FDA RESPONSE:

The modified — method is acceptable as long as it provides needed resolution of all the impurities above 0.1% and the impurities are identified. The Division asked to submit an IND amendment for the new — method and to make sure that the method is stability indicating.

2. Cubist plans to modify the existing manufacturing process for bulk daptomycin currently being used by — to produce clinical supplies. These changes have been outlined in the meeting package and will be submitted as an IND amendment. **Does FDA agree that the proposed comparability testing for bulk daptomycin and daptomycin drug product outlined in the meeting package is adequate to qualify material produced by the modified manufacturing process thereby allowing the material to be used in the Phase 3 clinical trials?**

FDA RESPONSE:

The comparability protocol for — versus — appears to be acceptable, but the acceptance criteria for the sameness should be provided and justified. In addition, the impurity profiles of the drug substance before and after the change should be included.

3. Due to limitations for purification capacity at —, Cubist needs to manufacture bulk daptomycin at — for commercial manufacturing. — process will be submitted in the NDA as the sole manufacturer of bulk daptomycin. **Is the comparability testing between the bulk material produced at — and — adequate to support an NDA? Is the comparability testing of the daptomycin drug product produced using material produced at — and — adequate to support an NDA?**

FDA RESPONSE:

The plan for bridging studies for the change in the manufacturing site from — to — acceptable for submission in the NDA. The division's understanding is that — material will not be used in the clinical studies for NDA submission. The data and acceptance criteria will be reviewed to determine acceptance of the drug substance from the new site. Also, the data for the drug product manufactured from the new source of the drug substance will be reviewed in the NDA.

4. Primary drug product stability data for the NDA will be generated using bulk daptomycin produced at — and drug product produced by the commercial drug product manufacturer (either Abbott —). Please be aware that the manufacturing procedures to produce bulk drug are essentially the

same between — and the commercial supplier — **Is the proposed approach of using — bulk drug for primary drug product stability studies acceptable providing the equivalence between bulk material produced by — and — is established?**

FDA RESPONSE:
Primary drug product stability data for the NDA will be acceptable if comparability is demonstrated between the drug substance batches manufactured at — (clinical site) and at — (proposed commercial site).

5. Abbott will produce — daptomycin vials in — — with varying capacities. For the primary stability studies, — will operate at — — capacity. **Does the FDA agree with the proposed primary stability plan outlined in the meeting package?**

FDA RESPONSE:
This is acceptable.

6. Since daptomycin is produced using a — process, the firm claims that FDA guidelines permit identification of impurities which occur at 0.3% or greater. Cubist plans to identify any impurity in the bulk daptomycin that is present at this level. **Is this acceptable to the FDA?**

FDA RESPONSE:
The acceptance criteria of 0.3% limit referenced in the "Guide for Inspection on Fermentation of Bulk Drug Substance" are contingent on review of the impurity profile data and methods for optimized process.

Agreements: See discussion/recommendation section

Issues Requiring Further Discussion: See discussion/recommendation section

Enclosure: None

Action Items: None

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

Chairs Concurrence: Dr. Chi Wan Chen,
Office Director, DNDC-III

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

/s/

Chi Wan Chen
7/24/02 02:50:26 PM

MEMORANDUM OF TELECON

DATE: April 29, 2003 **TIME:** 1:15 PM **LOCATION:** S-348

APPLICATION NUMBER: NDA 21-572

DRUG NAME: CIDECIN® (daptomycin for injection)

BETWEEN:
Name:

David Schubert	Vice President, Regulatory Affairs and Quality
Judy Newberne	Director, Regulatory Affairs

Representing: Cubist Pharmaceuticals, Inc.

AND
Name:

Janice Soreth, MD	Director, DAIDP
David Ross, MD, PhD	Medical Team Leader
Susan Thompson, MD	Medical Officer
Sumathi Nambiar, MD, MPH	Medical Officer
LT Daniel Nguyen, RPh	Regulatory Health Project Manager

Representing: Division of Anti-Infective Drug Products, HFD-520

BACKGROUND:

On April 10, 2003 the Division informed the sponsor of the discrepancies in the data sets for study 9801. The Division emphasized the importance of resolving these discrepancies. This teleconference was held to further discuss action plans in addressing the discrepancies within the data sets.

MEETING OBJECTIVE(S):

To clarify action plans in resolving data set issues discovered by the Division.

DISCUSSION AND RECOMMENDATIONS:

The sponsor conveyed the following to the Division:

1. The sponsor will provide a written response outlining their understanding of the problem with the data sets.
2. The sponsor will inform the Division of which data sets are involved.
3. The sponsor will explain how the individual data sets, and ISS and ISE data sets were derived.
4. The sponsor will provide a time frame for submission of corrected data sets.

ACTION ITEMS:

- The sponsor will comply with the requests within the Discussion and Recommendation section after consulting with the contractor who constructed the data sets.
- Further discussion of data set issues will be addressed in a face-to-face meeting to be arranged between the sponsor and the Agency.

LT Daniel Nguyen, RPh
Regulatory Health Project Manager
Minutes Recorder

David Ross, MD, PhD
Medical Team Leader

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