

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021883Orig1s000

OTHER ACTION LETTERS



NDA 21-883

Vicuron Pharmaceuticals, Inc., a subsidiary of Pfizer
Attention: Helen Milton, PhD
Director, Worldwide Regulatory Strategy
c/o Pfizer, Inc.
235 East 42nd Street
New York, NY 10017

Dear Dr. Milton:

Please refer to your new drug application (NDA) dated December 21, 2004, received December 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dalbavancin powder for injection, (b) (4) 500 mg.

We acknowledge receipt of your submissions dated July 2, August 29, September 17(2), 19 and 25, October 26, and November 6, 8, and 26, 2007.

The June 19, 2007, submission constituted a complete response to our June 21, 2006 action letter.

We also acknowledge receipt of your submission dated December 14, 2007. This submission is currently being processed and was not reviewed for this action. You may incorporate this submission 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 deficiencies:

1. FDA inspection of the (b) (4) revealed significant deviations from the Current Good Manufacturing Practice (cGMP) regulations. A satisfactory resolution of these violations is required before this application can be approved.
2. Microbiological studies in support of the (b) (4) r post-constitution storage time (as stated in the proposed labeling) have not been provided. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E.

The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀.

The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than (b) (4)

Findings from these studies may also be useful for developing manufacturing controls, such as (b) (4) holding periods, as part of your Quality by Design program.

3. An adequate justification for a non-inferiority (NI) margin has not been provided for the study VER001-8. Hence the application lacks evidence from a second adequate well-controlled study to support the proposed indication of complicated skin and skin structure infections. In order to address this deficiency, you should provide data to support the justification for the NI margin for study VER001-8 or alternatively data from another adequate and well-controlled study to support the proposed indication of complicated skin and skin structure infections. Upon resubmission of this NDA, it is possible that review of the issue of the non-inferiority margin could benefit from discussion at an Advisory Committee meeting.

We are deferring additional review of the labeling at this time, until the above referenced deficiencies are resolved.

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 non-clinical 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide any additional information from microbiological surveillance data.

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 314.110. 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

12/20/2007 03:32:58 PM



NDA 21-883

Vicuron Pharmaceuticals, Inc., a subsidiary of Pfizer
c/o Pfizer Inc.
Attention: Ms. Elina Srulevitch-Chin
Director, Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Srulevitch-Chin:

Please refer to your new drug application (NDA) dated December 21, 2004, received December 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dalbavancin (powder for injection), (b)(4) 500 mg.

Your submission of December 20, 2005 constituted a complete response to our September 21, 2005 action letter.

We also acknowledge receipt of your submissions dated February 24, 2006, April 13, 2006, April 24, 2006, May 2, 2006, May 5, 2006, May 12, 2006, May 22, 2006, and June 6, 2006.

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:

1. Determine the specific cause for high bacterial endotoxin levels discovered in active pharmaceutical ingredient (API) and drug product (DP) lots, as reported to the Agency on May 12, 2006.
2. Submit a remediation plan to address bacterial endotoxins, providing data to demonstrate that endotoxin levels are consistently controlled to the corrected and revised specification limits both in the API and in the DP.

In addition, you must submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will 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 an informal 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 the application is approved.

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

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment: Agreed upon labeling as of June 21, 2006

**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
6/21/2006 05:33:53 PM
for Mark J. Goldberger, MD MPH



NDA 21-883

Vicuron Pharmaceuticals, Inc.
Attention: Martin Stogniew, Ph.D.
Executive VP, Scientific Affairs
455 South Gulph Road
King of Prussia, PA 19406

Dear Dr. Stogniew:

Please refer to your new drug application (NDA) dated December 21, 2004, received December 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dalbavancin powder for injection, (b) (4) 500 mg.

We also acknowledge receipt of your submissions dated February 10, 2005, February 17, 2005, February 18, 2005, February 24, 2005, March 1, 2005, March 7, 2005, March 25, 2005, March 30, 2005, April 1, 2005, April 7, 2005, April 8, 2005, April 19, 2005, May 4, 2005, May 9, 2005, May 10, 2005, May 17, 2005, May 18, 2005, June 1, 2005, June 10, 2005, June 15, 2005, June 21, 2005, July 8, 2005, July 15, 2005, July 18, 2005, July 19, 2005, August 2, 2005, August 4, 2005, August 12, 2005, August 24, 2005, September 6, 2005, September 7, 2005, and September 8, 2005.

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

1. Isolated Intermediate Storage: Provide data, based on a stability-indicating HPLC assay, to support the storage temperatures and expiry dates for the intermediates (b) (4). The proposed storage temperatures and expiry periods for these intermediates are not adequately supported in your application, and inappropriate storage could adversely affect the strength and the purity of the drug product.
2. Labeling: Submit proposed annotated labeling based on the Agency's attached draft labeling. Note that comments have been provided for your consideration. Final labeling discussions with the Agency will be required prior to approval.

Submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anti-Infective and Ophthalmology Products, and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will 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 an informal meeting or telephone conference with the Division of Anti-Infective and Ophthalmology Products 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 the application is approved.

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

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, MD, MPH
Director, Office of Antimicrobial Products
Food and Drug Administration
Center for Drug Evaluation and Research

Attachment: Agency Proposed Labeling

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**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
9/21/2005 07:00:17 PM
for Mark J. Goldberger, MD, MPH