B. Overview of Materials Consulted in Review

The following materials were consulted during the review process

- Final study reports, submitted electronically
- Case report forms
- Data sets submitted by sponsor and some additional data sets requested by FDA
- Proposed package insert
- Literature review

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were performed at two clinical trial sites for study 9801. No audits were performed for sites that enrolled patients in study 9901.There were many protocol deficiencies at both sites related mainly to eligibility determinations and laboratory assessments. Most of these deviations were considered not to impact the study significantly, hence data from these two sites were not excluded from the analyses.

A summary of audited sites is displayed in the following table.

Investigator Name (Number)	Location	Study number	Number of patients randomized
Tidman (168)	Blue Ridge, GA	9801	32
Pien (66)	Honolulu, Hawaii	9801	42

A random sample of 10% of the case report forms for both studies were reviewed by the medical officer for concurrence with the sponsor's evaluability and outcome assessments. Overall, no major inconsistencies were seen in the evaluability or outcome assessments. Hence, this sample was considered to be adequately representative of the quality of data and the sponsor's data were used for FDA analyses.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the sponsor, the protocol, informed consent form (ICF), and all other written documents provided to the investigator or subject were reviewed and approved by an Institutional Review Board (IRB) or

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Independent Ethics Committee (IEC) at each site before the study was initiated. Copies of the approval letter and all other correspondence with the IRB/IEC were sent to ——— , a Contract Research Organization (CRO) located ——— All of these documents are retained in the Trial Master Files.

The sponsor and the investigators agreed to submit to the IRB/IEC any subsequent protocol amendments, reports of all serious adverse events, and any other information relevant to the safety of the subjects or the conduct of the trial.

The sponsor also stated that the study was conducted in accordance with the ethical principles articulated in the Declaration of Helsinki (Republic of South Africa, amendment October 1996), with the Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH), and with the local laws and regulations for the use of investigational therapeutic agents. All subjects provided voluntary written informed consent. The ICF was signed and dated by both the subject and the investigator or designee. A copy of the signed ICF was provided to the study subject, and the original was retained in the source documents. Any modifications to the ICF requested by the IRB or IEC were reviewed and approved by Cubist prior to implementation.

E. Evaluation of Financial Disclosure

The sponsor (Michael Bonney, President and Chief Operating Officer, Cubist Pharmaceuticals Inc.) has submitted form FDA 3454, Certification: Financial interests and arrangements of clinical investigators. The sponsor certifies that he has not entered into any financial arrangement with the listed clinical investigators whereby the value of the compensation will be affected by the outcome of the studies as defined in CFR 54.2(a). He also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Both study 9801 and 9901, comparing the use of daptomycin with comparator drugs (vancomycin/semi-synthetic penicillins), showed that daptomycin was non-inferior to the comparator drugs in the treatment of

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complicated skin and skin structure infections due to Gram positive bacteria using a non-inferiority margin of 10 %. Gram positive bacteria studied include *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible strains), *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*.

Data submitted were not adequate to include infected diabetic ulcers in the indications and usage section. Viridans group streptococci should not be included in the list of pathogens as their role as pathogens in skin and skin structure infections is unclear, except for members of the *S. intermedius* (*milleri*) group. The number of patients with *S.intermedius* isolates was very few in both studies. As patient characteristics and clinical success rates differed significantly between the two studies, the results of the two studies should be considered separately and not included in the product label in an integrated manner as proposed by the sponsor.

B. General Approach to Review of the Efficacy of the Drug

All data in this NDA were submitted electronically and are available in the electronic document room.

DAP-SST-9801
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B8B-MC-AVAE/AVAG
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C. Detailed Review of Trials by Indication

In this application, the sponsor is only seeking approval for the indication of complicated skin and skin structure infections. Results from two primary comparative studies, DAP-SST-9801 and DAP-SST-9901 were submitted in the NDA to support this indication of. Both studies had similar study design and primary endpoints. In this review, study 9801 is described in detail and the differences between the two studies are summarized in table number 3.

An additional study (B8B-MC-VAE/AVAG) was submitted as a supportive study. This study was conducted by Lilly and was a multi-indication supportive protocol that included patients with skin and skin structure infections due to susceptible Gram positive bacteria. The dose of daptomycin used in this study was 2 mg/kg q 24h for a total duration of 5

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which is different from that used in the other two phase 3 clinical studies. Hence, results of this study are not included in the overall efficacy analyses and will not be discussed further in this review.
Parts of this review are excerpted from the final study reports provided by the sponsor. Comments by the medical officer are provided in Italics.

DAP-SST-9801

Objectives
The primary objective of this study was to compare the safety and efficacy of daptomycin to that of vancomycin or selected semi-synthetic penicillins in the treatment of complicated skin and skin structure infections due to Gram positive bacteria.

Design
This was a multicenter, international, investigator-blinded, randomized, Phase 3 trial.

Population and procedures
Inclusion criteria
Patients were eligible for inclusion in the study if they met all of the following criteria:
General inclusion criteria

- Age 18-85 years
- If female, the patient must have been post-menopausal for at least one year, or have had a hysterectomy or a tubal ligation or, if of child-bearing potential
  - have maintained her normal menstrual pattern for the 3 months prior to study entry and
  - have taken hormonal contraceptives for at least one month prior to study entry, or agree to use spermicide and barrier methods or be using another acceptable method of contraception and agree to continue with the same method during the study, and
  - have a negative serum pregnancy test (serum β-hCG) immediately prior to enrollment. If obtaining the serum pregnancy test result would have caused a delay in treatment, a subject could be entered on the basis of a urine pregnancy test sensitive to at least 50 mU/mL of β hCG, pending results of the serum test.
- Signed, written, informed consent must have been obtained after the nature of the study had been fully explained and before any protocol-specific procedure was performed. In the event that the subject was unable to give consent, the subject's legal representative could do so

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by means approved by the investigator's Independent Ethics Committee (IEC).

Specific inclusion criteria

- A diagnosis of skin and soft tissue infection known or suspected to be due to Gram positive bacteria. *Staphylococcus epidermis* and corynebacteria were not to be considered pathogenic unless also identified in blood and deep tissue sites.
- Diagnosis of bacterial skin and soft tissue infection in the presence of some complicating factor, including infections involving deeper soft tissue or requiring significant surgical intervention. Complicating factors include a pre-existing skin lesion or some underlying condition that adversely effects either the delivery of drug to the affected area, the immunologic response, or the tissue healing response.
- At least 3 of the following clinical signs and symptoms of skin infection must have been present:
  - Temperature >38°C rectal or >37.5°C oral
  - WBC count >12 x10 ^{3} /L or with ≥10% bands
  - Pain
  - Tenderness to palpation
  - Erythema (extending at least 1 cm beyond wound edge)
  - Swelling
  - Induration
  - Pus formation
- Skin and soft tissue infections appropriate for this study included:
  - Wound infections, including wounds due to:
    - Traumatic injury
    - Surgical incision
    - Animal or human bites provided tissue damage existed
    - Foreign body (e.g., septic phlebitis associated with intravenous catheter sites)
  - Major abscesses, with or without recognized preceding trauma that required antibiotic therapy in addition to surgical incision and drainage.
  - Infected ulcers (except multiple infected ulcers) associated with diabetes, vascular insufficiency or pressure.

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