer
Thamban Valappil, PhD, Statistical Reviewer
Judit Milstein, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:
Timothy Babinchak, MD, Director, Clinical Research and Development
Theresa Booth-Genthe, Associate Director, Regulatory Operations
Patricia Bradford, PhD, Infectious Disease Discovery Research
Randall Brenner, Associate Director, Global Regulatory Affairs
Evelyn Ellis-Grosse, PhD, Director, Clinical Research and Development
Robert Herbertson, Associate Director, Clinical Biostatistics
Ishwari Kavdikar, Associate Director, Regulatory Affairs Europe
Evan Loh, MD, Assistant Vice President, Clinical Research and Development
Christine Rosser, Senior Manager, Global Regulatory Affairs
John Saverese, MD, PhD, Senior Director, Global Regulatory Affairs
Gilbert Rose, MD, Senior Manager, Global Regulatory Affairs
Ken Schanbacher, Project Management
John Speth, PhD, Senior Director, Clinical Pharmacology

BACKGROUND:
Tigecycline, a glycylcycline related to the tetracycline antibiotics class is currently being developed as an IV formulation for the treatment of Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra-Abdominal Infections,

Wyeth plans to submit a NDA for Tigecycline in December 2004 that will initially include Complicated Skin and Skin Structure Infections (cSSSI) and Complicated Intra-Abdominal Infections.

After the internal team meeting held on May 19, 2004, the Division forwarded to the sponsor additional questions posed by the microbiology reviewer, included in attachment # 1.

MEETING OBJECTIVES:

1. To discuss the content, format and rolling submission schedule for the upcoming e-CTD NDA submission scheduled for December 2004.

2. To discuss the priority review status and potential Advisory Committee Meeting.

3. To present a review of the Phase 3 data currently available for the complicated skin and skin structure infections study.

DISCUSSION POINTS:

The Division inquired about the possibility of submitting all the Case Report Forms (CRFs), for the Phase 3 trials. Considering the large amount of data that this involves, Wyeth will investigate the feasibility of this request. Wyeth will also investigate the feasibility of submitting final study reports early for individual Phase 3 studies, ahead of the planned submission of the complete Module 5.

DECISIONS (AGREEMENTS) REACHED:

The Division concurs with Wyeth's proposal for the eCTD format and the Study Tagging file (technical questions 1 and 2). It also agreed that Wyeth's Regulatory Operations group could contact directly the Agency's technical group regarding technical aspects of the eCTD submission.

The Division concurs with Wyeth's "rolling submission" plan. Wyeth will provide the CFN numbers for all manufacturing sites, as well as the street address for the plant locations at the time of the Module 3 (Quality) submission.

Wyeth will submit the patient line listing ahead of the December 15, 2004 submission to facilitate the generation of a random sample and identification of CRFs required for this part of the review.

CRFs of all patients with a Serious Adverse Event (sAE), including patients who where considered indeterminates and failures for any reason will be submitted.

The Division concurs with Wyeth proposal for the submission of the Microbiology data (Regulatory Question 1).

Decision on the priority review status of the application will be made at the time of the filing of the NDA (Regulatory Question 4)

Wyeth will submit the CRF for the only patient enrolled in Study # 302 (Clinical Question 1).

Data for Studies #307 and #309 will be presented in an integrated way; However, separate analyses for controlled and uncontrolled studies will also be provided. The overall experience with resistant Gram-negative infections can be presented in the Integrated Summary of Efficacy . Narratives of the current 25 cases will be provided. (Clinical Question 3)

The Division concurs with Wyeth's proposal for the data presentation for patients that developed resistance to tigecycline. Narratives will also be provided for any case with tigecycline resistance, regardless of outcome (Clinical Question 4).

Proposed population PK/PD analyses for CSSI and cIAI Phase 3 studies is acceptable (Clinical Question 5).

Proposal for samples located post study closure and database lock is acceptable, for as long as they represent a small number of cases (Clinical Question 6).

Proposal for the planned format and integrated safety presentation for the clinical program is acceptable (Clinical Question 7).

Proposal for the table of studies format is acceptable (Clinical Question 8).

Data definition tables (label variables), ITT analysis for efficacy (primary endpoint), and SAS programs for the primary analysis (primary endpoint) will be provided (Statistical Question 1)

Wyeth will submit an amendment to the IND with the same data submitted to the National Committee for Clinical Laboratory Standards (NCCLS) in January, 2004, to support the in vitro susceptibility test quality control ranges for tigecycline.

MIC_{50} and MIC_{90} values generated for anaerobic microorganisms, using both media, need to be performed using arithmetic means (Microbiology Question 1 and 2)

For selected pathogens including resistant Gram negative microorganisms, PCR and sequencing of the genes will be performed. Also, ribotyping of any isolate from patients with more than 1 occurrence will be performed.

Wyeth will provide a rationale on why "reasonably accurate approximations/extrapolations can be made regarding the relationship between MIC and efficacy in animal models (Microbiology Question 5).

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Decision on the need for an Advisory Committee Meeting will be made after initial review of the data. Usually, Advisory Committee Meetings are held 1-2 months prior to the due date for the application.

ACTION ITEMS:

Wyeth will investigate the feasibility of providing the CRFs for all the patients in Phase 3 studies.

The Division will provide some comments about datasets to be included in the NDA submission (see Attachment 2).

A separate CMC meeting will be scheduled to discuss the Chemistry Questions. Since the time between the face to face meeting and the issuance of the minutes, a CMC telecon was scheduled for June 24, 2004.

ATTACHMENTS/HANDOUTS:
Attachment # 1: additional microbiology questions
Attachment # 2: comments regarding datasets and tables

FDA microbiology comments (IND 56,518 SN 319 – 26 Apr 04)

The sponsor is asked to submit a detailed description of the specimen collection, transport, microscopic examination, culture methods, organism identification, and susceptibility test methods that will be used during clinical trials for review by the Agency prior to initiating clinical studies.

Please confirm that the following provisional breakpoints will be used during clinical studies.

Provisional MIC breakpoints:

Susceptible
Intermediate
Resistant ≥

Provisional disc diffusion breakpoints

For all organisms other than *Proteus*, *Providencia*, and *Morganella* species.

Susceptible
Intermediate
Resistant

For *Proteus*, *Providencia* and *Morganella* species.

Susceptible
Intermediate
Resistant

It is suggested that all isolates from clinical studies be re-identified at a central laboratory and MIC and disc diffusion susceptibility testing be done a central laboratory. This will allow for a more accurate determination of the MIC and disc diffusion susceptibility results for isolates.

The sponsor is asked to provide to the Agency the data presented to the National Committee for Clinical Laboratory Standards (NCCLS) at the 11-23 January 2004 to support the in vitro susceptibility test quality control ranges for tigecycline.

The sponsor is requested to submit to the Agency prior to presentation at the NCCLS data that will be used to support in vitro susceptibility test interpretive breakpoints for review.

The sponsor is asked to provide a summary of the studies that were done to determine that fresh media (<12 hrs post autoclave) needs to be used for broth microdilution susceptibility testing. Is this also the case for anaerobes and fastidious organism testing? What effect does the use of media older than 12 hours have on the MIC? Will quality control ranges for broth microdilution testing be able to monitor whether the test medium is of the appropriate age? How will the need for media no older than 12 hours for aerobic susceptibility testing be conveyed to laboratories?

Attachment # 2- Comments regarding the datasets and tables

1. Please be careful to follow the CRT format which is described in the Electronic Submissions section of the Guidance web page. (Guidance on Regulatory Submissions in Electronic Format: General Considerations and New Drug Applications at www.fda.gov/cder/guidance/index.htm)

2. CRT's should contain variables which allow us to figure out which analysis population a patient is in.

3. Please include a variable which identifies why a patient discontinued or was non-evaluable (or indeterminate). This can be a number variable with the data definition table explaining what each number stands for. For example: 1 = lost to follow up, 2 = no clinical response determined, 3 = died within two days of start of therapy… etc…

4. Exceptions to the protocol that don't meet inclusion/exclusion criteria but were included/exempted should have an identifying variable in the CRT's so that we may identify these patients.

5. We welcome your proposed analysis of the affects of concomitant medications on nausea. In the CRT for concomitant medications, please do not provide any trade names. Please only use generic drug names, and if possible, include a variable for the Drug Class.

6. It is acceptable to use Costart instead of MedDRA terminology, for as long as the submission has only one data dictionary for the entire application.

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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.

/s/

Frances LeSane
6/23/04 05:13:46 PM

John Alexander
6/23/04 05:33:49 PM

CONSULTATION RESPONSE

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

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0093-1
March 18, 2004	May 31, 2005 **PDUFA DATE:** June 15, 2005	

TO: Janice Soreth, MD
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Judit Milstein
Project Manager
HFD-520

PRODUCT NAME:	**NDA Sponsor:** *Wyeth Pharmaceuticals*
Tygacil™ (Tigecycline for Injection) 50 mg/vial **NDA # 21-821**	

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Tygacil. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Tygacil acceptable from a promotional perspective.

Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664

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: April 11, 2004

NDA#: 21-821

NAME OF DRUG: **Tygacil** (Tigecycline for Injection) 50 mg/vial

NDA HOLDER: Wyeth Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infectives (HFD-520), for a re-assessment of the proprietary name "Tygacil", regarding potential name confusion with other proprietary or established drug names. This name was previously reviewed by DMETS in May 2004 (DMETS consult number 04-0093) and found acceptable. Draft container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Tygacil is an anti-infective glycylcline class antibiotic for intravenous infusion. Tygacil is structurally similar to tetracyclines, thus it should be used with caution in patients with hypersensitivity to tetracyclines. In addition, the tooth discoloration associated with tetracyclines is relevant in Tygacil usage, since bone discoloration was found in rat studies. Tygacil is indicated for

The recommended dose is 100 mg initially followed by 50 mg every 12 hours; Tygacil is infused over 30 to 60 minutes. Duration of treatment is dependent on the severity, site of infection and clinical response, but the recommended duration of treatment is 5 to 14 days for complicated skin and skin structure infection and complicated intra-abdominal infections. Use in patients under the age of 18 is not recommended. Tygacil is available as an orange lyophilized powder with each vial containing 50 mg without preservatives or excipients. This should be reconstituted with 5.3 mL of 0.9% sodium chloride for injection or 5 % dextrose injection solution to achieve a concentration of 10 mg/mL (the vial contains a 6% overage). The solution is swirled until the drug dissolves. For the initial 100 mg dose, two vials should be reconstituted and added to a 100 mL bag for infusion. For the 50 mg dose, five milliliters should be withdrawn from one vial and added to 100 mL IV bag for infusion. The solution should be yellow to orange in color and if not, should be discarded. After dilution in the IV bag, the solution may be maintained at room temperature for up to 6 hours or refrigerated for up to 24 hours.

No dosage adjustment is warranted in patients with mild to moderate hepatic failure, but in patients with severe hepatic impairment the dose should be reduced to 100 mg, followed by 25 mg every 12 hours. No dosage adjustment is necessary in patient with renal impairment or in patients undergoing hemodialysis. Tygacil has been found to cross the placenta and may cause fetal harm when administered to pregnant women. Tygacil is listed in the pregnancy category – Tygacil is supplied in a single-dose 5 mL glass vial containing 50 mg of lyophilized powder for infusion, which is supplied as 10 vials per box. Tygacil is maintained at room temperature.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Tygacil 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[4]. The Saegis[5] 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.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Tygacil. 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 Tygacil acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names, Tysabri and Tagamet, which were thought to have the potential for confusion with Tygacil. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

APPEARS THIS WAY
ON ORIGINAL

[1] 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.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] 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 Drugs@fda.gov, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by Expert Panel

Product Name	Dosage form(s), Established name, Available Strengths	Usual adult dose*	Other**
Tygacil™	**Tigecycline, 50 mg Vial for Injection**	**Initial intravenous loading dose of 100 mg, followed by 50 mg every 12 hours for 5 to 14 days. The rate of infusion should be approximately 30-60 minutes every 12 hours.**	
Tysabri®	Natalizumab Concentrate for Infusion 300 mg/15 mL, (20 mg/mL)	Administer 300 mg once every month by slow (over 60 minutes) intravenous infusion.	LA/SA
Tagamet® (Tagamet HB 200)	Cimetidine Tablets: 200 mg, 300 mg, 400 mg, 800 mg Liquid: 300 mg per 5 mL Injection: 150 per mL	200 mg up to 1600 mg daily (in divide doses)	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

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 Tygacil were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Tygacil was identified by the Expert Panel Discussion to have a similar appearance and sound to Tysabri and Tagamet. Upon further review of the names gathered from EPD, Tagamet will not reviewed further due to a lack of convincing look-alike similarities with Tygacil. In addition, the products have numerous differentiating characteristics including product strength (150 mg, 200 mg, 300 mg, 400 mg, and 800 mg compared to 50 mg), indications for use (ulcer/GERD compared to [illegible]), and dose (200-1600 mg in divided doses compared to 100 mg followed by 50 mg every 12 hours).

Tysabri was identified as having sound-alike and look-alike similarities to Tygacil. Tysabri is the proprietary name for natalizumab, a recombinant humanized anti-α4 integren that is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations [illegible]. Tysabri was voluntarily withdrawn from the market by the sponsor on February 28, 2005; however, the BLA (125104) remains active and the product may potentially be marketed at a later time. The usual recommended dosage for Tysabri is 300 mg, administered once a month as a slow (over 60 minutes) intravenous infusion. The drug is to be administered in a free-standing medical clinic,

infusion center, or in an outpatient hospital setting and is not intended for administration in the home setting. Tysabri was marketed in single-use vials containing 300 mg of natalizumab in 15 milliliters with strength of 20 mg/mL. This is to be further diluted with preservative-free 0.9% sodium chloride injection to attain a total infusion volume of 100 mL. Tysabri should be stored at 2-8°C, and protected from light. The names Tysabri and Tygacil each contain three syllables. The first syllable of each name "Ty" is identical and the second syllable of each name has the short "a" sound in common. The final syllable of each name, however, "cil" vs. "bri" share no apparent phonetic properties and may serve to distinguish the names phonetically. The names may also look-alike when scripted since the shared letters of "Ty" and "a" has the same placement in each name. However, differing placement of letter upstrokes, "b" compared to "l" in Tysabri and Tygacil, respectively, as well as the distinctive down-stroke of the "g" in Tygacil" may serve to differentiate the names orthographically.

Although Tygacil and Tysabri are both injection products which are diluted further for intravenous infusion over a 60 minute time frame, there are product differences including strength (300 mg/15 mL compared to 50 mg), dosing regimen (100 mg then 50 mg every 12 hours compared to 300 mg monthly), and conditions of use (chronic treatment of relapsing forms of multiple sclerosis compared to treatment of acute infection), respectively. These differences along with lack of convincing sound-alike/look-alike properties will minimize the potential for error.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Tygacil, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL

B. CARTON LABELING

C. INSERT LABELING

1. Dosage and Administration Section

   Preparation and Handling

   a. Since the initial usual dosage of Tygacil is 100 mg, the directions for reconstitution for this dose should appear first. Thus, please switch these two sentences, "Thereafter, 5 mL of the reconstituted.....For a 100 mg dose, ...bag."

   b. Please reposition this sentence "Note: the vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug." to immediately follow the first sentence in this section. This is a more natural flow of information for the practitioner, which will aid in proper interpretation and completion of the infusion.

   c. Please consider the addition of the storage criteria for the reconstituted and diluted solutions as documented in the storage section. As practitioners will be reviewing this information for the reconstitution of the drug product, placement of this information in this section could be of an aid to correct storage and usage.

2. How Supplied Section

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Tygacil. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name Tygacil acceptable from a promotional perspective.

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 301-827-2102.

_____
Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: _____
Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Kimberly Culley
5/6/05 12:43:07 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/6/05 02:04:34 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS, in her absence

CONSULTATION RESPONSE

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

DATE RECEIVED:	DESIRED COMPLETION DATE:	ODS CONSULT #: 04-0093
March 11, 2004	May 7, 2004	

TO: Janice Soreth, MD
Director, Division of Anti-Infective Drug Products
HFD-520

THROUGH: Judit Milstein
Project Manager
HFD-520

PRODUCT NAME:	IND Sponsor: Wyeth
Tygacil™ (Tigecycline for Injection) 50 mg **IND # 56,518**	

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Tygacil. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends submitting container labels and labeling for review and comment when available.

3. DDMAC finds the proprietary name Tygacil acceptable from a promotional perspective.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
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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: May 24, 2004

IND#: 56,518

NAME OF DRUG: **Tygacil** (Tigecycline for Injection) 50 mg

IND HOLDER: Wyeth

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infectives (HFD-520), for assessment of the proprietary name "Tygacil", regarding potential name confusion with other proprietary or established drug names. Draft container labels, carton and insert labeling were not provided for review and comment. The sponsor has submitted a market research package prepared by the — with data supporting the selection of the proposed trade name for review and comment.

PRODUCT INFORMATION

Tygacil is an anti-infective glycycline class antibiotic, which is structurally similar to tetracycline class antibiotics, and is indicated for

Tigecycline is a lyophilized powder that should be reconstituted with 5.3 mL normal saline and shaken until the powder dissolves. After reconstitution, 5 mL of the solution should be withdrawn from the vial and added to the IV bag for infusion. The vial contains a 6% overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug. Intravenous infusions of 100 mL of tigecycline, (an initial

loading dose of 100 mg, followed by 50 mg maintenance doses) should be administered over approximately 30-60 minutes every 12 hours. It is supplied in single-dose vials containing 50 mg lyophilized powder for infusion after reconstitution with normal saline (0.9% sodium chloride injection, USP). Tygecycline lyophilized powder may be stored at room temperature for up to [illegible]. Once reconstituted, tigecycline may be stored at room temperature (25°C, 77°F) for up to 6 hours, or for 24 hours when refrigerated (2-8°C). Warnings associated with the tetracycline class should also be observed for tigecycline.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Tygacil 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[4]. The Saegis[5] 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 Tygacil. 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 Tygacil acceptable from a promotional perspective.

2. The Expert Panel identified one proprietary name, Tikosyn, that was thought to have the potential for confusion with Tygacil. It was also noted that Tygacil sounds like the product is a penicillin (e.g., Ticarcillin) rather than a tetracycline. This product is listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

3. Through independent review, Tyzine, Tigan, Ticarcillin, and Tylenol were identified as potential look-alikes to Tygacil. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, Drugs@fda.gov, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by Expert Panel and through Independent Review

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Tygacil	Tigecycline, 50 mg vial, For Injection	Loading dose: 100 mg over 30-60 min Maintenance Dose: 50 mg over 30-60 min, Intravenous.	NA
Tyzine	Tetrahydrozoline HCL 0.05%, and 0.1% solution, nasal inhalation	2 to 4 drops of 0.1% solution in each nostril as needed, not to exceed every three hours.	SA/LA
Tylenol	Acetaminophen Tablets: 325 mg (oral) Extended-release tablets: 650 mg (oral) Capsules: 500 mg (oral) Caplets: 160 mg, 325 mg, and 500 mg (oral) Tablets (Chewable): 80 mg, 160 mg (oral) Suppositories: 80 mg, 120 mg, 125 mg, 325 mg, and 650 mg (rectal) Solution: 48 mg/mL, 80 mg/mL, 100 mg/mL, 80 mg/5 mL, 120 mg/5 mL, 160 mg/5 mL, 167 mg/ 5mL, 500 mg/ 15 mL (oral) Suspension: 80 mg/mL, 100 mg/mL, 80 mg/5 mL, 160 mg/5 mL (oral) Syrup: 16 mg/mL (oral) Sprinkle Capsules: 80 mg, 160 mg (oral)	325 mg to 1,250 mg q 4-8 hours as needed.	LA
Ticar	Ticarcillin Disodium Injection, Intravenous 1 gm, 2 gm, 20 g, and 30 gm	200 mg-300 mg/kg/day or 3.1 g every 4-6 hours IV over 30 minutes.	SA
Tikosyn	Dofetilide Capsules: 125 mcg, 250 mcg, and 500 mcg	Individualized based on weight, age, and serum creatinine, averages between 125 mcg to 500 mcg twice daily.	SA
Tigan	Trimethobenzamide Hydrochloride Capsules: 300 mg Suppositories: 100 mg and 200 mg Ampules: 100 mg/mL Multi-dose Vials: 100 mg/mL in 20 mL vials.	200 mg to 300 mg three or four times a day.	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike).

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

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 Tygacil were discussed by the Expert Panel (EPD).

D. 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 Tygacil 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 124 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 Tygacil (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
Outpatient RX: Tygacil 50mg IV to be given by home health nurse today #1	Tygacil 50 mg IV to be given by home health nurse today. Dispense #1.
Inpatient RX: [illegible]	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

E. INDEPENDENT NAME ANALYSIS

The analysis conducted by — identified the five names discussed by DMETS in Section III of this review and the following names that were not identified as potential sound or look-alike products by DMETS (Gelusil, Pipracil, Tequin, Terazol, Tizac, Ticlid, Trasylol, Vagisil, Agnigel, Actagen, Actigall, Adatosil, Amerigel, Cefprozil, Cefzil, Flagyl, Igepal, Karigel, LamisilAT, Lamisil, Metamucil, Miglitol, Obezine, Octigen, Psorigel, Rifalazil, T-Gel, T=Gesic, Tagamet, Talacen, Targretin, Tedrigen, Tegafur, Tagagel, Tyrosum, Zyprexa, Tegison, Tegretol, Verapamil, Vivactil, Cyclogyl, and Dermasil). Following review of these proprietary names identified by — , DMETS concurs that none of the aforementioned names poses a significant safety risk. We concur with the overall findings of the study.

F. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Tygacil was identified by the Expert Panel Discussion, to have a similar appearance and sound to Tikosyn. Similarly, through independent review, five additional drug names, Tyzine, Tylenol, Tigan, Ticarcillin, and Tylcalsin were also determined to have potential for confusion with Tygacil. The POCA tool did not identify any additional names as having significant phonetic or orthographic similarity. The — study identified the names in section E above. However, following review of these names, they did not pose any potential for significant confusion. Tylcalsin was listed in Micromedex as a tradename for a brand of soluble aspirin. However, no information is available through commonly used references such as the Physician's Desk Reference (PDR), Drug Facts and Comparison, Electronic Orange Book, NDC Directory, DestinationRX.com, RX.com and the 2003 Red Book. Therefore, Tylcalsin will not be discussed further.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any proprietary or established 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. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Tygacil.

1. Tyzine may look similar to Tygacil when scripted. Tyzine is indicated for decongestion of nasal and nasopharyngeal mucosa. Both names begin with letters that may look similar when scripted (tyz and tyg). The rest of the letters may also look similar, particularly if the vertical length of the 'e' of Tyzine is accentuated (see below). However, there are differentiating product characteristics, such as dose (50 mg or 100 mg vs. 2 to 4 drops), dosage form (for injection vs. nasal solution), strength (50 mg vs. 0.05% and 0.1%), frequency of administration (every 12 hours vs. as needed up to every 3 hours), route of administration (intravenous vs. intranasal), and indication of use (infection vs. nasal decongestion). Despite the orthographic similarities, the product characteristics may help to distinguish the two products and decrease potential for error.

2. Tylenol may look similar to Tygacil. Tylenol is indicated for nonnarcotic analgesia and as an antipyretic. Both names begin with the same two letters 'ty', and end with letters that may look similar when scripted (ol vs. il). However, Tygacil contains two downstrokes (yg) and Tylenol contains one (y). Additionally, the downstroke in Tylenol is followed by an upstroke 'l', giving Tylenol two upstrokes, and Tygacil only one (see below). There are differentiating product characteristics that may help to mitigate errors, such as dose (50 mg or 100 mg vs. 325 to 1,250 mg), dosage form (for injection vs. tablet, capsule, suppository, oral solution), frequency of administration (every 12 hours vs. every four to six hours), route of administration (intravenous vs. oral or rectal), indication of use (analgesia and pyrexia vs. anti-infective), and storage location (injectables vs. over-the-counter). Although a 50 mg or a 100 mg dose of Tylenol is likely in the pediatric population, Tygacil is not indicated for pediatric use. Additionally, since Tygacil is a tetracycline-like product, use in pediatric patients would be questioned by the pharmacist. Overall, the different product characteristics may help to distinguish the two products and help to minimize error.

Tygacil

Tylenol

3. Ticarcillin may sound similar to Tygacil depending upon pronunciation. Ticarcillin is indicated for the treatment of infections caused by susceptible strains of bacterial organisms. Both names contain letters that may sound similar (tic vs. tyg and arcill vs. acil). Additionally, if the 'in' of Ticarcillin is not accentuated, it may increase the potential for phonetic similarities. Although both products are injectable antibiotics, there are other differentiating product characteristics, such as dose (initial bolus dose of 100 mg followed by 50 mg vs. 200-300 mg/kg/day or 3.1 g), strength (50 mg vs. 3.1 g), frequency of administration (every 12 hours vs. every 4 to 6 hours). Since this is an anti-infective an additional concern is that the name Tygacil may lead practitioners to believe that this product is in the penicillin class, particularly Ticarcillin. This stems from the fact that the name Tygacil begins with letters that have similar phonetic pronunciations (ti vs. ty), and contains the letters "cil" which are generally found in penicillin containing products. Additionally, the USAN stem for penicillin products is 'cillin.' Although, this proprietary name does not contain the USAN stem, the similarities may contribute to the fact that practitioners may think this product is a penicillin, rather than a glycycline class antibiotic, which is very similar to tetracyclines. Healthcare practitioners should be educated about the different pharmacological class and that this product is not a penicillin product. Despite the phonetic similarities and the potential similarities to a penicillin like product, the dose, strength, and frequency of administration of Tygacil may help to differentiate the two products from each other.

4. Tikosyn may sound similar to Tygacil when pronounced. Tikosyn is indicated for the conversion of atrial fibrillation, atrial flutter, and the maintenance of normal sinus rhythm after conversion. Both names contain letters that may sound similar when pronounced (tyg vs. tik and osyn vs. acil). However, there are product characteristics that may help to differentiate the two products and minimize confusion, such as dosage form (for injection vs. capsules), strength (50 mg vs. 125 mcg, 250 mcg, and 500 mcg), route of administration (intravenous vs. oral), indication of use (infection vs. arrhythmia), and storage location (injectables vs. oral solids). The potential for overlapping doses is minimized by the dosing regimen of Tikosyn, which is based on a formula involving the

weight, age, and serum creatinine of the patient. This yields a final dose of either 125 mcg, 250 mcg, or 500 mcg twice daily. Additionally, Tikosyn has limited distribution to only hospitals, prescribed only by providers who have received appropriate dosing and treatment education, and is administered only in settings where the patients' electrocardiogram can be continuously monitored for 72 hours (e.g. cardiac telemetry unit, ICU, CCU). Thus, the differentiating product characteristics and limited distribution of Tikosyn may help to minimize error involving these two products.

5. Tigan may look similar to Tygacil when scripted. Tigan is indicated for the treatment of postoperative nausea and vomiting and for nausea associated with gastroenteritis. Both names contain letters that may look similar (tig vs. tyg and an vs. ac). However, the length of the names are different. Tigan contains five letters, whereas Tygacil contains seven letters (see below). Additionally, the upstroke for the letter "l" in Tygacil may help to differentiate the orthographic presentations of the two names. Although both products have an injectable dosage form, there are differentiating product characteristics that may help to minimize confusion, such as dose (100 mg, 200 mg or 300 mg vs. 50 mg or
100 mg), strength (100 mg, 200 mg, or 300 mg vs. 50 mg), frequency of administration (three or four times a day vs. every 12 hours), route of administration (oral, rectal, or intramuscular vs. intravenous), and indication of use (nausea and vomiting vs. infection). Although the pediatric dose of Tigan (100 mg) and the loading dose of Tygacil (100 mg) may overlap, the route of administration (intravenous vs. intramuscular) may help differentiate the products. Additionally, Tygacil is only for use in adult patients which may also help differentiate the overlapping doses. Thus, the product characteristics may help to minimize confusion and potential for error involving Tigan and Tygacil.

tigan
tygacil

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Draft labels, carton and insert labeling were not submitted for review and comment. Please submit when available.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Tygacil. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

B. DMETS recommends submitting container labels and labeling for review and comment when available.

C. DDMAC finds the proprietary name Tygacil acceptable from a promotional perspective.

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 Sammie Beam, project manager, at 301-827-2102.

/S/

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: _____
Denise P. Toyer, PharmD.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

NDA# 21-821 (IND # 56,518)
ODS Consult# 04-0093

Voice	Inpatient	Outpatient
Tagasil	Tagacit	Fygacil
Tigacil	Tigacil	Sygacil
Tigacil	Tygacil	Syqacil
Tigacil	Tygacil	Tygacil
Tigacil	Tygacil	Tygacil
Teasels	Tygacil	Tygacil
Tigasil	Tygacil	Tygacil
Tigasil	Tygacil	Tygacit
Tigasil	Tygacil	Tygaril
Tigasil	Tygacil	Tygaril
Tigecil	Tygacil	Tygaril
Tigecyl	Tygacil	Tyqacil
Tigersil	Tygacil	Tyqacil
Tigosil	tygacil	Tyqacil
Tygasel	Tygacil	Tyqacil
Tygasil	Tygacil	Tyqacil
Tygasil	Tygacil	Tyqacil
Tygasil	Tygacil	Tyqaril
Tygisil	Tygacil	Zygacil
Tygosil	Tygracil	
Tygosil	Typacil	
tyvacil		

cc: NDA# 21-821 (IND # 56,518)

HFD-520: Judit Milstein, Project Manager
HFD-520: Janice Soreth, Division Director
HFD-040: Andy Haffer, Senior Regulatory Review Officer, DDMAC
HFD-430: Robert Kang, Project Manager, DDRE
HFD-420: Sammie Beam, Project Manager, DMETS
HFD-420: Linda Wisniewski, Safety Evaluator, DMETS
HFD-420: Denise Toyer, Team Leader, DMETS
HFD-420: Lisa Hubbard, Project Manager, DMETS
HFD-520: Chuck Cooper, Medical Officer, DAIDP

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

/s/

Denise Toyer
8/12/04 02:19:29 PM
DRUG SAFETY OFFICE REVIEWER
Entering for Linda Wisniewski, Safety Evaluator

Carol Holquist
8/13/04 08:58:44 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,518

Wyeth Pharmaceuticals
Attention: Randall B. Brenner
Associate Director
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your Investigational New Drug Application (IND submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tigecycline (GAR-936).

We also refer to the meeting between representatives of your firm and the FDA on February 18, 2004. The purpose of the meeting was to provide a complete status update on tigecycline's clinical and preclinical program and discuss general issues in preparation for the December 2004 Electronic Common Technical Document (eCDT) 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

MEETING MINUTES

MEETING DATE: February 18, 2004

TIME: 2:00-3:30 p.m.

LOCATION: Corporate Building, Conference Room S-300

APPLICATION: IND 56,518 Tigecycline

SPONSOR: Wyeth Pharmaceuticals

TYPE OF MEETING: Guidance

MEETING CHAIR: Janice M. Soreth, MD, Director

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:
Janice M. Soreth, MD, Director, Division of Anti-Infective Drug Products (DAIDP)
Lillian Gavrilovich, MD, Deputy Director
John Alexander, MD, MPH, Medical Team Leader
Charles Cooper, MD, Medical Officer
Albert Sheldon Jr., PhD, Microbiology Team Leader
Wendelyn Schmidt, PhD, Pharmacology and Toxicology Reviewer
Robert Osterberg, PhD, Pharmacology and Toxicology Team Leader
Thamban Valappil, PhD, Statistical Reviewer
Daphne Lin, PhD, Statistical Team Leader
Charles Bonapace, PharmD, Clinical Pharmacology Reviewer
Venkat Jarugula, PhD, Clinical Pharmacology Team Leader
Judit Milstein, Regulatory Project Manager
Edward Cox, MD, Acting Director, Office of Drug Evaluation IV
Dave Roeder, Associate Director for Regulatory Affaire, ODE IV
John Powers, MD, Lead Medical Officer, ODE IV
Marc Goldberger, MD, MPH, Acting Deputy Director, CDER

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
Dr. Evan Loh, Assistant Vice President, Clinical Research and Development
Dr. Gilbert Rose, Senior Director, Clinical Research and Development
Dr. Evelyn Ellis-Grosse, Director, Clinical Research and Development
Dr. John Speth, Senior Director, Clinical Pharmacology
Mr. Steven Troy, Senior Director, Clinical Pharmacology
Dr. Don Raible, Senior Director, Clinical Pharmacology
Mr. Randall Brenner, Associate Director, Regulatory Affairs
Dr. Patricia Bradford, Infectious Disease Discovery Research
Mr. Robert Herbertson, Associate Director, Clinical Biostatistics
Ms. Christine Rosser, Senior Manager, Regulatory Affairs
Hal Feldman, Associate Director, Safety Pharmacology
Tim Babinchak, Associate Director, Clinical Research and Development

BACKGROUND:
Tigecycline, a glycylcycline related to the tetracycline antibiotics class is currently being developed as an IV formulation for the treatment of Complicated Skin and Skin Structure Infections (cSSSI), Complicated Intra-Abdominal Infections, —— — .n the adult population.

Wyeth plans to submit a NDA for Tigecycline in December 2004 that will initially include Complicated Skin and Skin Structure Infections (cSSSI) and Complicated Intra-Abdominal Infections ——
—

During the October 2, 2003 teleconference the Division suggested a face-to-face meeting to review the current status of the tigecycline program.

In addition, following the Division's internal team meeting, additional questions were posed to the sponsor with regard to drug-drug interaction studies between tigecycline and oral contraceptives, relationship between the use of tigecycline and osteoporosis, vestibular toxicity of tigecycline and discoloration of the thyroid gland with the use of tigecycline. The sponsor was asked to comment on these issues at the time of the meeting.

MEETING OBJECTIVES:
To review with the Division the current status of the tigecycline clinical and preclinical program and discuss general issues in preparation for the December 2004 Electronic Common Technical Document (eCDT) submission.

SUMMARY OF UNDERSTANDINGS

1. Wyeth's clinical pharmacology program for tigecycline is acceptable for registration.

2. No hERG assay will be requested at this moment pending satisfactory results on the Phase 3 clinical data. If a QT prolongation signal emerges from the analysis of this data, appropriate steps will be discussed with the FDA at that time.

3. In order to satisfy the Pediatric Research Equity Act (PREA), a waiver will be granted for pediatric patients < 8 years or age. A deferral of studies for pediatric patients > 8 years of age will be granted.

4. Wyeth's proposed plan that dilution susceptibility testing be performed with fresh media (<12 hrs post autoclave) for aerobic organisms is acceptable.

5. The Division is willing to work with Wyeth on facilitating early submission and review of complete sections of the NDA application.

QUESTIONS AND ANSWERS

Following introductions, the questions (**bolded**) from the sponsor's briefing package dated January 20, 2004 were discussed as follows:

1. **In response to the FDA request for an update to the clinical pharmacology program for tigecycline, the attached presentation provides all data available to date. As such, we seek FDA's concurrence that the Phase 1 program is adequate for registration and will support proposed labeling.**

The Division concurs with Wyeth's program.

Wyeth also indicated that based on the metabolic pathway of tigecycline, no additional in vivo drug-drug interaction studies are planned. Drug-drug interaction studies with digoxin and warfarin have been completed.

With regard to the possible interaction between tigecycline and oral contraceptives, Wyeth has no plans to conduct drug-drug interaction studies; however, Wyeth intends to include a statement in the PRECAUTIONS section of the package insert similar to the one carried by other tetracyclines.

2. **To date all preclinical and clinical data support our position that tigecycline, consistent with the tetracycline class of compounds already in clinical use, does not have an impact on QTc interval. A data package summarizing all data available to date is provided as Attachment 2. In addition, centralized ECG readings will be evaluated from Phase 3 clinical trials and a confirmatory hERG assay will be completed prior to registration. Does the FDA agree that pending the results of the Phase 3 data and hERG assay as well as the information available to date, this information is adequate to support registration of tigecycline?**

After the initial submission of the package insert, and following the Division internal team meeting, Wyeth submitted a review provided by Dr. — not available for the initial background package provided to the FDA on January 20, 2004. Based on Dr. — findings, Wyeth would like the Division's concurrence that a hERG channel assay would not provide additional useful information at this time, given the advanced stage of clinical development.

The Division concurs with Wyeth's proposal, pending satisfactory results from the Phase 3 clinical data. If a QT prolongation signal emerges from the analysis of these data, appropriate steps will be discussed with the FDA at that time.

In response to the questions forwarded by the Division, Wyeth also indicated that the original animal histopathology studies did not focus on the possibility of osteoclastic activity, vestibular activity, or thyroid discoloration. However, they will review the original histopathology reports, looking for signals that could be related to those events and will provide the data to the Division.

3. **Due to the global nature of this clinical program, patients are enrolled in our clinical studies from more than 45 countries worldwide. Specifically, there are a significant number of patients from Eastern European countries as well as Latin America and India. Wyeth is committed to 100% data quality and has been auditing these sites on an ongoing basis. This consists of a three-tiered approach to auditing including; Site monitoring by clinical research associates (CRA's), co-monitoring by clinical scientists/senior CRA's for GCP standards and protocol adherence, and site/CRO and central lab auditing by our Global Compliance Auditing group. Is there anything specific that the FDA will require to ensure including all of these patients in our analyses at the time of registration?**

The Division requested that Wyeth report any irregularities found during the conduct of the clinical trials, and what steps were taken to address them. The Division could not ensure that data from all the patients would be viewed as acceptable. Inspection of selected clinical sites is expected to be part of the NDA review process.

4. **Wyeth would like to review our current strategy for obtaining a Written Request for tigecycline and the plans for addressing the pediatric rule. Specifically, we seek insight into the FDA's position on the pediatric rule moving forward as it relates to tigecycline, and we would like to discuss our plans to conduct a single multiple dose pediatric study in a broad range of indications, including those being studies in the adult population.**

   In order to satisfy the Pediatric Research Equity Act (PREA), a waiver will be granted to pediatric patients < 8 years or age. A deferral of studies for pediatric patients ≥ 8 years of age will be granted. For the proposed indications, extrapolation of data on adults, in combination with pharmacokinetic and safety data will satisfy the requirements for pediatric patients ≥ 8 years of age.

   For Pediatric Exclusivity purposes, the Division encouraged Wyeth to submit a Proposed Pediatric Study Request (PPSR), for a broad range of indications, in patients ≥ 8 years of age.
   The Division proposed a database of safety data of 300-500 pediatric patients. The potential benefit for pediatric patients < 8 years or age, especially in those patients with resistant gram negative organisms, should be addressed by Wyeth in consultation with their pediatric experts.

5. **The current plan for tigecycline is to recommend that dilution susceptibility testing be performed with fresh media (<12 hrs post autoclave) for aerobic organisms. This was discussed at the January meeting of the NCCLS. The purpose of the fresh media is to minimize the impact of oxygen on tigecycline during testing. The NCCLS approved all QC ranges for agar dilution susceptibility testing for anaerobes and disk diffusion tests using standard methods. In addition, the QC ranges were approved for *E. coli, S. aureus,* and *E. faecalis* for broth dilution susceptibility testing with the caveat that fresh media was to be used. Does the FDA concur with our plans moving forward?**

   The Division agrees with Wyeth's proposal, and requests the sponsor to submit to the Division the same information package submitted to the NCCLS. The agency also suggested and encouraged the sponsor to continue to work on the

6. **Wyeth would like to discuss with the FDA our plans for PK/PD determinations for breakpoint susceptibilities to support MIC breakpoints? In addition, we look for the FDA insight as to the process for breakpoints, specifically how the FDA collaborates with NCCLS.**

   The Agency takes a conservative approach in the establishment of the breakpoints. The information on PK/PD, in vitro spectrum of activity, mechanisms of resistance, and animal therapeutic models of infection is taken into consideration in the establishment of provisional breakpoints. However, the final decision on breakpoints is made base on the susceptibility patterns and microbiological and clinical outcomes.

   The Agency reviews and establishes breakpoints independently of the NCCLS.

7. **Is the FDA in agreement with the statistical methodology presented in the Statistical Analysis Plans for studies 300 and 301? Also, we request FDA input on your views on multiplicity with an analysis of non-inferiority**

   For cSSI, the primary efficacy analysis of clinical cure at the test of cure visit will be assessed using PP and ITT as co-primary populations.

   No multiplicity

adjustments are needed. In addition, the Division requested the submission of analysis by age, gender and race. A detailed SAP should be submitted.

8.

Additional questions and comments:

The sponsor's proposal for early submission of selected complete sections of the NDA is acceptable. The Division mentioned during the meeting the availability of a Continuous Marketing Application (CMA) pilot program. The Division noted after the meeting that Wyeth would not qualify for this program as no request for Fast Track designation has been submitted.

At the present time, no decision has been made about the possibility of priority review or the need for an Advisory Committee meeting, as those decisions will be made based on the data provided in the submission. The Division requested Wyeth to request a meeting in the fall to discuss these issues.

A pre-NDA meeting will be requested for the month of May.

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/s/

Frances LeSane
3/18/04 02:34:37 PM

John Alexander
3/18/04 06:01:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,518

Wyeth Pharmaceuticals
Attention: Norris H. Pyle
Senior Regulatory Coordinator
Worldwide Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Pyle:

Please refer to the telecon between representatives of your firm and FDA on November 21, 2002. The purpose of the telecon was to discuss the Chemistry, Manufacturing, and Controls (CMC) plans to support the development of an NDA for tigecycline.

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 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 telecon

MEMORANDUM OF TELECON

TELECON DATE: November 21, 2002

TIME: 11:00 a.m.-12:00 p.m.

APPLICATION: IND 56,518/Tigecycline

TYPE OF MEETING: EOP2, CMC

MEETING CHAIR: Bonnie Dunn, Ph.D.

FDA ATTENDEES, TITLES, AND DIVISION

Bonnie Dunn, Ph.D., Acting Chemistry Team Leader for HFD-520, and Deputy Director, Division of New Drug Chemistry III
Shrikant Pagay, Ph.D., Chemistry Reviewer
Judit Milstein, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Dr. Richard Saunders	Assistant Vice President, Pharmaceutical Sciences
Dr. Sherry Ku	Director, Pharmaceutical Sciences
Dr. John Carrano	Assistant Vice President, Analytical Research and Development
Dr. Ingo Georgoff	Therapeutic Area Leader
Dr. Karl Blumberg	Director, Technical Services
Dr. Karel Bernady	Senior Director, CMC Regulatory Affairs
Mr. Norris Pyle	Senior Regulatory Coordinator, CMC Regulatory Affairs
Mr. Randall Brenner	Senior Manager, Worldwide Regulatory Affairs
Dr. Evan Loh	Senior Director, Clinical Research and Development

BACKGROUND:
Tigecycline, a glycylcycline antibiotic, is an analog of minocycline, a semisynthetic derivative of tetracycline. Tigecycline has been formulated for I.V. administration as single use vial. Based on Wyeth information, clinical studies have shown a broad spectrum of antibacterial activity, including inhibition of gram-positive, gram-negative, and anaerobic bacteria.

A separate End-of-Phase 2 meeting to discuss clinical/preclinical issues was held July 30, 2002.

MEETING OBJECTIVES:

To obtain the Agency's concurrence on Wyeth's CMC plans to support the development of an New Drug Applicaton for tigecycline.

SUMMARY OF UNDERSTANDINGS

1. The Agency considers the as the starting material , is considered an intermediate.

2. is the starting material for the

3. Wyeth's approach to setting specifications for to ensure its removal from the drug product is acceptable.
4. Wyeth asked if the NDA applicant can have a protocol for extending the shelf life of the drug substance. FDA stated that they would have to call Wyeth back about this.

QUESTIONS AND ANSWERS

After introductions, the questions posted by the sponsor (**bolded text**) in the briefing package submitted on October 21, 2002, were addressed as follows:

Question 1. Does the Agency concur on defining as the starting material for Tigecycline?

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Judit Milstein
1/5/03 12:27:14 PM
CSO

Bonnie Dunn
1/6/03 12:36:34 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 56,518

Wyeth Pharmaceuticals
Attention: Randall B. Brenner
Senior Manager, Worldwide Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19010-8299

Dear Mr. Brenner:

Please refer to the telecon between representatives of your firm and FDA on September 12, 2002. The purpose of the meeting was to discuss Wyeth's clinical development plan for tigecycline.

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 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 telecon

MINUTES OF THE TELECON

MEETING DATE: September 12, 2002

TIME: 3:30-5:00 p.m.

LOCATION: Teleconference

APPLICATION: IND 56,518, GAR-936 (Tigecycline)

TYPE OF MEETING: Guidance

MEETING CHAIR: John Alexander

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION
Janice Soreth, M.D., Division Director
John Alexander, M.D., Medical Team Leader
Chuck Cooper, M.D., Medical Reviewer
Thamban Valappil, Ph.D., Statistical Reviewer
Daphne Lin, Ph.D., Statistical Team Leader
Fred Marsik, Ph.D., Microbiology Reviewer

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:
Patty Bradford, Ph.D., Assoc. Director, Discovery Research
Randall Brenner, Sr. Manager, Regulatory Affairs
Angel Cooper, Clinical Scientist, Clinical R&D
E.J. Ellis-Grosse, Ph.D., Director, Clinical R&D
Susan Franks, Sr. Coordinator, Regulatory Affairs
Evan Loh, M.D., Sr. Director, Clinical R&D
Gopal Muralidharan, Ph.D., Assoc. Dir., Clinical Pharmacology
Steve Projan, Ph.D., Director, Antibacterial Research
Denise Sarkozy, Principal Statistician, Clinical Biostatistics
Jack Savarese, M.D., Ph.D., Sr. Director, Regulatory Affairs
Andrew Trofa, M.D., Assoc. Director, Clinical R&D

BACKGROUND:

An objective of the clinical development plan for tigecycline is to demonstrate clinical and microbiological efficacy of this antibiotic against target resistant pathogens (*E faecium, E faecalis, S aureus, K pneumoniae, S pneumoniae, Enterobacter* spp. *& A baumannii).*

On July 17, 2002, Wyeth submitted three protocol synopses for studying tigecycline against various resistant pathogens (RP) as follows:

1. Gram-Positive Bacteria: A Phase 3, randomized, observer blind study randomizing tigecycline:linezolid (3:1) in the treatment of hospitalized subjects with selected infections due to VRE & MRSA.

2.

3

MEETING OBJECTIVES:

To discuss Wyeth's clinical development for tigecycline and provide comments on the proposed clinical protocols.

DISCUSSION

After introductions, Wyeth summarized the current status of the tygecycline program and the rationale for each planned protocol. The Division encouraged Wyeth to continue the development of tigecycline for the treatment of infections with resistant pathogens. Review of the protocols submitted to the IND will provide more detailed comments than the ones offered in this meeting.

Wyeth's proposed protocols were discussed as follows.

1. **Gram-Positive Bacteria: A Phase 3, randomized, observer blind study randomizing tigecycline:linezolid (3:1) in the treatment of hospitalized subjects with selected infections due to VRE & MRSA.**

   a. This protocol, as designed, would support a

   b. Efficacy results from the resistant pathogens studies should not differ from those observed in the site specific studies.

   c. A relatively small number of high quality patients, with convincing evidence of infection might be sufficient to include

   d. The Phase 3, randomized [tigecycline:linezolid (3:1)] trial in the treatment of hospitalized subjects with selected infections due to VRE and MRSA as proposed in the briefing package does not provide for any type of statistical comparison between tigecycline and linezolid, except a 95% confidence interval around the point estimate of success for the individual treatment. A non-inferiority trial with a 1:1 randomization would be more appropriate.

   e. The final labeling claim will be based on the review of the study results in the NDA.

ACTIONS:

Wyeth will submit protocols for these studies to the IND when ready. The Division will provide comments on a timely manner.

Judit Milstein, 10-18-02
J. Alexander, M.D., M.P.H., 10-31-02

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Judit Milstein
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John Alexander
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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 7, 2001

Location: CORP S-300

Application: IND 56,518

Drug: GAR-936

Type of Meeting: Delta Issues regarding GAR-936

Meeting Chair: Janice Soreth, M.D., Division Director

FDA's Attendees: **Anti-Infective Drug Products (DAIDP)**

1. Mark Goldberger, M.D., Acting Office Director, ODE IV
2. Janice Soreth, M.D., Director
3. Renata Albrecht, M.D., Acting Director, DSPIDP (HFD-590)
4. John Alexander, M.D., M.P.H., Medical Team Leader
5. Charles Cooper, M.D., Medical Officer
6. Daphne Lin, Ph.D., Team Leader Statistics
7. Thamban Valappil, Ph.D., Statistician
8. Frances V. LeSane, Chief, Project Management Staff

Wyeth-Ayerst's Representatives:

1. Randall Brenner, Manager, Worldwide Regulatory Affairs
2. C. Jo White, M.D., Asst. Vice President, Clinical Research and Development
3. Michele Wible, Ph.D., Senior Statistician, Clinical Statistics
4. David Shlaes, M.D., Vice President, Infectious Disease
5. Jack Savarese, MD., Senior Director, Regulatory Affairs
6. Steve Projan, Ph.D., Director Anibacterial Research
7. —

Objective:

To futher discuss Wyeth Ayerst's delta issues for the Phase 3 clinical developmental plan for Tigecycline (GAR-936) indications.

Background:

At the End of Phase 2 meeting held July 30, 2001, FDA and Wyeth Ayerst agreed that more discussion on the delta plan for Tigecycline (GAR-936) was needed.

DISCUSSION AND RECOMMENDATIONS:

After introductions, Wyeth Ayerst made a presentation (slides attached) and noted the history of the 10% delta issue discussed at the EOP2 meeting. Note the following comments and concerns discussed with Wyeth Ayerst:

1. FDA indicated that a 10% delta was recommended as the most straightforward means to NDA approval. However, a somewhat wider delta would not necessarily preclude approval. Clinical trial results with wider deltas might lead to presentation before the Advisory Committee, and/or require detailed description in the CLINICAL STDIES section of the label. Clinical trials demonstrating efficacy against resistant organisms would also add to the totality of the evidence.

2. To maximize the likelihood of approval, Wyeth Ayerst Phase 3 clinical trials should show benefit from trials of serious infections that have acceptable comparators and an adequate number of patients. For each protocol, FDA will make comments as they are submitted.

3.

Issues Requiring Further Discussion:

If needed by Wyeth Ayerst, the issues around the design of a

In conclusion, FDA is planning an Advisory Committee Meeting February 19 and 20, 2002. The agenda for day one will include delta concerns. Day two will address issues of design and evaluation of trials with resistant pathogen.

Minutes Preparer: Frances V. LeSane
Chief, Project Management Staff

Chair Concurrence: Janice Soreth, M.D.
Division Director

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Janice Soreth
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MEMORANDUM OF MEETING MINUTES

Meeting Date: July 30, 2001
Location: CORP S-300
Application: IND 56518
Drug: GAR-936
Type of Meeting: End of Phase 2 Meeting
Meeting Chair: Janice Soreth, M.D., Acting Division Director

FDA's Attendees:
Dianne Murphy, M.D., Office Director, ODE IV
Mark Goldberger, M.D., Director –DSPIDP (HFD-590)
Janice Soreth, M.D., Acting Director
Lillian Gavrilovich, M.D., Deputy Division Director –
Nasim Moledina, M.D., Medical Officer.
Terry Peters, D.V.M., Veterinary Medical Officer
Jenny J. Zheng, Ph.D., Biopharmaceutics Reviewer
Daphne Lin, Ph.D., Team Leader Statistics
David B. Katague, Ph.D., Team Leader Chemistry
Harold V. Silver, Microbiologist
Thamban Valappil, Ph.D., Statistician
Albert T. Sheldon, Ph.D., Team Leader Microbiology
Charles Cooper, M.D., Medical Officer
John Alexander, M.D., M.P.H., Acting Medical Team Leader
Jose R. Cintron, R.Ph., M.A., Project Manager

Wyeth-Ayerst's Representatives:
Randall Brenner, Manager, Worldwide Regulatory Affairs
Edward Zito, Ph.D., Director, Clinical Research and Development
Joanne M. Killinger, Ph.D., Vice President, Drug Safety and Metabolism
Andrew Trofa, M.D., Associate Director, Clinical Research and Development
C. Jo White, M.D., Asst. Vice President, Clinical Research and Development
Donald Raible, M.D., Director, Clinical Pharmacology
Gopal Muralidharan, Ph.D., Director, Clinical Pharmacokinetics
Kay Clark, R.N., Associate Director, Clinical Research and Development
Jacqueline Wrenn, Ph.D., Principal Research Scientist I, Drug Safety
Mauricio Leal, Ph.D., Principal Research Scientist II, Drug Metabolism
Michele Wible, Ph.D., Sr. Statistician, Clinical Statistics
Susan Franks, Sr. Coordinator, Worldwide Regulatory Affairs
Patricia Bradford, Ph.D., Director, Microbiology Research

Objective:

The objectives of the meeting were to discuss Wyeth Ayerst's clinical developmental plan for tigecycline (GAR-936), discuss potential issues, and address any questions regarding Phase 2 study results and future Phase 3 studies.

Executive Summary/Background:
Representatives from Wyeth-Ayerst (WA) met with the Division of Anti-Infective Drug Products (DAIDP) for the planned End of Phase 2 meeting to discuss tigecycline (GAR-936).

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

- The meeting opened with Mr. Brenner thanking the DAIDP for taking the time to meet with WA followed by introductions from all meeting attendees. Mr. Brenner then briefly outlined the proposed format of the meeting, which would be a brief overview of the clinical program followed by questions, proposed to the DAIDP for comments and/or concurrence.

- Dr. Zito gave overview of the completed, ongoing and planned Phase 3 clinical studies. The DAIDP was asked whether the proposed Phase 3 clinical program for the — indications — cSSSI and IAI) would support approval, specifically focusing on the number of studies for each indication. The Division agreed that the number of planned studies support filing the NDA.

- Mr. Brenner noted that Wyeth Ayerst is aware of the general move toward a delta of 10%. However, considering the size and similar design of the trials for each indication, WA asked whether a delta of 15% would be acceptable if a meta-analysis of the combined studies showed a delta of 10%. The Division still recommended a delta of 10% for each individual trial. The Division feels strongly that this is important for serving the public health and is needed for non-inferiority trials. In order to ensure a level playing field, the Agency was recommending that WA utilize a delta of 10% as had been recommended to other companies. Dr. Diane Murphy advised that this topic will be discussed at an upcoming Advisory Committee meeting (date to be determined), and that WA could publicly state their position during the open public hearing. The Sponsor was advised to amend any protocol that had already been submitted to the Division and to change any future protocol not yet submitted.

- **Variable dosing design**: WA specifically mentioned the — which has a range of dosing from 5-21 days. The Division expressed concerns over this type of dosing design, and recommended that WA select a maximum duration of therapy at which all patients will be evaluated for efficacy. Patients who are cured prior to that day will be counted - as a "cure", and this will allow for a range of dosing in WA product label. Patients who require dosing longer than that specified in the protocol will be designated as failures.

- Dr. White asked whether serology testing is acceptable for atypical bacteria such as *Legionella*. Mr. Silver responded by providing criteria for atypical pathogen infections, in " Atypical Bacterial Pneumonias" which would address this issue.

- The Division expressed some concerns regarding the completion of WA Phase 2 program (one study is still ongoing) relative to the Phase 3 dose. Specifically, bone marrow hypocellularity was observed in pre-clinical studies and the Division asked whether WA had seen any evidence in the clinical data. Dr. Raible presented data from Phase I studies which demonstrated that subjects stayed within the normal range for reticulocytes, hemoglobin, hematocrit and WBCs. Dr. White presented mean data on hemoglobin and white bloods cells from Phase 2 studies and indicated that there was nothing to suggest a safety concern in this area. However, the Division asked that WA provide detailed

information on any out-of-range patients from the Phase 1 or 2 studies to be assured that the mean data are not masking any abnormal findings. Dr. Wrenn also addressed the question where recovery studies in rats and dogs showed a return of hematology parameters to normal levels within three weeks of a drug-free period.

- The Division asked about WA's justification for their Phase 3 dose and the confidence in the dose selected for the Phase 3 trials, specifically regarding (Dr. Zito had presented very preliminary data from WA's Phase 2 . study, which showed a preliminary efficacy rate of 61 %). Dr. Bradford gave an overview of how the clinical dose was selected based on the time above a fraction of the MIC. To support dose selection, WA committed to provide a detailed justification with their position that time above MIC is not the appropriate variable for estimating efficacious dose, but rather AUC or the time above a fraction of the MIC. The Division also asked for WA's justification for the microbiological susceptibility breakpoints. During this discussion, Mr. Silver provided WA with a draft Guidance Document entitled, "Development, Analysis, and Presentation of Microbiological Data for Antibacterial Drug Products", as well as a table showing FDA's recommended format for line listings for the clinical microbiological data. Additionally, Mr. Harold Silver requested that WA adhere to the guidelines outlined in NCCLS document M23 with regard to the selection of MIC breakpoints. Mr. Silver questioned why WA does not currently have separate MIC breakpoints for fastidious organisms and requested that WA provide a separate rationale for this approach.

- **Serology testing for the atypical bacteria:** Mr. Silver requested that all serological tests used to diagnose pneumonias caused by atypical bacteria be performed with FDA-approved methodology. A detailed methodology for each test and the package inserts for the testing kits should be provided upon submission. Normal values for each test should be provided from the reference laboratory.

- **Biopharmaceutics Issues**: Dr. Leal presented WA's position on why they feel a ^{14}C mass balance study does not need to be conducted, but felt that information on fecal excretion is not fully understood. FDA suggested that WA conduct a single dose study (non-radioactive) where fecal samples are collected to determine exactly how much GAR-936 is excreted in the stool. If WA were able to demonstrate that a large percentage is excreted in the stool, then a ^{14}C mass balance study would not be necessary.

- **Pre-clinical issues:** The Division asked that WA provide draft or final study reports (draft is acceptable) for all Absorption, Distribution, Metabolism and Excretion studies, as well as reproductive toxicity study reports.

- Dr. Soreth was asked about WA protocol design for resistant pathogens, specifically Vancomycin Resistant Enterococcus (VRE). Since the meeting time was running short, the Division suggested that another meeting or teleconference be set up to address this protocol. The Division did stress that when asked about the number of isolates needed to

- **Issues Requiring Further Discussion:** Issues that were not discussed due to time constraints were:
    1. WA's pediatric study plans
    2. Interaction studies
    3. Concurrence on the overall pre-clinical development plan.
    4. Questions about the selected Phase III comparators and study designs.

The Division agreed that the remaining issues can be discussed at future teleconferences, and that Division would comment on the Phase 3 comparators as each protocol is submitted.

Minutes Preparer: Jose R. Cintron, R.Ph., M.A.
Senior Regulatory Management Officer

Chair Concurrence: Janice Soreth, M.D.
Acting Division Director

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