

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-110

OTHER ACTION LETTER(s)



NDA 22-110

COMPLETE RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated December 6, 2006, received December 19, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vibativ (telavancin hydrochloride) for injection, 250 mg and 750 mg.

We also acknowledge receipt of your amendments dated January 21, February 12, March 26, August 6 and 22, September 22, 24, and 30, and October 10 and 30, 2008, and your correspondence dated January 24 and April 14, 2008.

The January 21, 2008, amendment constituted a complete response to our October 19, 2007, action letter.

We have reviewed the two Phase 3 trials evaluating the safety and efficacy of Vibativ (telavancin hydrochloride) compared to vancomycin in the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by gram positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). The results from these trials demonstrate noninferiority of Vibativ (telavancin hydrochloride) relative to vancomycin in the treatment of cSSSI.

Upon completion of the review of your application, as amended, we have determined that we cannot approve the application in its present form. Due to concerns regarding nephrotoxicity and potential teratogenicity, additional safety information and risk management measures are required. These requirements are described below, along with our recommendations to address them.

CLINICAL:

1. To date, FDA has received only summary data and narratives for patients who died, experienced serious adverse events, or discontinued study medication due to adverse events from the two completed Phase 3 trials comparing Vibativ (telavancin hydrochloride) to vancomycin for the treatment of hospital-acquired pneumonia. In order to further evaluate the

potential for nephrotoxicity, we request that you submit safety data and analyses pertaining to renal function from these patients from trials of hospital-acquired pneumonia.

The submitted data should include (but not be limited to) case report forms for patients with reported adverse events related to renal impairment, analyses performed related to renal laboratory parameters, and any exploratory analyses performed to assess factors associated with nephrotoxicity. Datasets that include basic demographic data, co-morbid medical conditions, concomitant medications, and laboratory results should be included. You may incorporate by reference relevant information from your pending NDA (NDA [redacted]) for telavancin hydrochloride for hospital-acquired pneumonia. b(4)

2. Patients participating in the cSSSI trials (0017 and 0018) in whom test-of-cure or follow-up laboratory data indicated a serum creatinine level of greater than two times the baseline value should be identified, and follow-up information for such subjects including creatinine levels and renal related adverse events (e.g., need for dialysis or death) should be obtained and submitted.

RISK EVALUATION AND MITIGATION STRATEGY (REMS):

3. For the reasons described below, you must submit a proposed Risk Evaluation and Mitigation Strategy (REMS).

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Vibativ (telavancin hydrochloride) to ensure the benefits of the drug outweigh the risk of teratogenicity (seen in non-clinical/animal data to date). The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

- A. Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Vibativ (telavancin hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Vibativ (telavancin hydrochloride). FDA has determined that Vibativ (telavancin hydrochloride) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Vibativ (telavancin hydrochloride). FDA has also determined that Vibativ (telavancin hydrochloride) is a product for which patient labeling could help

prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Vibativ (telavancin hydrochloride).

B. Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe, dispense, and administer Vibativ (telavancin hydrochloride), such as any specialists who may prescribe the drug, pharmacists, and obstetrician/gynecologists, will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about the risk of teratogenicity.

The communication plan must include, at minimum, the following:

- (1) Dear Healthcare Provider Letter(s) to be distributed at product launch that include information on fetal effects of Vibativ (telavancin hydrochloride) seen in animal studies and appropriate pregnancy prevention measures including a definition for women of child-bearing potential to help in determining the childbearing status of all women, appropriate pregnancy testing requirements, and detailed information about appropriate contraceptive methods to prevent pregnancy. If women who have taken Vibativ (telavancin hydrochloride) get pregnant, they need to notify their physician.
- (2) A description of who will be the audience for the communication plan, stating specifically the types and specialties of healthcare providers, in addition to those listed above, to which the communications will be directed.
- (3) A schedule for when and how the Dear Healthcare Provider Letter(s) will be distributed to healthcare providers.

C. Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Vibativ (telavancin hydrochloride). Additionally, all relevant proposed REMS communication materials should be appended to the

proposed REMS. Once FDA finds the content acceptable, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for the assessments should include but may not be limited to:

- A survey of patients' or prescribers' understanding of the serious risks of Vibativ (telavancin hydrochloride)
- Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed
- A report on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. (has enrollment begun, number of participants enrolled, expected completion date, whether any difficulties completing the study/clinical trial have been encountered, registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act) You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) [or 21 CFR 601.70] and including any updates to the status information since the annual report was prepared. Failure to submit a complete REMS assessment under 505-1(g)(3) could result in enforcement action.
- A narrative summary and analysis of maternal and fetal outcomes of all pregnancy exposures and circumstances that led to the patient becoming pregnant in pregnancies that were reported spontaneously, and to the pregnancy registry (as described below)
- Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your application. Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

PROPOSED REMS FOR NDA 22-110

On the first page of subsequent submissions related to the proposed REMS, prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-110 PROPOSED REMS-AMENDMENT

LABELING

4. Please submit draft labeling revised as follows:
 - A. A boxed warning containing information regarding the potential for teratogenicity based on findings in animal studies should be included. Although Vibativ (telavancin hydrochloride) will be classified as pregnancy category C, the boxed warning should include a statement that females of childbearing potential should have a negative pregnancy test prior to administration.
 - B. The warning containing information regarding potential for nephrotoxicity. A baseline serum creatinine assessment, along with on-therapy (day 3) and end-of-therapy serum creatinine assessments should be performed.
 - C. The data regarding efficacy and safety in treatment of patients with moderate and severe renal impairment (CrCL < 30 mL/min) is currently insufficient to recommend treatment of cSSSI with Vibativ (telavancin hydrochloride). Until additional information is available which establishes a dosing regimen likely to produce higher cure rates, language should be included in the **WARNINGS AND PRECAUTIONS** section of the labeling to advise clinicians of the potential risks.
 - D. A statement regarding the incidence, nature and reversibility of the nephrotoxicity, populations at increased risk, and recommended avoidance of other concomitant nephrotoxic drugs (such as non-steroidal anti-inflammatory drugs) where alternative therapies may be substituted should be included in the **WARNINGS AND PRECAUTIONS** section of the label. Additional information regarding information to be included in this section for nephrotoxicity can be found in the guidance document "Warnings and Precautions, Contraindications, and Boxed Warning Sections of labeling for Human Prescription Drug and Biological Products – Content and Format" at <http://www.fda.gov/cder/guidance/5538dft.pdf>.
 - E. The following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d) should be added: "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**".

The updated draft labeling [21 CFR 314.50(l)(1)(i)] should be submitted in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Additional labeling recommendations may be provided after the review of information submitted in response to this action letter.

POSTMARKETING REQUIREMENTS UNDER 505(o):

5. In accordance with section 505(o)(3)(A), based on the signal of serious risk of teratogenicity seen in non-clinical studies, we have determined that, if this application is approved, a postmarketing study will be needed to further assess this risk.

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize 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 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

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 the signal of teratogenicity.

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 signal of serious risk.

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to develop and maintain a pregnancy registry to assess the signal of teratogenicity.

- A. **Pregnancy Registry:** A pregnancy registry must be established to evaluate the safety of this product in pregnant women and their offspring. You will be required to evaluate the safety of Vibativ (telavancin hydrochloride) use during pregnancy by developing and maintaining a prospective, observational pregnancy exposure registry study conducted in the United States. The study should compare pregnancy and fetal/infant outcomes of women exposed to Vibativ (telavancin hydrochloride) during pregnancy to an unexposed control population. The registry should identify and record major congenital anomalies, minor anomalies that occur in groups of three or more, spontaneous abortions, stillbirths, elective terminations, functional deficits in the child, and any serious pregnancy outcomes. Infants should be assessed through at least the first year of life. For more information, please refer to the FDA Guidance for Industry on Establishing Pregnancy Exposure Registries (<http://www.fda.gov/cder/guidance/3626fn1.htm>). A full protocol for the pregnancy registry should be submitted as part of your complete response to this action letter and the registry should be ready to be implemented shortly thereafter.

SAFETY UPDATE:

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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Page 8

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fn1.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call J. Christopher Davi, MS, Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:

Appendix A – REMS template
Appendix B – Supporting Document template

APPENDIX A - REMS Template

<<If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.>>

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background
2. Goals
3. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Assessment of the REMS
4. Information Needed for Assessments
5. Other Relevant Information

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

/s/

Edward Cox
2/20/2009 04:59:32 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-110

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated December 6, 2006, received December 19, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for telavancin (TD-6424) sterile lyophilized powder for injection, 250 mg and 750 mg.

We also acknowledge receipt of your submissions dated December 19, 2006 (2), December 21, 2006, January 22, 2007, January 23, 2007, February 7, 2007 (2), February 27, 2007 (2), March 9, 2007 (2), March 16, 2007, April 17, 2007, April 26, 2007, May 4, 2007, May 8, 2007, May 22, 2007 (2), May 24, 2007, June 6, 2007, June 7, 2007, June 11, 2007, June 25, 2007, July 19, 2007, July 20, 2007, July 25, 2007, July 31, 2007, August 7, 2007, August 10, 2007 (2), August 16, 2007, August 27, 2007, September 7, 2007, September 13, 2007, September 26, 2007, September 27, 2007, September 28, 2007, October 1, 2007, October 7, 2007 (2), and October 11, 2007.

We also acknowledge receipt of submissions dated October 17 and 18, 2007. These submissions are currently being processed and were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following:

1. FDA inspection of the Ben Venue facility in Bedford, Ohio revealed significant deviations from the Current Good Manufacturing Practice regulations. A satisfactory resolution of these violations is required before this application can be approved.
2. Financial disclosure information for three (3) sub-investigators was not included in the application. This information will need to be submitted.

3. The benefit to risk ratio of the drug product is in question because of the following:
- Decreased efficacy in clinical cure rates were noted to occur in patients with decreased baseline creatinine clearance.
 - Relative to vancomycin, decreased efficacy in clinical cure rates was noted to occur in patients with increasing age.
 - Relative to vancomycin, there is an imbalance in the reported rate of serious renal disorders and vascular disorders. This imbalance in reported events extends to patients discontinued due to Renal and Urinary Disorders, laboratory values for serum creatinine changes and is present in the treatment emergent adverse events for Renal and Urinary Disorders, and in Vascular Disorders.
 - The thorough QT/QTc study demonstrated that the baseline and placebo corrected QTcF interval was lengthened greater than 10 milliseconds.
 - The drug product appears to be a teratogen in at least one and possibly three species.
 - There is insufficient information to recommend a dosing regimen for patients with a creatinine clearance of less than 10 mL/min including patients on hemodialysis.

Please submit either through additional clinical data or re-analyses of previously conducted clinical trials, a justification of why the risks associated with the issues identified above do not outweigh the potential benefit observed as a result of the treatment of complicated skin and skin structure infections (cSSSI) with telavancin. Alternatively, please submit revised labeling which may minimize the intended population according to their identified increased risks.

4. Figure 8 from 5.3.5.4.1 of the December 6, 2006, submission displayed below appears to identify *S. aureus* isolates which are sensitive to telavancin and resistant to vancomycin, (
-) Figure 9 from 5.3.5.4.1 of the December 6, 2006, submission displayed below appears to identify Enterococcal spp. isolates which are sensitive to telavancin and resistant to vancomycin. (

b(4)

- Please confirm whether you have identified any *S. aureus* or Enterococcal spp. isolates (particularly *Enterococcus faecium* and *Enterococcus faecalis*) which are sensitive to vancomycin and resistant to telavancin.
- Please identify the clinical disease from which there were vancomycin resistant (MIC of >16 mcg/mL)/telavancin sensitive *S. aureus* or Enterococcal spp. (particularly *Enterococcus faecium* and *Enterococcus faecalis*) isolates.
- If there are clinically relevant isolates (any bacterial organism) which are sensitive to telavancin (MIC ≤ 1 mcg/mL) and resistant to vancomycin, please identify them along with the clinical condition from which they were isolated.

Telavancin and Vancomycin MIC Values of *S. aureus* (n=6,564) from Clinical and Surveillance Studies

Vancomycin MIC Values (µg/mL)	1024									1		
	256								1	1		
	128								1	2		
	64								2	1		
	32							1	1			
	R 16											
	I 8					3	6	7	11		2	
	4				2	6	15	17	21			
	S 2		1		25	134	208	27	5			
	1	1	1	37	1012	2875	647	87				
0.5			76	199	702	381	34					
0.25	2	1		1	4	2	1					
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
									S			NS

Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies
Source: 5.3.5.4.1.6 Figure 8, December 6, 2006, submission

Telavancin and Vancomycin MIC Values of Enterococcal spp. (n=2,835) from Clinical and Surveillance Studies

Vancomycin MIC Values (µg/mL)	1024									2	2	3	14	39	16	1								
	512									5	7	8	13	23	157	230	28							
	256									2	13	9	6	10	35	71	87	22	3					
	128	1								4	3	3	8	17	16	4								
	64									1	4	3	6	3	7	3								
	32									1	3	2	1	4	3									
	R 16									1	1	1	7	4	2	1			1					
	I 8											4	2	5	6	3	2							
	4											14	5	5	3				1					
	S 2											1	14	50	201	126	30	6						
1												34	126	147	511	180	32	3						
0.5												2	13	81	143	73	66	43	2					
													0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32
																				S	I	R		

Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies
Source: 5.3.5.4.1.6 Figure 9, December 6, 2006, submission

5. Pregnancy Category C is appropriate if animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. The submitted application presents theoretical reasons why it may be appropriate for a pregnant woman to take telavancin, but it does not appear to identify clinical cases of cSSSI where clinical isolates have been demonstrated to be sensitive to telavancin and resistant to other anti-infectives such as vancomycin. Isolates such as the ones identified in item 4 above may represent such cases if the clinical source is from a cSSSI clinical case. Please identify specific clinical cSSSI cases, not necessarily in pregnant women, in which the clinical circumstances would suggest that if the case had been a pregnant woman, it may have been appropriate for her to take telavancin.

We are deferring additional review of the labeling at this time, until all other deficiencies in the application have been submitted and reviewed.

When you respond to the above deficiencies, as required under 21 CFR 314.50(d)(5)(vi)(b), please submit a safety update which includes data currently available from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level. The safety update should include any significant changes or findings in the safety profile.

1. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
2. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
3. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study. In addition, provide narrative summaries for serious adverse events.
4. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
5. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
6. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. If you do not follow one of these options, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Anti-Infective and Ophthalmology Products (DAIOP) to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact J. Christopher Davi, MS, Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

Edward Cox
10/19/2007 05:07:48 PM