CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-572

Administrative Documents

CUBIST

SUBMISSION OF PATENT INFORMATION PURSUANT TO 21 C.F.R. § 314.53

Patent No.	Expiration Date	Type of Patent	Patent Owner
5,912,226	June 15, 2016	Drug Product	Eli Lilly and Company
6,468,967	September 24, 2019	Method of Use	Cubist Pharmaceuticals, Inc.

65 Hayden Avenue. Lexington, MA 02421 P 781.860.8660 F 781.861.0566 www.cubist.com

CUBIST

DECLARATION OF TIMOTHY J. DOUROS, ESQ.

The undersigned declares that U.S. Patent No. 5,912,226 covers the formulation, composition, and/or method of use of daptomycin. Daptomycin is the subject of this application no. 21 572 for which approval is being sought.

Timothy J. Douros
Chief Intellectual Property Counsel
Cubist Pharmaceuticals, Inc.

65 Hayden Avenue, Lexington, MA 02421 P 781.860.8660 F 781.861.0566 www.cubist.com

DECLARATION OF TIMOTHY J. DOUROS, ESQ.

The undersigned declares that U.S. Patent No. 6,468,967 covers the formulation, composition, and/or method of use of daptomycin. Daptomycin is the subject of this application no. 21 572 for which approval is being sought.

Timothy J. Douros
Chief Intellectual Property Counsel
Cubist Pharmaceuticals, Inc.

65 Hayden Avenue, Lexington, MA 02421 P 781.860.8660 F 781.861.0566 www.cubist.com

EXCLUSIVITY SUMMARY for NDA #: 21-572 SUPPL #: N/A

Trade Name: Cubicin™ Generic Name: Daptomycin for injection
Applicant Name: Cubist Pharmaceuticals, Inc.
Division: HFD- 520
Approval Date: September 12, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      If yes, what type(SE1, SE2, etc.)? _____

   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 /_X__/ 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 /_X__/

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

_____

_____

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

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /_X__/

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 /_X__/

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

_____

_____

(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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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: _____

_____

_____

LT Raquel Peat, MS, MPH
Signature of Preparer
Title: Regulatory Health Project Manager

October 8, 2003
Date

Janice Soreth, M.D.
Signature of Division Director

October 9, 2003
Date

cc:
Archival NDA
HFD- 520 /Division File
HFD- Peat /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

DEBARMENT CERTIFICATION

Cubist Pharmaceuticals, Inc. 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.

Michael W. Bonney, President and CEO

Date 1/10/03

65 Hayden Avenue, Lexington, MA 02421 P 781.860.8660 F 781.861.0566 www.cubist.com

NDA 21-572

Office/Division Director Memo for Cubicin (daptomycin for injection)

Indication: Complicated Skin and Soft Tissue Infections

September 11, 2003

The pre-clinical and clinical reviewers have done an excellent job of detailing the issues in their disciplines and in the safety and efficacy of this product. There is clearly a need for additional products to treat severe infections due to Gram-positive organisms including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcal (VRE) infections. This submission addresses some but not all of these issues and needs. I will only very briefly mention preclinical findings, efficacy and safety, and then identify what I see as currently unresolved issues.

Preclinical:

The major target organs of daptomycin toxicity toxicity in rat, dog, and monkey were muscle and peripheral nerves. Muscle damage consisted of muscle degeneration/ regeneration and usually resolved within 1 month of cessation of treatment. Muscle changes were sometimes accompanied by increases in creatine phosphokinase (CPK). Peripheral nerve damage occurred at higher doses and included loss of patellar/gag reflexes, loss of pain perception, decreases in nerve conduction velocity, and axonal degeneration. The dosing interval (q12h v. q24h) appeared to play a role in the development of muscle toxicity in animals, favoring q24h.

Efficacy:

Two multicenter, multinational, randomized, active control studies were conducted by Cubist in hospitalized patients with serious skin infections, with over 500 patients receiving daptomycin. I agree with the overall conclusions as stated in the Medical Officer Reviews. In these two adequate and well-controlled trials in complicated skin and skin structure infections (cSSSI), daptomycin performed in a similar fashion to appropriate controls. Infections included major abscesses, post-surgical wound infections, and infected ulcers. The data were insufficient to demonstrate efficacy in [redacted] Analyses of various subgroups based upon age, sex, underlying disease and severity of infection did not show any convincing trend favoring either daptomycin or control. Analyses looking at efficacy based upon infecting organism also showed comparability across the relevant organisms. Sufficient data exist to support clinical efficacy for cSSSI due streptococci of Groups A, B, and C. While a breakpoint of 0.5 µg/mL can be justified by strict application of a MIC_{90} plus one rule, a 1 µg/mL breakpoint can be supported by the MIC distribution data, a lack of resistance, and clinical efficacy data. Sufficient data exist to include MRSA with the indication of cSSSI. Not surprisingly, however, there were insufficient numbers of VRE to include

this organism with the indication. There were sufficient data to include vancomycin-susceptible *Enterococcus faecalis*.

Safety:

Clinical data for over 1400 patients given daptomycin were evaluated. I agree with the overall conclusions as stated in the reviews and as described in product labeling. The overall safety profile of this product is similar to that of the control regimens. Skeletal muscle appears to be a target organ for toxicity as demonstrated in pre-clinical studies as well as in the clinical trials, and this is likely to be a problem that will require on-going assessment and potential re-evaluation in the post-marketing period. The manifestations of this are both laboratory and clinical. The overall difference in frequency of CPK elevations is not great between daptomycin and control, but higher-grade elevations are slightly more common on daptomycin. There have been several cases with clinical symptoms including one with myositis that resolved after therapy was discontinued. At present, there is no information regarding risk factors such as age or baseline CPK that might predispose to this toxicity. Since the overall number of patients that have been exposed to daptomycin is in the 1000+ range, it is likely that the frequency and severity of this toxicity and potential antecedent factors will not be better defined until actual use in practice, in conjunction with post marketing studies *in vivo* and *in vitro*.

Both pre-clinical and some early clinical trial data suggest that peripheral neuropathy may be an adverse event associated with daptomycin use. The pre-clinical information suggested that higher exposures were necessary for this toxicity to be expressed and the Phase 3 clinical trials did not show clear-cut evidence of this toxicity. These latter studies were conducted in a patient population with underlying diabetes and/or significant limb infection that could make such assessment difficult. Again post-marketing information may better define the significance of this toxicity.

To date, neither liver nor cardiac electrophysiologic (Q-T prolongation) toxicity appears to be an issue. There was no excess of transaminase increases or alkaline phosphatase elevations in daptomycin-treated patients.

Unresolved Issues:

There is a continued need for new products to treat serious Gram positive infections, and daptomycin, with its unique mechanism of action and its spectrum of activity, would appear to be an important new product in the therapeutic armamentarium. Tempering this enthusiasm are the results of studies conducted in other serious conditions beyond the current indication. In a pilot study of patients with either *Staphylococcus aureus* bacteremia or actual endocarditis conducted by Lilly, the original developer of this product, unexpectedly lower efficacy for daptomycin was seen. It would appear that lower peak levels in the BID dosing regimen used in this trial and possibly insufficient penetration into vegetations with the may have contributed to this finding. In a Community Acquired Pneumonia trial conducted by Cubist daptomycin performed also performed less well than would have been expected. It is believed that reduced

penetration into the lung was a factor in these results. The pneumonia data was sufficiently convincing that a statement appears in the Indications and Usage section of the product label that daptomycin is not indicated for community acquired pneumonia.

Additional study of daptomycin in serious illness is clearly necessary. A small study of right sided bacterial endocarditis using the to be approved 4 mg/kg OD regimen is currently underway. Results of this study are to be monitored after the first thirty patients are enrolled. Ideally it would also be appropriate to evaluate the usefulness of this product in serious enterococcal infections. The company does not currently have such a trial underway and the possibility of doing this should be the subject of further discussion.

Finally, the optimal dose for patients with renal insufficiency needs to be determined. Dose adjustment for patients with CrCL of $\leq$ 50mL/min, including patients on dialysis (hemodialysis and CAPD), needs to be determined in a Phase 4 study. Cubist has agreed to perform such a study. In the meantime, the basis for current dosing recommendations rests upon the clinical efficacy and safety data in patients with normal renal function combined with limited data in subjects and patients with renal impairment.

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
9/12/03 05:24:25 PM
MEDICAL OFFICER
Office/Division Director Memo
Ready for sign-off

Mark Goldberger
9/12/03 05:26:12 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): NDA 21-572, Cidecin® (daptomycin for injection), 4mg/kg.

Applicant: Cubist Pharmaceuticals

Date of Application: December 19, 2002
Date of Receipt: December 20, 2002
Date of Filing Meeting: February 13, 2003
Filing Date: February 18, 2003

Indication(s) requested: complicated Skin and Skin Structure Infections (cSSSI) including those complicating diabetic foot and decubitus ulcers caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, *Enterococcus faecilis* (vancomycin-susceptible strains only)

Type of Application: Full NDA ____X____ Supplement _____
(b)(1) ____X_____ (b)(2) ___ _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___ ____ P___X_____
Resubmission after a withdrawal or refuse to file _N/A_____
Chemical Classification: (1,2,3 etc.)___1___
Other (orphan, OTC, etc.)____N/A_____

Has orphan drug exclusivity been granted to another drug 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 the application is affected by the application integrity policy (AIP), explain.

User Fee Status: PAID (December 23, 2002) Waived (e.g., small business, public health) ___no_____
Exempt (orphan, government) ___no_____
Form 3397 (User Fee Cover Sheet) submitted: YES__X_____ NO_____
User Fee ID#____4484_____
Clinical data? YES ___X____ NO _____ Referenced to NDA# __N/A_____
Date clock started after UN _____

User Fee Goal date: __June 20, 2003_____

Action Goal Date (optional) _June 20, 2003_____

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

- Form 356h included with authorized signature? YES✔ NO
  If foreign applicant, the U.S. Agent must countersign.

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

- If electronic NDA, does it follow the Guidance? YES✔ NO

  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO NA✔

- Patent information included with authorized signature? YES✔ NO

- Exclusivity requested? YES; If yes, _____years NO✔

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES✔ NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. 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 the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, …."

- Financial Disclosure included with authorized signature? YES✔ NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO NA✔
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES✔ NO

Refer to 21 CFR 314.101(d) for Filing Requirements

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/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers: IND 57,693 and IND 27,627

End-of-Phase 2 Meeting? Date: May 9, 2000
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s) November 9, 2001 and December 3, 2001
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES✔ NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES✔ NO NA

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO NA✔

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA✔

Advisory Committee Meeting needed? YES, date if known _____ NO✔

Clinical

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

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES✔ NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? YES✔ NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES✔ NO

If 505(b)(2), complete the following: N/A

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").

Name of listed drug(s) and NDA/ANDA #: N/A

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO NA✔

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)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO NA✔

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?
YES NO NA✔

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

__X__ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 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.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(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): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for 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.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO NA✔

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

YES NO NA✔

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

YES NO NA✔

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO NA✔

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 13, 2003

BACKGROUND

The Applicant submitted a New Drug Application (NDA) on December 20, 2002 for Cidecin® (daptomycin for injection) for the treatment of complicated Skin and Skin Structure Infections (cSSSI) including those complicating diabetic foot and decubitus ulcers caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis*, *Enterococcus faecilis* (vancomycin-susceptible strains only)

The daptomycin clinical program consisted of studies conducted by both Eli Lilly and Company (Lilly) and Cubist Pharmaceuticals, Inc. (Cubist). Lilly conducted primarily Phase 1 single and multiple dose safety and pharmacokinetic studies and a small Phase 2 program which consisted of two studies. Cubist obtained worldwide marketing rights for daptomycin from Lilly and filed its own IND application in December, 1998. The pre-clinical data previously generated by Lilly was used to support Cubist's initial Phase 2 and 3 clinical trials. Cubist has modified Lilly's clinical strategy of administering divided daily doses of daptomycin to emphasize once-daily dosing of daptomycin. This was done based on preclinical studies, clinical data analysis, and modeling that show that once-daily dosing maximizes antibacterial efficacy while minimizing adverse effects.

ATTENDEES: Mark Goldberger, Janice Soreth, David Ross, Susan Thompson, Sumathi Nambiar, Philip Colangelo, Charles Bonapace, Terry Peters, Wendelyn Schmidt, Joel Jiang, Daphne Lin, Albert Sheldon, Peter Coderre, Bonnie Dunn, Zi Qiang Gu, Alfred Sorbello, Paul Buehler, Brenda Friend, Edward Cox, Elizabeth DuvallMiller, David Roeder and Raquel Peat

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Susan Thompson and Sumathi Nambiar
Secondary Medical:	David Ross
Statistical:	Joel Jiang
Pharmacology:	Wendelyn Schmidt
Statistical Pharmacology:	N/A
Chemist:	Zi Quang Gu
Environmental Assessment (if needed):	Karyn Campbell
Biopharmaceutical:	Charles Bonapace
Microbiology, sterility:	Peter Cooney
Microbiology, clinical (for antimicrobial products only):	Peter Coderre
DSI:	Ni Aye Khin and Brenda Friend
Project Manager:	Raquel Peat
Other Consults:	ODS

Per reviewers, all parts in English, or English translation? YES__X___ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES___ X _____ NO__ _____

MICROBIOLOGY CLINICAL – File___X_____ Refuse to file_____

STATISTICAL – File ___X_____ Refuse to file _____

BIOPHARMACEUTICS – File ___X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File ___X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES_X____NO_____ File__X___ Refuse to file _____

ADDITIONAL COMMENTS:

It was decided that the sponsor would be granted a priority review with a user fee goal date of June 20, 2003. The Clinical Pharmacology and Chemistry reviewers both had filing deficiencies to be forwarded to the sponsor (see comments below) that do not affect filing of the application.

COMMENTS TO BE FORWARDED TO THE SPONSOR ARE AS FOLLOWS:

- Identification solely by a single ultraviolet method is not regarded as being specific for the identity of the new drug substance and the new drug product. A specific method such as infrared spectroscopy is recommended for the identity test. Incorporate an additional analytical method into your release specifications. This will include having a validated method and data to support the method, and then an acceptance criteria based on those data. However, the use of two chromatographic procedures, where the separation is based on different principles — or a combination of tests into a single procedure (—) is generally acceptable.

- Submit specific rotation and inorganic elements in the drug substance specification as recommended by the Division in pre-NDA CMC meeting on December 3, 2001.

- Although the sponsor has assessed the potential of daptomycin to act as an inhibitor of human CYP P450 isoforms, the sponsor has not assessed the potential for daptomycin to act as a substrate of CYP P450 isoforms. The sponsor should evaluate the potential for daptomycin to act as a substrate for human CYP P450 isoforms using *in vitro* methods. In addition, the sponsor should attempt to identify the primary metabolites of daptomycin in plasma and urine.

- Many of the clinical pharmacology study reports by Eli Lilly and Co. are difficult to read. In order to facilitate the clinical pharmacology review, the sponsor is encouraged to submit enhanced versions (either electronic or paper) of final study reports performed by Eli Lilly and Co.

REGULATORY CONCLUSIONS/DEFICIENCIES:

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

_____ The application is unsuitable for filing. Explain why:

45- day filing meeting minutes recorded by:
LTJG Raquel Peat, M.S., M.P.H.
Regulatory Health Project Manager, HFD-520

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-572	Efficacy Supplement Type SE-	Supplement Number n/a	
Drug: Cubicin™ (daptomycin for injection) Intravenous Injection		Applicant: Cubist Pharmaceuticals, Inc.	
RPM: LT Raquel Peat		HFD- 520	Phone # 301-827-2125
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	Other (Antibiotic- Systemic) 1P
• Other (e.g., orphan, OTC)	none
❖ User Fee Goal Dates	September 19, 2003
❖ 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	( ) Paid
• User Fee waiver	(X) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	none
• OC clearance for approval	none
❖ 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.	( )
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of ~~notification~~ and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Enclosed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness 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)*	none
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 (X) Press Release ( ) 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)	Enclosed Final Label
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	Enclosed
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Enclosed
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Tradename & Promotional Reviews
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	none
• Applicant proposed	Yes-Enclosed in Chemistry Review
• Reviews	Yes- Enclosed in Chemistry Review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes: September 11, 2003
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
❖ Memoranda and Telecons	Enclosed
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	May 9, 2000
• Pre-NDA meeting (indicate date)	December 3, 2001
• Pre-Approval Safety Conference (indicate date; approvals only)	none
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	none
• 48-hour alert	none
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	none
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	September 12, 2003
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	September 12, 2003 (Review/Appendix A) and September 23, 2003 (Appendix B)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	September 10, and 12, 2003
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	
❖ Statistical review(s) *(indicate date for each review)*	September 12, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	September 12, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	none
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	May 23, 2003
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	September 12, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	P. 115 of the Chemistry Review
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	June 16, 2003
❖ Facilities inspection (provide EER report)	Date completed: June 17, 2003 (X) Acceptable- See Chemistry Review ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested- August 11, 1003 ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	August 19, 2003
❖ Nonclinical inspection review summary	none
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	none
❖ CAC/ECAC report	none

MEMORANDUM

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

DATE: March 14, 2003

TO: David Schubert
Vice President, Regulatory Affairs and Quality
Cubist Pharmaceuticals
65 Hayden Avenue
Lexington, MA 02421
Phone: (781) 860-8455
FAX: (781) 861-1408

THROUGH: Review Team for NDA 21-572

FROM: Raquel Peat, LTJG
Regulatory Health Project Manager
Division of Anti-Infective Drug Products
(301) 827-2125
(301) 827-2325 (Fax)

SUBJECT: Information Request

Statistical Questions:

- In which data set is the information of Sponsor-Defined Clinical Outcome at the Test-of-Cure Evaluation provided? What is the right variable to describe Sponsor-Defined Clinical Outcomes at the Test-of-Cure Evaluation, and at the Post-Study Evaluation? (e.g. Study C9901, Table 11-6). The same questions to the information of Investigator-Determined Clinical Outcomes at the Test-of-Cure Evaluation, and at the Post-Study Evaluation. (e.g. Study C9901, Tables 11-13 and 11-14).

- The "formats" data sets (e.g. formats.sc2 or its transport formatted file) are not found. If they are already included in the data set package please tell whereabouts, if not, please submit them as per studies (C9901 and C9801) accordingly.

Chemistry Comments:

- We propose that two identification methods be used for identity test as recommended in ICH Q6A. The two identification tests can be the — — could be used.

- Please include specific rotation in the drug substance specification as recommended by the

Division in pre-NDA CMC meeting on December 3, 2001.

- Based on reviewing the information provided in the NDA, we recommend that inorganic elements —— be monitored as an in-process test during the manufacturing in order to confirm the quality of the drug substance. The acceptance criteria for these inorganic elements should be listed on the drug substance specification sheet.

- It is recommended that a limit of not more than — % for individual specified impurity be included as part of the drug substance specification.

- The following limits are recommended for the related impurities and degradants in the drug substance specification based upon the manufacturing data and the qualification level obtained from non-clinical and/or clinical evaluation of Daptomycin.

Daptomycin Drug Substance Release Specifications

Description	Specifications Proposed in NDA	Specifications Recommended
Related Impurities and Degradants (% Area)		
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT %
—	NMT —	NMT %
Individual Unspecified Impurity a	NMT —	NMT —
Total Impurities — %)	NMT —	NMT —

Clinical Comments:

- Please clarify how patients with missing outcomes were handled in the sponsor defined clinical outcomes at the test of cure evaluation. Section 9.7.1.8 of the final study report states that if the patient had no evaluation after the end of therapy they could be judged a failure. The statistical analysis plan of the protocol (Section 4.2) states that patients who had no evaluation from end of therapy through test of cure visit inclusive were considered failures provided they received > 2days of study medication.

- If the test of cure visit was missing were all patients classified as failures irrespective of the outcome at the end of therapy? If the patient was classified as cure at the end of therapy visit but missed the test of cure visit was the patient classified as Non-evaluable or as a failure?

- If the end of therapy visit was missing was the patient classified as Non-evaluable or as a failure?

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

/s/

Raquel Peat
3/14/03 12:58:18 PM
CSO
Fax sent on March 14, 2003.
ready for sign off

From: Peat, Raquel
Sent: Wednesday, March 26, 2003 2:36 PM
To: David Schubert (E-mail)
Subject: FW: Daptomycin CAP study - Question for Cubist

Importance: High
Sensitivity: Confidential

Clinical Question:

Regarding the submitted CRF's for the two Community Acquired Pneumonia studies: It appears that patient information/data which appears in patient narratives is sometimes not included in the Case Report Forms. For example, in the patient narrative of patient 056501 the laboratory values and other clinical information associated with the patient's terminal event are not included in the CRF. In this and other CRF's for patients who died, there does not appear be a systematic collection of information surrounding the patient's death. Please clarify the procedures by which information is collected for the patient narrative and the circumstances under which data may appear one in one format (e.g. patient narrative) and not in another (e.g., the CRF).

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/s/

Raquel Peat
4/17/03 01:33:26 PM
CSO
Email sent to sponsor on March 26, 2003

MEMORANDUM OF MEETING MINUTES

Meeting Date:	**December 3, 2001**
Location:	**Corp S-300, 2-3pm**
Applications:	**IND 57,693**
Drug:	**Daptomycin**
Meeting Chair:	**Dr. Chi Wan Chen, Director, ONDC Div III**

FDA's Attendees:
Chi Wan Chen, Ph.D.- Director, ONDC Div III
David Katague, Ph.D.-Chemistry Team Leader
Shrikant Pagay, Ph.D.-Chemistry Reviewer
LTJG Raquel Peat, M.S.- Project Manager

Cubist's Attendees:
Robert McCormack, Ph.D.-Sr. Vice President, Drug Development
Thomas Kelleher, Ph.D.- Sr. Director, Manufacturing
James Desiderio, Ph.D.- Sr. Director, Global Project Management
Mary Kathryn Kottke, Ph.D.- Manager, Regulatory Affairs
Sandra O'Conner, M.S.-Manager, Product Development

PURPOSE:

The purpose of the meeting was to discuss the format and content of Cubist's CMC Technical Data Section for the daptomycin NDA.

The sponsor presented overall daptomycin manufacturing development plan. It was pointed out that during the initial development, —) was used for the purification process of the drug substance and changed to — at a later stage in the development.

The Division inquired if — based purification process or — —) based purification process was used in Cubist clinical program. Cubist indicated that majority of the materials used for the clinical studies were manufactured by the — purification process. Cubist plans to use the — process for their commercial process. The Division inquired about the purification process used in the manufacturing of the primary stability batches. Cubist responded that the — purification process was used. They anticipate having — of stability data at the time of filing.

Another important consideration is changes in manufacturing facility — is the sole bulk drug substance supplier for NDA submission and — provided drug substance for clinical trials and for primary stability studies. Abbott is the drug product manufacturer for clinical, primary stability and for commercial production.

The rest of the meeting focused on specific questions provided by the sponsor in the briefing package.

CMC Questions

1.a. Does the Agency agree that it is acceptable to use — drug substance for primary stability studies of drug product and drug substance, provided the drug substance manufactured by — are comparable?

FDA Response:
The Division will accept primary stability batches of the drug substance manufactured at — provided that comparability is demonstrated for the drug substance manufactured at — and — sites. FDA will also accept the primary stability study batches of the drug product from the drug substance manufactured at —

1.b. Cubist will be conducting its characterization of daptomycin- related impurities in the following manner:

- *Complete structural characterization for those impurities that are detected at levels of —*
- *Characterization based on — analysis for those impurities that are detected at levels of — to less than —, and*
- *Total impurity levels determined on release will include all impurities detected at levels of — as measured by —*

FDA Response:
The proposal is acceptable. The Division recommended that (1) — characterized impurities be considered as specified unidentified impurities; (2) all specified impurities, whether identified or unidentified, be individually listed and controlled as part of the drug substance specification; and (3) any unspecified impurity be limited to NMT 0.1%. The Division suggested that the sponsor follow ICH Q3A format for impurities. Please provide acceptance criteria based on the available data.

1.c. Primary drug product stability batches have been manufactured — — capacity, but less than the anticipated commercial size.

FDA Response:
This is acceptable.

1.d Does the Agency agree that the drug substance produced by — purification process and — purification process are comparable.

FDA Response:
The Division noted that there might be differences in the batch data between the two processes. Parameters such as — — should be explained and justified in the NDA submission (refer to VI.D Table 2 of 10/9/01 document). In

addition, without complete impurity profiles, the Division is unable to determine whether the drug substance manufactured using — processes are comparable.

I.e. Does the Agency agree that the approach for comparability testing be limited to drug product alone. The drug substance is sourced from — and — manufacturing sites and processed using —

FDA Response:

The Division suggested that Cubist provide comparability data for the drug substance (instead of the drug product as proposed by the sponsor) manufactured at — and — process. The Division is requesting new and/or historical data for the — drug substance for comparison purposes.

Note: The Division noted that under item 1a., the primary stability studies for the drug substance and drug product will be conducted from — drug substance, data and any new data from — can serve in the bridging studies with the drug substance manufactured at — site. Therefore, it is recommended that Cubist provide comparability data for the drug product as well as from the drug substance manufactured at — site.

2. *Does the Agency agree that the release testing as listed in Section VI. is adequate to support the filing of NDA?*

FDA Response:
The Division recommends that impurities, specific rotation, heavy metals and inorganic elements be added to Table 4 of Section VI.E, or provide justification for their omission.

The Division inquired whether a — method was adequate for — testing. Cubist responded that daptomycin has a — due to —

3. *The sponsor asked if stability data can be updated for submission during the review process. The sponsor will provide in the NDA, — of stability data for the drug product on primary batches (— drug substance) and limited data on validation batches (from — drug substance). Does Agency accepts stability data update during the review process for the validation batches of the drug product?*

FDA Response
The division will accept stability data up to 3 months before the action date for both the validation batches and the primary stability batches of the drug product.

The Division inquired whether statistical analyses will be performed on stability data. The sponsor will be performing statistical analyses.

The sponsor inquired whether it was possible to obtain a — expiration date based on — of data under the recommended storage conditions and — of data under accelerated conditions. The Division stated that this would be evaluated on a case-by-case basis based on analytical data submitted.

4. *The sponsor plans to submit executed batch records for the primary drug product stability lots and the process validation lots with the NDA. Does the Agency require the submission of additional batch records?*

FDA Response
The Division does not require additional executed batch records but would recommend that one executed batch record each for a representative primary stability batch and a validation batch be submitted.

5. *The sponsor intends to submit supplementary CMC studies (Refer to Section V.5, of 10/9/01 document for listing of all the proposed studies). Does the Agency agree that these CMC studies are adequate to support the filing of the NDA?*

FDA Response:
The proposed studies are acceptable. It is suggested to follow ICH Q1A® for the in-use stability studies of the reconstituted solution. The specific information is listed under item 7, Storage Conditions (2.2.7). This would apply to the diluents used to support the label.

6. *Does the Agency accept submissions of the CMC Technical Data Section of the NDA as a rolling CMC submission?*

FDA Response:
The Division indicated that rolling submission for CMC document are not accepted but it is possible to submit the complete CMC section 60-90 days in advance of the rest of the NDA.

The Division inquired about Cubist's plans for submitting an environmental impact statement. Cubist responded that they would be filing an abbreviated environmental assessment.

DECISION (AGREEMENTS) REACHED

1. The Division will accept the primary stability batch data for the drug product and the drug substance manufactured at the — provided the sponsor shows comparability between the drug substance manufactured at — sites.

2. The Division agreed that the stability data for the primary stability batches of the drug product manufactured — capacity, but less than the anticipated commercial size, is acceptable.

3. The sponsor will provide comparability testing for the drug substance manufactured at [redacted]

4. The Division agreed that it is acceptable to update the stability data during the review period. Stability data up to 3 months before the action time is acceptable for both the primary stability batches and the validation batches.

5. The Division does not require additional executed batch records.

6. The Table of Contents for the CMC Technical Data Section submitted in the briefing package was adequate for filing.

7. The Division will accept pre-submission of CMC Technical Data Sections 60-90 days before the anticipated submission of the remainder of the NDA.

Please see specific Agency response for the remaining questions.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSION: None

MINUTES PREPARER: _____
LTJG Raquel Peat
Project Manager

CHAIR CONCURRENCE: _____
Chi Wan Chen
Director, ONDC Div 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 02:53:30 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 3, 2001
Time: 1-2 p.m., EST
Location: S-300
Application: IND 57,693
Drug: Daptomycin
Sponsor: Cubist
Type of Meeting: Pre-NDA Meeting (Type B)
Meeting Chair: Dr. Janice Soreth, Division Director
Meeting Recorder: Jose Cintron, Regulatory Health Project Manager

FDA Attendees:
Janice Soreth, M.D.-Division Director
David Ross, M.D., Ph.D.-Medical Team Leader
Susan Thompson, M.D.- Medical Officer
Daphne Lin, Ph.D. -Statistical Team Leader
Erica Brittain, Ph.D.-Statistical Reviewer
Ken Seethaler, Ph.D.-Pharmacology Reviewer
Jose Cintron, R.Ph., M.A.- Regulatory Health Project Manager

Cubist Attendees:
Micheal DeBruin, M.D.- Vice President, Clinical Research
James Desiderio, Ph.D.- Sr. Director, Global Project Management
Thomas Kelleher, Ph.D.-Sr. Director, Manufacturing
Mary Kathryn Kottke, Ph.D.- Manager, Regulatory Affairs
Robert McCormack, Ph.D.-Sr. Vice President, Drug Development
Sandra O'Connor, M.S.-Manager, Product Development

PURPOSE:

To address questions and comments from FDA Statistical and Medical Reviewers regarding DAP-VRE-00-07, Amendment 2 (Serial #096).

BACKGROUND:

IND 57,693 Serial #96 provides for protocol DAP-VRE-00-07 entitled *"A Randomized, Double-Blind, Double-Dummy, Phase III, Comparative Study of Cidecin (Daptomycin) and Zyvox™ (Linzolid) in the treatment of Hospitalized Adults with Suspected Vancomycin-Resistant Enterococcal Infections"*. The Division sent a fax to the sponsor with clinical and statistical comments on the proposed protocol on November 30, 2001. The Division's comments and the sponsor's responses were discussed at the meeting.

DISCUSSION POINTS:

1. *Microbiologically-Evaluable (ME) and Modified-Intent-to-Treat (MITT) analyses should be co-primary, as opposed to ME as primary and MITT as secondary.* Cubist is in agreement with FDA's position and will conduct the analyses as recommended.

2. *In the ME analyses, death in which VRE may have contributed should be considered failures. Indeterminates are analyzed as failures in your primary analysis. A series of sensitivity analyses with respect to death should be conducted.* Cubist is in agreement with FDA's position and will conduct analyses as recommended.

3. *The study should be designed to maximize the fraction of the VRE population which falls into the bacteremia subgroup.* Cubist will focus, as much as possible, on the more seriously ill subset of patients with VRE infection. Cubist will encourage enrollment of patients with complicated intra-abdominal infections as an additional source of bacteremic VRE patients.

4. *Does the definition of MITT as requiring "a target pathogen recovered", mean that a MITT patient must have documented VRE infection?* Cubist confirmed that the MITT definition requires that patients have documented VRE infection.

5. *FDA recommends that the protocol address general statistical issues that have been raised with the sponsor for a number of previous protocols, including plans for sensitivity analyses, distinguishing unknown outcomes from failed outcomes, etc.* Cubist will ensure that statistical issues, as identified above, are addressed in the protocol.

6. *FDA wants to clarify if the proposed sample size of 720 patients are ALL confirmed VRE patients, or are VRE patients a subgroup of this group of 720.* Cubist confirms the intent of the study is for all patients to have documented VRE infection.

7. *FDA requested a justification for the use of a 6 mg/kg/day daptomycin dose.* The daptomycin MICs for entercocci (2-4 mcg/ml) are higher than those for other pathogens. Taking into consideration the MIC, plasma pharmacokinetics and protein binding data, it was calculated that a dose of 6 mg/kg is required to maintain adequate blood levels of daptomycin over the dosing interval.

8. *What procedure will be followed for patients who require more than 28 days of therapy?* Cubist indicated that there might be a few patients who fall into this category. In short-term, these will be handled on a case-by-case basis, relying on evaluation of the patient through the fourth week on drug. The preference is to stay within the boundaries of the dosing guidelines for linezolid. As enrollment progresses, the number of days on therapy will be closely monitored to assess the number of patients requiring more than 28 days of drug treatment. For patients requiring extended dosing, the expectation is that the Week 4 schedule of evaluations would be implemented for the extended dosing period. Should the number of patients

requiring extended dosing be unexpectedly high, changes to the protocol may be warranted.

9. *Patients with underlying peripheral neuropathy, myopathy, and/or elevated CPK at baseline should be excluded.* The Division noted that daptomycin is associated with toxicity for which the mechanisms are incompletely understood. This particular study will enroll very sick patients likely to have a multitude of underlying conditions. The combination of these two observations is a source of some concern to the FDA. Cubist recognized their lack of understanding of the mechanism of daptomycin toxicity, but offered that this is one reason that the development program has moved forward in a judicious manner. They pointed out the sponsor now has significant clinical experience at the 4 mg/kg dose in a reasonable number of patients with moderate to severe infections, and Phase 1 data with repeated doses of daptomycin at 6 and 8 mg/kg/day. Elevated CPK levels are commonly observed in patients with moderate to severe infections, and can occur following such things as a contusion or a simple intramuscular injection. CPK values of 1,000 U/L at baseline were not uncommon in the complicated skin studies. Additionally, the relatively high degree of normal fluctuations in CPK levels from baseline further complicate the assessment of the adverse drug effects. The FDA acknowledged these points, but reiterated that the patients with underlying conditions should be excluded.

10. *The table on page 51,* " A level of > 4x ULN, or 800 U/L, for 3 days should be the threshold for discontinuation. The level can be reevaluated as experience at the 6 mg/kg dose is collected.

11. *Three dosing days rather than five should be required for inclusion in the clinically evaluable population.* Cubist agrees with FDA.

12. *FDA agrees that the definition of catheter-related VRE bactermia is growth of enterococci in at least two blood cultures, one drawn via routine venipuncture of a peripheral vein, and one drawn through a catheter. Both isolates must grow the same species of Enterococcus, and they should exhibit the same susceptibility pattern. It will be sufficient to use ≥ 15 colonies on semi- quantitative cultures of the catheter tip with the same Enterococcus (species and susceptibility) from a peripheral blood culture. With primary bacteremia, two peripheral blood cultures which grow Enterococcus of the same species and susceptibility pattern should be required in the absence of other identifiable source of infection. One blood culture which grows VRE would be sufficient in the situation where an identical organism is isolated from an appropriate clinical site.* Cubist is in agreement with FDA.

13. *In the definitions of microbiological response (page 43-44 of the protocol), references should be to VRE only and the TOC specified; others may be tabulated. Enterococcus eradication is the microbiological response of interest.* The Division stated that microbiological characterization should include an evaluation of gentamicin and penicillin susceptibility for each isolate. Cubist agrees with FDA.

14. *The protocol should include a provision for performance of a MITT analysis of all randomized patients who receive at least one dose of study medication and had VRE*

isolated at baseline, as well as a conventional per protocol analysis. The FDA recommended that an analysis of outcome by site of infection should be done. Cubist agreed with FDA.

15. *In order to detect potential hematological toxicity (major toxicity with linezolid), hematology studies are to be conducted at baseline, and on days 1,7,10,14, at end of therapy and at 7 and 14 days post therapy as designed in the protocol.* Cubist agrees with FDA.

ADDITIONAL POINTS OF DISCUSSION:

The FDA addressed questions regarding the protocol submitted by Cubist on November 27, 2001. (Serial no. 104).

1. *Are the following general study features (patient population, inclusion/exclusion criteria, primary and secondary efficacy parameters, and definition of bacteremia) acceptable for a VRE registration trial?* The study design features are acceptable for a VRE registration trial, with caveats discussed previously in discussion points above.

2. *Is the Statistical methods section of the protocol adequate to support a VRE registration study?* Yes, the statistical methods are adequate to support a VRE registration trial, with the caveat discussed previously in discussion points above (particularly that the ME and MITT analyses be co-primary).

3. *Is the currently designed protocol acceptable as a single trial for registration?* Yes, the current design is acceptable.

4. *Is a database of 360 patients receiving 6mg/kg q24 dose of daptomycin for 14-28 days sufficient for a demonstration of safety?* This number of patients is the minimally acceptable number for demonstration of safety. Additional patient experience at the 6mg/kg/day dose would provide a more convincing safety database.

5. *Discussion of requirements for statistical power in the VRE study.*
Cubist indicated that the FDA requirements for 5% delta between the daptomycin and linezolid arms in the VRE study are not attainable. Cubist plans to submit the VRE study in a supplemental filing, possibly with endocarditis data; the initial NDA will contain only complicated skin and skin structure infections and community-acquired pneumonia.

DECISION (AGREEMENTS) REACHED:

1. Cubist will preform Microbiologically-Evaluable (ME) and Modified-Intent-to-Treat (MITT) analyses.

2. Cubist agreed to conduct a series of sensitivity analyses with respect to death.

3. Cubist acknowledges FDA's position regarding representation of bacteremic patients

in the VRE study, and maintains its commitment to encourage enrollment of this subpopulation.

4. Cubist agrees to exclude patients with known or pre-existing peripheral neuropathy or muscle disease (e.g. myositis, muscular dystrophy). Assuming that the upper limit of normal (ULN) for plasma CPK levels is~200, the FDA agreed that it is acceptable for Cubist to use a cut-off of $\leq$2.5x ULN, or 500 U/L, as the maximum baseline CPK level for study entry.

5. Cubist agreed that three dosing days rather than five should be required for inclusion in the clinically evaluable population

ISSUES REQUIRING FURTHER DISCUSSION: none

MINUTES PREPARER_____
LTJG Raquel Peat
Project Manager

CHAIR CONCURRENCE_____
Janice Soreth, M.D.
Division Director

ATTACHMENTS/HANDOUTS: Faxed statistical/clinical comments

Statistical Questions/Comments

IND#: 57,693/Serial #96
Applicant: Cubist
Name of Drug: Datomycin-VRE-00-07, Amendment No. 2

Statistical Reviewer: Erica Brittain, Ph.D.
Medical Reviewer: Susan Thompson, M.D.
Project Manager: Raquel Peat

Medical Officer Comments for Protocol entitled "A Randomized, Double-Blind, Double-Dummy, Phase III, Comparative Study of Cidecin (daptomycin) and Zyvox (linezolid) in the Treatment of Hospitalized Adults with Suspended Vancomycin Resistant Enterococcal Infections."
November 29, 2001

1. We recommend that ME and MITT analyses be co-primary, as opposed to ME as primary and MITT as secondary.

2. We recommend that all deaths are failures in MITT analysis, with all deaths in which VRE may have contributed as failures in ME analysis. Note that this is actually slightly different from considering deaths as indeterminate, and indeterminates are analyzed as failures in your primary analysis. A series of sensitivity analyses with respect to death should be conducted.

3. It is important that a reasonable fraction of the VRE population fall into the bacteremia subgroup.

4. What exactly is meant by the definition of MITT as requiring "a target pathogen recovered"? Does this simply mean that a MITT patient must have documented VRE?

5. We recommend that the protocol address general statistical issues that may have been provided to the sponsor for a number of previous protocols. These include plans for sensitivity analyses, distinguishing unknown outcomes from failed outcomes, and so forth.

6. We want to clarify if the proposed sample size of 720 patients are ALL confirmed VRE patients. Or are the VRE patients a subgroup of this?

Clinical Questions/Comments

IND#: 57,693/Serial #96
Applicant: Cubist
Name of Drug: Datomycin VRE-00-07, Amendment No. 2

Medical Reviewer: Susan Thompson, M.D.
Project Manager: Raquel Peat

Medical Officer Comments for Protocol entitled "A Randomized, Double-Blind, Double-Dummy, Phase III, Comparative Study of Cidecin (daptomycin) and Zyvox (linezolid) in the Treatment of Hospitalized Adults with Suspended Vancomycin Resistant Enterococcal Infections."
November 29, 2001

1. Please outline a justification for the use of 6 mg/kg/day.

2. What procedure will be followed for patients who require more than 28 days of therapy?

3. Patients with underlying peripheral neuropathy, myopathy, and/or elevated CPK at baseline should be excluded.

4. The table on page 51 should be amended. At a CPK

5. Three dosing days rather that five should be required for inclusion in the clinically evaluable population.

6. We agree with the definition of catheter-related VRE bacteremia as given: Growth of Enterococcus in at least two blood cultures, one of which is drawn via routine venipuncture of a peripheral vein, and one of which is drawn through the catheter. Both isolates must grow the same species of Enterococcus and both isolates should exhibit the same susceptibility pattern. Alternatively, $\geq$15 colonies on semi-quantitative cultures of the catheter tip with the same Enterococcus (species and susceptibility) from a peripheral blood culture will suffice. However, to define Primary Bacteremia, two (not one) peripheral blood cultures should be required which grow Enterococcus of the same species and susceptibility pattern, in the absence of other identifiable sources of infection. One blood culture which grows VRE would be sufficient in the situation where an identical organism is isolated from an appropriate clinical site.

7. In the definitions of microbiological response (p. 43-44), references should be to VRE only and the TOC specified; other organisms may be tabulated, but the microbiological response of interest is the Enterococcus.

8. Included in the protocol should be a provision for performance of a MITT analysis consisting of all randomized patients who received at least one dose of study medication and had VRE isolated at baseline, as well as a conventional per protocol analysis. We agree that an analysis of outcome by site of infection should be done.

9. The major toxicity of linezolid is hematological. As defined in the protocol, hematology studies are to be performed at baseline and on days 1, 7, 10, 14, at end of therapy, and at 7 to 14 days post therapy. This should be adequate to detect potential toxicity due to linezolid.

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

5/10/02 02:22:41 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date:	May 12, 2000
Time:	10:00 AM
Location:	Conference Room S-300
Application:	IND 57,693
Sponsor:	Cubist
Type of Meeting:	End of Phase 2 Meeting CMC
Meeting Chair:	Dr. Chi Wan Chen, Ph.D.
Meeting Recorder:	Mr. Jose R. Cintron, R.Ph., M.A.

FDA DAIDP Attendees	**Titles**
Chi Wan Chen, Ph.D.	Office Director, DNDC-III
Mr. Jim Timper	Team Leader Chemistry
Jose Cintron, R.Ph.	Project Manager

Cubist's Attendees	**Titles**
Robert McCormack, Ph.D.	Vice President, Regulatory Affairs and Quality Assurance
Thomas Kelleher, Ph.D.	Senior Director, Manufacturing
Jan-Ji Lai, Ph.D.	Director, Analytical Chemistry
Mary Kathryn Kottke, Ph.D.	Manager, Manufacturing Development
Judy Newberne	Director, Regulatory Affairs
David Graham	Senior Director, Global Project Management
Tadd Loucks, Ph.D.	Director, Quality Control

Meeting Objectives:
To discuss the daptomycin commercial manufacturing plan and general CMC requirements

- **SPONSOR'S CMC QUESTIONS TO THE FDA. Discussion and Recommendations**: A summary of discussions and conclusions reached at the meeting is listed below:

1. Based upon previous communications with the Agency, Cubist was asked to investigate the use of a —— method rather than the —— method in determining related substances for daptomycin. The meeting package describes the attempts made to obtain a — method. Based upon these investigations, it was determined that a modified — method would be able to provide appropriate resolution of related substances. **Will this method be adequate to determine the impurity profile of the bulk daptomycin and daptomycin drug product for the New Drug Application?**