DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021821/S-021
NDA 021821/S-025
NDA 021821/S-027

SUPPLEMENT APPROVAL

Pfizer Pharmaceuticals, Inc.
Attention: Nia Tatsis, Ph.D.
Senior Manager
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Tatsis:

Please refer to your supplemental new drug applications dated February 23 (S-021), August 5, 2009 (S-025), and January 21, 2010 (S-027), received February 24, August 5, 2009 and January 21, 2010, respectively, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tygacil (tigecycline).

We acknowledge receipt of your amendments to supplemental applications S-021 and S-025 dated March 27 and September 11, 2009, May 10, July 13 and July 15, 2010.

Supplemental application S-021 is a "Changes Being Effected" supplemental new drug application that provides for changes to the **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS** sections of the labeling concerning a mortality imbalance in Tygacil (tigecycline) Phase 3 trials.

Supplemental application S-025 is a Prior Approval supplemental new drug application that provides for changes to the **Preparation and Handling** section and the Compatibilities and Incompatibilities subsections of the labeling as follows:

- "The reconstitution solution should be yellow to orange in color; if not, the solution should be discarded" added to **Preparation and Handling** section
- "metoclopromide" added to the Compatibilities subsection
- "amphotericin B lipid complex, esomeprazole and omeprazole" added to the Incompatibilities subsection

Supplemental application S-027 is a Prior Approval supplemental new drug application that provides for changes to the **WARNINGS AND PRECAUTIONS** section describing pancreatitis with the use of Tygacil (tigecycline).

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

1. The dates of major recent changes and the revision date in the Highlight section of the label were changed to 07/2010.
2. Bolding was removed from text in the first bullet of the **WARNINGS AND PRECAUTIONS** in the Highlight section.
3. In the last sentence of section 5.4 the ")" was moved to include the phrase "in comparator-treated patients".

CONTENT OF LABELING

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in this supplemental application.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Tygacil (tigecycline) was approved on June 15, 2005, we have become aware of increased mortality among Tygacil (tigecycline)-treated patients from the accumulating data from phase 3 and phase 4 clinical trials. In addition, in some trials, QT prolongation occurred more frequently in the Tygacil (tigecycline) arm compared to the comparator groups. Therefore, we consider the observed increased mortality in Tygacil (tigecycline)-treated patients to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of the serious risk of increased mortality in patients treated with Tygacil (tigecycline).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of the serious risk of increased mortality in patients treated with Tygacil (tigecycline).

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1665-1: A thorough QTc clinical trial in patients treated with Tygacil (tigecycline).

The timetable you submitted on June 29, 2010 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October, 2010
Trial Completion Date:	May, 2011
Final Report Submission:	October, 2011

Submit the protocol to your IND 56,518, with a cross-reference letter to NDA 21-821. Submit all final reports to your NDA 21-821. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carmen DeBellas, PharmD, Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar M.D. M.P.H.
Deputy Director for Safety
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21821	SUPPL-27	WYETH PHARMACEUTICALS INC	TYGACIL
NDA-21821	SUPPL-25	WYETH PHARMACEUTICALS INC	TYGACIL
NDA-21821	SUPPL-21	WYETH PHARMACEUTICALS INC	TYGACIL

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

/s/

SUMATHI NAMBIAR
07/16/2010