CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA

1.1. NDA 50-748

1.2. Applicant: Rhone-Poulenc Rorer Pharmaceuticals Inc.
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1.3. Submission/Review dates:

1.3.1. Date of submission: September 5, 1997

1.3.2. CDER stamp date: September 8, 1997

1.3.3. Date submission received by reviewer: September 8, 1997

1.3.4. Date Review begun: October 1, 1997

1.3.5. Date review completed: June 25, 1998

1.4. Drug identification:

1.4.1. Generic name: Dalfopristin/quinupristin

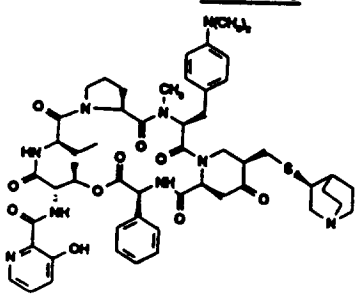
1.4.2. Trade name: Synercid

1.4.3. Chemical name: Synercid contains two drug substances, quinupristin (RP57669) and dalfopristin (RP 54476), in a 30:70 ratio. Quinupristin is a mixture of 3 peptide macrolactones: RP68888, RP 60844, and RP 67648. The chemical names of the 3 quinupristin components are as follows. RP 68888: N-[(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3*S*)-3-quinuclidinylthio]methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide. RP 60844: N-{(6R,9S,10R,13S,15aS,18R,22S,24aS)-6-ethyl-10,23-dimethyl-22-[4-(methyl amino)benzyl]-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-{[(3S)-quinuclidinylthio]methyl}-perhydropyrido[2,1-f]pyrrolo[2,1-1][1,4,7,10,13,16]oxapentaazacyclononadecin-9-yl}-3-hydroxypicolinamide. RP67648: N-{(6R,9S,10R,13S,15aS,18R,22S,24aS)-22-[4-(dimethylamino)benzyl]-6,10,23-trimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-{[(3S)-quinuclidinylthio]methyl}-perhydropyrido[2,1-f]pyrrolo[2,1-1][1,4,7,10,13,16]oxapentaazacyclononadecin-9-yl}-3-hydroxypicolinamide
Dalfopristin or RP 54476: (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-[[2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]-dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone.

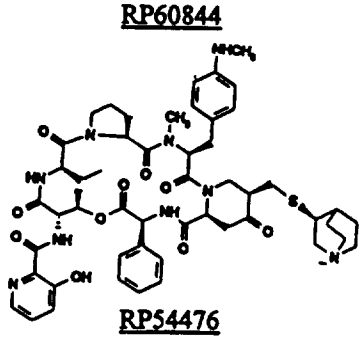
1.4.4. Chemical structure:

Quinupristin

RP68888



RP60844



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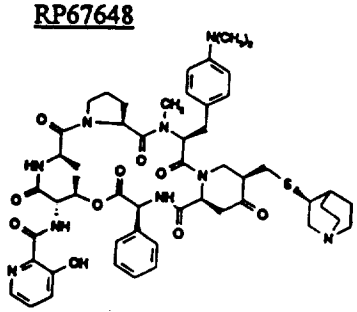
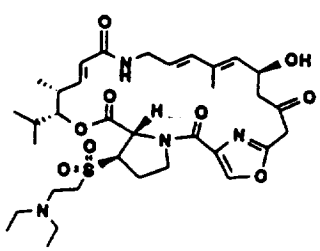


Dalfopristin

RP54476



1.4.5. Molecular formula: Quinupristin: RP 68888 - $C_{53}H_{67}N_9O_{10}S$; RP 60844 – $C_{52}H_{65}N_9O_{10}S$; RP 67648 – $C_{52}H_{65}N_9O_{10}S$. Dalfopristin: RP 54476 - $C_{34}H_{50}N_4O_9S$.

1.4.6. Molecular weight: Quinupristin: RP 68888 - 1022.24; RP 60844 – 1008.22; RP 67648 – 1008.22; Dalfopristin: RP 60844 - 690.85.

1.5. Pharmacologic category: Antimicrobial agent; streptogramin

1.6. Dosage form: preparation for injection

1.7. Route of administration: Intravenous

1.8. Proposed indication & usage section (Verbatim from Applicant's proposed labeling): The following is the proposed indication, with regards to skin and skin structure infections, as it appears in the proposed label:

"Synercid is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

"Complicated skin and skin structure infections caused by *Staphylococcus aureus* methicillin

Streptococcus pyogenes

1.9. Proposed dosage & administration (From Applicant's proposed labeling):

1.10. Related drugs:

1.11. Material reviewed: This review was performed utilizing an electronic submission provided by the applicant. Contained in the submission were case report summaries and the accompanying documentation (statistical analysis, study reports, study protocols, safety reports, etc.). The documents were in Microsoft Word word processing format.

1.12. Regulatory background:

- 6/13/94 – End of Phase 2 meeting between FDA and RPR: RPR stated that their intention was to include the indication of complicated skin and skin structure infections in their Phase 3 development program. FDA agreed, and indicated that it was likely that two pivotal trials would be required to obtain this indication.
- 6/24/94 – During a follow-up teleconference, the FDA reiterated that two studies should be submitted in support of the complicated skin and skin structure infection indication. It was also agreed that data from European trials may form the basis of a portion of the submission, assuming that the quality and conduct of studies was similar to studies from the United States and that the bacteriology was similar.
- 6/11/96 – FDA requests in a letter that the vancomycin-resistant Enterococcus (VRE) indication be submitted in a separate NDA from the non-VRE indications; the latter submission would include complicated skin and skin structure infections.
- 11/18/96 – RPR agrees to submit two NDA's.
- 10/16/97 – FDA requests further information regarding descriptive characteristics of wounds and skin infections.
- 10/28/97 – RPR submits information regarding descriptive characteristics of patients with skin and skin structure infections; no new information is available, other than that contained in the CANDA.

- 1/26/98 – FDA requested that RPR define which microbiology laboratory results (central versus local) took precedence if conflicting results were obtained. RPR responded that the central laboratory results took precedence. FDA also requested a listing of all *S. aureus* isolated together with their antimicrobial sensitivities; if not performed, the reason for the omission was to be supplied.
- 1/28/98 – During a videoconference, RPR presented data including slides, background package, and questions in preparation for presentation before the Division of Anti-infective Drug Products (DAIDP) Advisory Committee on February 19, 1998.
- 1/30/98 – RPR submitted the missing sensitivity data requested on 1/26/98.
- 2/12/98 – A meeting between RPR and FDA was held in preparation for the Advisory Committee. Regarding the indication of complicated skin and skin structure infections, the FDA agreed that equivalence with the comparator was met in both studies. Concern was expressed, however, with the low evaluability rates and low efficacy rates in both study arms in each of the two studies. RPR stated that they felt that they had gone beyond the requirements in the Division's Points to Consider by conducting two studies rather than just one in support of this indication.
- 2/19/98 – The DAIDP Advisory Committee met to discuss Synercid. In response to the question: "Do studies 304 and 305 provide evidence that Synercid is safe and effective for the treatment of complicated skin and skin structure infections?", seven members of the committee voted yes, two voted no, and 1 abstained. In response to the question: " Does the committee recommend approval of Synercid for this indication?", six members of the Committee voted yes and four voted no.

2. Table of Contents:

3. Chemistry/Manufacturing Controls - Please see the review by the Chemist, Mr. Jim Timper.

4. Animal Pharmacology/Toxicology - Please see the review by the Pharmacologist, Dr. Ken Seethaler.

5. Microbiology - Please see the review by the Microbiologist, Dr. Frederic Marsik.

6. Human Pharmacokinetics/Pharmacodynamics - Please see the review by the Biopharmacologist, Dr. He Sun.

7. Human Clinical Experience

7.1. Foreign experience – Synercid is not currently approved in any country.

7.2. Post-marketing experience - Not applicable.

8. **Clinical studies**

8.1. **Introduction** - The two controlled studies contained in the Applicant's submission included a treatment arm with Synercid (7.5 mg/kg q12 hrs) versus a comparator arm. The comparator consisted of oxacillin (2g q6 hrs) in Study JRV 304 and cefazolin (1g q8 hrs) in Study JRV 305. Vancomycin (1g q12 hrs) could be substituted as the comparator if a) suspected or confirmed [redacted] resistant staphylococcus was isolated or b) a documented history of immediate hypersensitivity to penicillins, cephalosporins, or carbapenems was obtained. The two studies were otherwise very similar; minor differences will be discussed in the Study Design for study JRV 305. The total number of patients enrolled in each study was as follows: JRV 304 - 450, JRV 305 - 445, for a total of 995 patients studied with complicated skin and skin structure infections.

8.2. **Complicated Skin and Skin Structure Infections - Protocol JRV 304** (Taken from Volume 1.249, pages 2-134 and Volume 1.250, pages 3-79).

8.2.1. **Title** - Phase III Randomized Multicenter Comparative Study of Synercid® (quinupristin/dalfopristin) versus Standard Therapy in the Treatment of Complicated Gram-positive Skin and Skin-structure Infections.

8.2.2. **Objective/Rationale** - The objective of this study is to evaluate the safety and therapeutic effectiveness of Synercid iv 7.5 mg/kg q 12h versus standard therapy in the treatment of gram-positive complicated skin and skin structure infections.

8.2.3. **Study Design** - Study JRV 304 is an open-label, Phase 3, randomized, comparative trial. This multicenter trial was conducted at 43 centers in the United States, including three in Puerto Rico.

8.2.4. **Study Details** - Please see Appendix 1 for a schedule of Study Procedures. This is reproduced from Volume 1.250, page 8.

8.2.4.1. **Study Summary** - Study JRV 304 enrolled 450 patients age 18 or older with complicated skin and skin-structure infections between February of 1995 and April of 1996. Patients had a baseline evaluation performed, and 229 were randomized to receive Synercid (7.5 mg/kg q12 hrs) and 221 to receive a comparator. Patients randomized to the comparator arm received oxacillin (2g q6 hrs). Vancomycin (1g q12 hrs) was substituted as the comparator if oxacillin could not be administered due to: a) suspected or confirmed [redacted] resistant staphylococcus or b) documented history of immediate hypersensitivity to penicillins, cephalosporins, or carbapenems. Vancomycin dose could be adjusted based on vancomycin blood levels. The duration of study drug treatment was up to 14 days. Patient assessments were scheduled at baseline (prior to initiation of study drug therapy), study day 4, within 24 hours after last study drug infusion (the "end of treatment" visit), and at 14 to 28 days post treatment (the "test of cure" visit). The primary efficacy parameter was the clinical response in the clinically evaluable population determined either at the test of cure assessment or at the end of treatment assessment, if the test of cure assessment was not performed.

8.2.4.2. **Patient Population**

8.2.4.2.1. **Patients** - 450 inpatients with complicated skin and skin-structure infections were enrolled.

8.2.4.2.2. **Demographics**

- Age - 18 years or older
- Sex - Male or non-pregnant, non-lactating female, who is post menopausal or surgically sterilized, or is using birth control pills or implants or an IUD or barrier protection for at least two months. Effective contraception must continue for at least 30 days after treatment discontinuation. For all women (except those post menopausal or surgically sterilized), laboratory pregnancy test (serum or urine) must be negative at baseline visit.

8.2.4.2.3. **Inclusion Criteria** - Eligible patients were required to meet all of the following criteria:

- Infection of skin and skin structure of sufficient severity to
  - require hospitalization for at least 24 hours
  - anticipate need for 3 or more days of parenteral antibacterial therapy
- Clinical appearance consistent with infection predominantly due to aerobic gram-positive organisms:
  - infections following clean surgical procedures
  - infections resulting from partial thickness burn wounds (less than 5% total body area)
  - erysipelas

- skin or skin structure infection at central venous catheter insertion site, with removal of catheter within 24 hours following study enrollment
- severe carbunculosis
- traumatic wound infections
- other, if approved by medical monitor prior to study enrollment

Medical Officer's Comment: *S. aureus* or *Streptococcus* spp. usually cause these complicated skin and skin structure infections. Since Synercid's spectrum of antimicrobial activity includes predominantly aerobic gram-positive bacteria, inclusion of these patients is appropriate. Coagulase negative staphylococci may serve as pathogens in clean surgical infections or skin and skin structure infections at central venous catheter insertion sites. In addition, aerobic gram-negative rods may uncommonly serve as pathogens in such infections as traumatic wound infections and infected partial thickness burns.

- Meeting at least one of the following criteria defining complicated skin and skin-structure infection:
  - requiring surgical intervention
  - infectious process which is suspected or confirmed to involve deeper soft tissue (fascia and/or muscle layers). Infections at a central venous catheter insertion site were considered as "complicated" skin and skin structure infections if the infection is of sufficient severity to warrant at least 3 days of intravenous antibacterial therapy
- Presence of purulent/seropurulent drainage and/or at least three of the following clinical signs/symptoms present:
  - tenderness to palpation
  - localized erythema greater than 1 cm from edge of the suspected site of infection
  - induration
  - fluctuance
  - temperature >38°C (101°F) rectal or >37.5°C (99.7°F) oral

Medical Officer's Comment: Although the signs and symptoms above are useful to assess an infection of skin or skin-structure, an assessment of the dimensions of the wound or affected area (width and depth) would have been helpful in evaluation of severity of infection and response to therapy.

- Specimen is available for laboratory evaluation prior to starting study medication from one of the following:
  - drainage
  - aspiration of material
  - biopsy of material
  - catheter tip
  - saline swab
- Infection for which empiric monotherapy with one of the study treatments is clinically appropriate.

Medical Officer's Comment: This inclusion criterion is particularly important for appropriate conduct of this study given the spectrum of activity of Synercid. Anaerobes and aerobic gram-negative rods will not be covered by the antimicrobial spectrum of Synercid; thus, Synercid would not adequately treat diseases likely to involve these types of organisms in a mixed infection. Examples of such infections include lower extremity infections in diabetic patients or superinfections of infected ischemic ulcerations which would be expected to include anaerobes and gram-negative aerobes as well as Synercid-susceptible gram positive organisms such as *S. aureus* or *Streptococcus* spp.

- Written informed consent

8.2.4.2.4. Exclusion Criteria - Patients with any of the following were to be excluded from the study:

- known significant immunocompromising disease and/or immunosuppressive therapy including:
  - HIV+ status with a CD4 count less than 200/μL
  - requirement for more than 40 mg/day of corticosteroids or other immunosuppressive therapy

    - severe neutropenia ($\leq 500/mm^3$)
- documented Type I hypersensitivity reaction to streptogramins or glycopeptides
- infection which would be likely to yield mixed pathogens (gram-positive and gram-negative or aerobic and anaerobic infections).

Medical Officer's Comment: Included in this exclusion category should be diabetic patients with lower extremity infections and patients with severe peripheral vascular disease and infected ischemic ulcerations. However, patients with diabetes mellitus or ischemic peripheral vascular disease who had acute injuries (traumatic or surgical) could be included.

- infections with a causative foreign body which was in place for more than 24 hours after initiation of study drug therapy.

Medical Officer's Comment: Patients with vascular grafts could be included unless the graft was considered to be the source of infection and/or blood cultures were positive.

- infections which were not expected to require at least 72 hours of study drug therapy
- receipt of more than one dose of systemic antibacterial treatment presumed to be effective within 24 hours prior to study drug administration. Previous antibiotic therapy was not considered effective if:
    - *in vitro* bacteriological data indicate resistance
    - clinical signs/symptoms of skin and skin structure infection persisted after at least 48 hours of previous antibacterial therapy, and the treatment was considered a clinical failure by the investigator

Medical Officer's Comment: In the "Data Standards Worksheet" (Volume 1.255, page 343), the Applicant outlined deviations from the protocol which were deemed acceptable. The Applicant allowed effective antibiotic therapy for no more than the calendar day prior to the first dose, or on the day of the first dose. Also acceptable was prior therapy during at least three calendar days within the previous seven days if the patient was a presumed failure. The Medical Officer required that patients fulfill the exclusion criteria as originally given in the protocol.

- another focus of infection requiring concomitant systemic antibacterial therapy that would interfere with the evaluation of the response to the study drug
- suspected presence of contiguous osteomyelitis or septic arthritis at study entry

Medical Officer's Comment: No specific studies were required to exclude osteomyelitis or septic arthritis.

- diagnosis of systemic shock at screening
- less than six months life expectancy
- previous participation in a Synercid trial
- use of another investigational compound within 30 days of starting study medication or during course of the study
- patients without means of contacting the investigator's staff during the course of the study or who will not agree to the test of cure assessment
- Gram stain and/or culture results indicative of predominant or exclusive pathogen(s) for current episode of skin and skin-structure infection due to gram-negative organisms, anaerobes, or mixed aerobes and anaerobes.
- baseline pathogen(s) presumed to be resistant to either Synercid or vancomycin prior to randomization
- infections likely to require significant surgical intervention(s) after more than 24 hours on study treatment. Significant intervention is defined as surgery that cannot be performed at the patient's bedside.
- infections which were totally cured by a surgical procedure
- baseline values for ALAT and/or ASAT >5x the upper limit of normal and/or conjugated bilirubin >3x the upper limit of normal

- serum creatinine concentration >170 μmoles/L (2.24 mg/dL) and/or creatinine clearance (measured or calculated) <30 mL/min

8.2.4.3. Endpoints (Efficacy)

8.2.4.3.1. Clinical - The primary efficacy parameter for comparing treatment regimens was the proportion of patients with a satisfactory clinical outcome (cure plus improvement) at the day 14-28 post treatment visit ("Test of Cure Assessment"). The clinical response was characterized as follows:

- Clinical cure: Resolution of all signs and symptoms of skin and skin-structure infection with no new signs associated with the original infection.
- Clinical improvement: In patients who were not cured, resolution or reduction of the majority of signs and symptoms of skin and skin-structure infection, with no new or worsened signs associated with original infection.
- Failure: Either (a) no resolution and no reduction of a majority of signs of the skin and skin-structure infection or (b) worsening of one or more signs or (c) new signs associated with the original infection (d) the patient required other antibacterial therapy to treat the original skin and skin-structure infection after administration of 24 hours of study drug therapy. Serous drainage alone was not considered a failure, as long as the bacteriological response was "Eradication" or "Presumed Eradication".

Medical Officer's Comment: The Medical Officer considered all patients who had study drug treatment discontinued after 72 hours of therapy due to an adverse event to be clinical failures.

- Indeterminate: Inability to assess the patient's signs and symptoms due to "lost to follow-up" or no information.
- Clinically unevaluable: Due to:
  - receipt of effective systemic or topical antibacterial therapy within 24 hours prior to starting experimental treatment

Medical Officer's Comment: The patient remained evaluable if classified as a clinical failure, despite receipt of antibiotics within 24 hours

  - insufficient study treatment (less than 72 hours of therapy)
  - missed two consecutive treatment doses, or more than 20% of scheduled doses of test drug
  - took non-study effective systemic or topical antibacterial therapy during study treatment up to the Test of Cure assessment (does not apply to failures)

Medical Officer's Comment: The patient remained evaluable if classified as a clinical failure, despite receipt of antibiotics during the study.

  - concurrent medical condition preventing evaluation of clinical response
  - infection which required significant surgical intervention(s) after 24 hours on study treatment prior to completion of 72 hours of study therapy. A single surgical intervention was allowed up to 24 hours after initiation of treatment

Medical Officer's Comment: Persistent infections or infections which required two or more significant surgical interventions of the infected area resulted in classification of the patient by the Applicant as a clinical failure of study drug therapy, and the Medical Officer agreed.

  - infection which was totally eradicated by a surgical procedure
  - return for the Test of Cure visit outside the 7-30 day after treatment window

Medical Officer's Comment: The Applicant allowed return for the Test of Cure visit between days 4 and 30. The Medical Officer concurred with this decision, with the exception of requiring at least 7 days to elapse after the last dose of study drug. The reason for not allowing patients to return at the early time point of between 4 and 7 days is that there may be insufficient time for manifestation of recurrent or persistent skin and skin-structure infection to occur, as well as inadequate time for complete clearance of study drug from the system.

* failure to perform a baseline culture as required by the protocol or isolation of an organism which is resistant to either study drug

Medical Officer's Comment: The Applicant did not exclude patients from the evaluable patient population based on absence of a baseline culture or lack of sensitivity of the bacterial isolate.

* Patients with cultures which grew only aerobic gram-negative rods and/or anaerobes
* Patients with diabetes and lower extremity infections or ischemic peripheral vascular disease with infected ulcerations, as well as any chronic ulceration of the lower extremity

Medical Officer's Comment: These patients should not have been included in the study, since the medical conditions of diabetes and peripheral vascular disease were listed in the exclusion criteria of the protocol. However, patients with these underlying conditions were included in the study by the Applicant and treated in the analysis as clinically evaluable. The Medical Officer, however, treated them as nonevaluable.

8.2.4.3.2. Bacteriological - The bacteriologic response was based on the skin and skin-structure culture result performed at the Test of Cure assessment or at the end of therapy, if no Test of Cure Assessment was performed. Bacteriological efficacy was to be compared between treatment regimens based on the pretreatment pathogens isolated during the trial. Skin and skin-structure cultures were to be obtained for microbiology assessments at the screening visit and, if available, at the Baseline, Day 4, End of Treatment, and Test of Cure Assessments. The culture was to be taken from drainage, an aspirate, a saline swab, a biopsy, or an infected catheter tip. The protocol required that a specimen be obtained for culture from all patients before beginning study drug. Gram's stain was to be performed on any specimen from the skin and skin-structure infection study site. If the Gram stain or culture was indicative of gram-negative infection, treatment with the study drug was to be discontinued. At least two sets of blood cultures were to be obtained at baseline from separate sites, and were to be repeated until two sets of negative cultures were obtained. Each pathogen isolated from skin and skin-structure samples or blood was to be identified as to genus and species, and all pathogens were to be tested for susceptibility to oxacillin. In addition, all pathogens were to be sent to the Central Laboratory, where they were to be identified and the minimum inhibitory concentrations (MIC's) determined for susceptibility to Synercid, vancomycin, and oxacillin. If discrepancies between the local and central laboratories arise, the Central Laboratory's determination was to prevail.

Medical Officer's Comment: On the Medical Officer's review of the data from individual patients, some bacterial isolates were found to have the MIC data missing. When RPR was queried by fax on this point (1/23/98), they submitted by fax (1/30/98) a listing of patients with missing central laboratory MIC data, but local laboratory MIC data supplied. The subsequent overall analysis of bacteriological efficacy did not change significantly based on the Medical Officer's review of these results.

The following definitions of bacteriological efficacy were used:

- Eradication: Demonstration of complete elimination of baseline pathogen(s) from subsequent cultures of the infected site
- Presumed eradication: No material available for culture with signs of clinical cure/improvement
- Persistence: Presence of baseline pathogen(s) from the original site of infection during or after study therapy
- Superinfection: Emergence of a new or resistant pathogen which was not identified as the original causative pathogen, and associated with signs and symptoms of skin and skin-structure infection during treatment or up to follow-up
- Multiple pathogens with partial eradication (MPPE): Identification of more than one etiologic pathogen at baseline and eradication of one or more of those pathogens with the persistence of one or more of those pathogens at the Test of Cure Assessment
- Colonization: Appearance of new organisms(s) during or after therapy at the original site of infection, not accompanied by clinical signs and symptoms of skin and skin-structure infection
- Indeterminate: No information

- Bacteriologically unevaluable:
  - No MIC's performed for any gram-positive pathogens isolated
  - Clinically unevaluable
  - lack of at least one pretreatment microbiology culture indicative of at least one gram-positive pathogen
  - *Staphylococcus epidermidis* or other coagulase-negative staphylococci as the sole pathogen unless the underlying infection was a surgical wound infection or a catheter site infection.

Medical Officer's Comment: The Applicant considered coagulase-negative staphylococci to be pathogens if recovered in pure culture from adequate specimens, including ≥ 2 blood cultures if only found in blood (Volume 1.249, page 46 of Final Study Report).

8.2.4.4. Study Drug Administration

8.2.4.4.1. Study Drug and Dosage(s) to be Studied – Synercid 7.5 mg/kg every 12 hours.

8.2.4.4.2. Route of Administration – Intravenous

8.2.4.4.3. Comparator – The comparator regimen was oxacillin 2 grams q6 hours intravenously. If oxacillin could not be administered clinically due to either suspected or confirmed resistant staphylococcus or documented history of immediate hypersensitivity to penicillins, cephalosporins, or carbapenams, the alternative comparative therapy was vancomycin 1 gram q12 hours intravenously. The dosage of vancomycin could be changed from the initial regimen based upon vancomycin blood levels and clinical considerations.

The investigator determined the duration of therapy. Study patients were considered evaluable if they received a minimum of 72 hours of study drug treatment. If the patient was to be discharged from the hospital, arrangements were to be made for study medication to be administered on an outpatient basis for the duration of the trial. The suggested maximum treatment duration for the study was 14 days.

8.2.4.4.4. Method of Randomization – Treatment assignment was provided by the phone-in central randomization system to the pharmacist who prepared the treatment accordingly. A site identification code was provided to the pharmacist for access to the randomization system, which was accessible 24 hours a day using a toll-free telephone system.

8.2.4.4.5. Method of Blinding to be Used—This was an open-label study. In order to minimize potential bias, the Applicant constructed algorithms for evaluability (clinical and bacteriologic) and efficacy (clinical and bacteriologic) responses, and all patients were evaluated with these tools. In patients for whom this was not possible, a Steering Committee comprised of six physicians blinded to treatment assignment reviewed the data.

8.2.4.5. Study Evaluations

8.2.4.5.1. Baseline Assessment – Assessment of inclusion and exclusion criteria, signature of informed consent form, demographics and medical history, vital signs, weight, height, temperature (maximum temperature reading before or 4 hours after administration of any antipyretic), physical examination, signs and symptoms of skin and skin-structure infection for clinical evaluation (drainage characteristics, tenderness to palpation, fluctuance, erythema, induration, and location), Gram stain of skin and skin-structure infection specimen, microbiology culture samples, two sets of blood cultures, urinalysis, hematology and blood chemistry samples, calculation of creatinine clearance, pregnancy test (serum or urine) for females, listing of all antibacterial therapy taken within the previous 14 days and of all medications taken within 48 hours of first test drug administration.

8.2.4.5.2. During-Treatment – Vancomycin blood levels as clinically indicated, serum liver function test monitoring at 72 hour intervals, peripheral venous tolerance assessment, two sets of blood cultures (if the previous culture was positive or the patient clinical status worsened), vital signs, maximum temperature reading (taken before or 4 hours after administration of an antipyretic), recording of adverse events, concomitant therapies, and concomitant surgical intervention.

8.2.4.5.3. Day 4 Assessment – Vital signs, maximum temperature reading, physical examination, signs and symptoms of skin and skin-structure infections for clinical evaluation, microbiology culture (aerobic and anaerobic) samples if material is available, two sets of blood cultures if positive cultures at Baseline Assessment, urinalysis, hematology and blood chemistry samples, calculated creatinine clearance, peripheral venous tolerance assessment, recording of any adverse event, concomitant

therapy, and recording of any concomitant surgical intervention. At the Day 4 Assessment, the investigator decided whether it was appropriate to continue the patient on study medication.

8.2.4.5.4. **End of Treatment Assessment** – Vital signs, maximum temperature reading, physical examination, signs and symptoms of skin and skin-structure infection, microbiology culture samples if material available, two sets of blood cultures (as clinically appropriate), urinalysis, hematology and blood chemistry samples, calculated creatinine clearance, peripheral venous tolerance assessment, recording of any adverse events, and recording of all concomitant therapies and concomitant surgical interventions.

8.2.4.5.5. **Test of Cure Assessment (Day 14-28 Post Treatment)** – Vital signs, maximum temperature reading, physical examination, signs and symptoms of skin and skin-structure infection for clinical evaluation, microbiology culture if material is available, two sets of blood cultures (if the previous cultures were positive or the patient clinical status worsened), urinalysis, hematology and blood chemistry samples, calculated creatinine clearance, peripheral venous tolerance assessment, recording of any adverse events, recording of all concomitant therapies and any surgical interventions.

8.2.4.6. **Safety Considerations**

8.2.4.6.1. **Definition of Adverse Event and How Monitored** – An adverse event is any undesirable event occurring with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reaction. It also includes any undesirable clinical or laboratory change that does not commonly occur in the patient. All clinical adverse events were to be reported on the case report form.

8.2.4.6.2. **Description of Who is to be Contacted re: Serious Adverse Events** – If an adverse event was serious, it was to be reported within 24 hours by telephone to one of the individuals listed in Appendix VII of the protocol (Volume 1.250, page 63). Withdrawal from the study and therapeutic measures were at the discretion of the investigators; if discontinued from the study, a full explanation was to be made on the case report form. The investigator was to supply the monitor with as much information as possible at the time of the initial phone call. In the event of a death, the determined cause and a copy of the autopsy findings were to be provided to the Applicant.

8.2.4.6.3. **Withdrawal Procedures** - The reason and date of end of study treatment for all study patients were to be documented on the case report form. The investigator was to complete the End of Treatment procedures at the time a patient was discontinued from treatment. Patients were to be discontinued from study treatment immediately if they met any of the following conditions:

- the patient's clinical status worsened
- skin and skin-structure infections requiring significant surgical intervention(s) after 24 hours of study drug therapy
- the patient has a serious adverse experience that requires discontinuation of study treatment for resolution
- liver function tests (ALAT/ASAT) greater than 5 times the upper limit of normal on treatment if the baseline was more than 3 times the upper limit of normal
- doubling of baseline liver function tests on treatment if baseline was more than 3 times the upper limit of normal
- conjugated bilirubin more than 5 times the upper limit of normal on treatment
- the patient receives any concomitant effective antibacterial agents, either systemic or topical forms which has antibacterial action against the causative skin and skin structure pathogens that can interfere with the interpretation of the study data.
- the patient wishes to withdraw from the study
- the patient leaves the institution and will not complete study therapy
- skin and skin-structure infection with a foreign body in place requiring removal after 24 hours on study treatment

8.2.4.6.4. **Serious Adverse Events** - A serious adverse experience was defined as one that was fatal or life threatening, required inpatient hospitalization or was disabling. Death, congenital anomaly, cancer, or overdose were always considered serious. Progression of a patient's underlying condition leading to one of the above was to be reported as a serious (but expected) adverse event which was (1) unrelated to the study drug, or (2) caused by failure of the anticipated therapeutic effect of the study drug. "Life-threatening" meant that the patient was at immediate risk of death from the event as it occurred. "Requires inpatient hospitalization" was defined as hospital admission required for treatment of the

adverse event. A serious adverse event had to be reported within 24 hours by telephone to the Applicant and in writing within 5 days. Withdrawal from the study and therapeutic measures was to be at the discretion of the investigator. A full explanation for the discontinuation from the study was to be made on the appropriate case report form.

8.2.4.7. Statistical Analyses Proposed

8.2.4.7.1. Sample Size - A clinical response of cure or improvement was anticipated to occur in 90% of the patients treated with standard therapy. It was assumed that Synercid and standard therapy were equivalent. Based on this assumption, it was estimated that 150 evaluable patients per treatment group were required to insure with 80% probability that the lower bound of the 95% confidence interval around the difference between the two treatment groups does not exceed 10%. Assuming a 60% clinical evaluability rate, this study had to enroll approximately 500 patients to insure an adequate sample size of evaluable patients. Additionally, in order that 70% of the clinically evaluable patients were also bacteriologically evaluable, the study sites were required to have a pathogen isolation rate of at least 70%.

8.2.4.7.2. Efficacy - The primary efficacy analysis for this study was performed using the clinical response at the Test of Cure Assessment in the subset of clinically evaluable patients. The results were presented as a two-tailed 95% confidence interval around the difference in response rates for the two treatment groups. The two treatments were considered equivalent if the lower limit of the 95% confidence interval for the difference exceeded a specific value, which was determined by the higher observed success rate. The guidance given in the FDA "Points to Consider" was followed. The specified value was 10% if the larger success rate equaled or exceeded 90%, 15% if the larger success rate equaled or exceeded 80% and was less than 90%, and 20% if the larger success rate was less than 80%. In those patients who were both clinically and bacteriologically evaluable, the Applicant's primary efficacy analysis was performed using the overall response at the Test of Cure Assessment. Clinical response and bacteriologic response were analyzed for this subset of patients, and bacteriologic response by pathogen was also determined. Analyses were also carried out on the intent-to-treat population; patients classified as indeterminate were included with failures.

8.2.5. Review of Curriculum Vitae for All Investigators

Medical Officer's Comment: Review of the submitted curricula vitae demonstrates that the investigators who enrolled patients in this study are qualified by training and experience to conduct the study in Protocol JRV-304.

8.2.6. Study Results

8.2.6.1. Study Population - Demographics and Primary Diagnosis of Infection - The demographics of all patients in the intent-to-treat population and of the FDA clinically evaluable population are given in Table 1 on the following page, divided by treatment group. The type of skin and skin-structure infection is also listed in the table.

TABLE 1
DEMOGRAPHICS AND DIAGNOSIS

	INTENT-TO-TREAT POPULATION		FDA'S CLINICALLY EVALUABLE POPULATION	
	Synercid	Comparator	Synercid	Comparator
Number of Patients	229	221	105	106
Age (year)	52.9±16.9	52.8±17.5	53.9±16.5	53.7±16.4
Age less than 65 yr. (Y/N)	162/67	154/67	73/32	78/28
Weight (kg)	86.5±26.6	85.5±27.3	88.5±27.6	89.2±32.5
Sex (M/F)	132/97	128/93	60/45	66/40
Race (Caucasian/Black/etc.)	146/50/33	137/50/34	(74/17/14)	(66/22/18)
Surgical intervention (Y/N)	83/146	81/140	42/63	45/61
Diagnosis				
Clean surgical infection	46	33	20	20
Erysipelas	66	60	27	31
Partial Thickness Burn	4	2	2	1
SSSI at CVC Insertion Site	2	2	2	0
Severe Carbunculosis	8	8	5	4
Traumatic Wound Infections	65	76	33	31
Other	38	40	16	19

Medical Officer's Comment: The demographics of the two treatment arms were comparable for the parameters of age, sex, and race in both the Medical Officer's clinically evaluable patient population and the intent-to-treat population. Additionally, similar numbers of patients of each presenting condition (erysipelas, clean surgical infection, partial thickness burn wound, infection at central venous catheter insertion site, severe carbunculosis, traumatic wound infections, and "other") were enrolled in each treatment arm.

8.2.6.2. Clinically Evaluable Patients: The total enrolled and the number of evaluable patients as determined by RPR and by the Medical Officer are given in Table 2 below.

TABLE 2
CLINICAL EVALUABILITY

	RPR		MEDICAL OFFICER	
	Synercid	Comparator	Synercid	Comparator
Total Enrolled	229	221	229	221
Clinically Evaluable (%)	136 (59.4%)	120 (54.3%)	105 (45.9%)	106 (48.0%)

Medical Officer's Comment: It can be seen from the data in Table 2 that the percentage of clinically evaluable patients in this study was less than 50% after analysis by the Medical Officer. However, this represents a decrease of only 13.5% compared to the Applicant's clinically evaluable patient population in the Synercid arm and 6.3% in the Comparator arm (see below). This low evaluability rate in large part resulted from violations from the protocol as written, as detailed below.

Given on the next page are the Applicant's reasons for exclusion of patients from the clinically evaluable population and the corresponding number of patients who were excluded for each reason:

	SYNERCID	COMPARATOR
1. Missing Required Efficacy Data	70	66
2. Efficacy Visit Too Early or Too Late	0	1
3. Condition Precluding Eval of Response	0	1
4. Prohibited Antibiotic Prior to Study Drug	5	6
5. Prohibited Antibiotic: Post-Study Drug	1	2
6. Prohibited Concomitant Antibiotic	2	1
7. Insufficient Num/Type & Signs/Sx Base	9	23
8. Poor Study Drug Compliance	1	0
9. Insufficient Duration of Treatment	5	1
TOTAL	93	101

Medical Officer's Comment: The most frequent reason for rendering a patient nonevaluable was "Missing required efficacy data", with approximately equal numbers of patients in each treatment arm. This category largely encompassed patients who did not have a Test of Cure visit either because they were lost to follow-up or because the patient received non-study antibiotics. Somewhat more patients were excluded from the Comparator arm due to insufficient signs and symptoms at baseline. Overall, the numbers of patients excluded from the clinically evaluable patient population were similar between treatment arms.

Given below are the reasons for changes to the Applicant's clinically evaluable patient population from evaluable to nonevaluable made by the Medical Officer. The numbers in parentheses represent the proportion of these patients that were assessed as clinical successes by the Applicant.

	SYNERCID	COMPARATOR
1. Incorrect Diagnosis[1]	22 (68%)	11 (83%)
2. Infection Type[2]	6 (17%)	5 (60%)
3. Missing Required Efficacy Data	4 (50%)	5 (100%)
4. Efficacy Visit Too Early or Too Late[3]	4 (100%)	3 (100%)
5. Condition Precluding Eval of Response	3 (67%)	4 (25%)
6. Prohibited Antibiotic Prior to Study Drug	1 (100%)	3 (100%)
7. Prohibited Antibiotic: Post-Study Drug	0	2 (100%)
8. Prohibited Concomitant Antibiotic	0	1 (100%)
9. Insufficient Num/Type & Signs/Sx Base	1 (100%)	1 (0%)
10. Missing Efficacy Visit	1 (100%)	0
11. Protocol Design Violation	1 (100%)	0
TOTAL	43 (65%)	35 (77%)

[1]Category 1 "Incorrect Diagnosis" includes those patients deemed unevaluable by the Medical Officer due to their underlying condition falling outside the parameters defined as appropriate for inclusion in this study. Specifically, these patients had polymicrobial infections caused by pathogenic organisms other than gram-positives. The Medical Officer did not review these patients in detail.

[2]Patients in category 2 "Infection Type" had underlying conditions such as an infected foot lesion in a patient with diabetes mellitus or superinfection of a chronic lower extremity ulcer in a patient with ischemic vascular disease. Patients with these types of underlying conditions should not have been enrolled in the study according to the protocol, since these lesions would be expected to yield mixed pathogens, including gram-negative and/or anaerobes.

[3]The Medical Officer accepted patients who returned between days 7 and 30 for the test of cure visit.

Medical Officer's Comment: Twice as many Synercid patients as Comparator patients were found nonevaluable due to an incorrect diagnosis by the Medical Officer. Together with the higher number of patients found nonevaluable in the Synercid arm due to missing required efficacy data by the Applicant, these patients largely account for the proportionally larger decrease in the clinically evaluable population in the Synercid arm. Of note, the percentage of clinical successes in those patients changed to nonevaluable by the Medical Officer due to an incorrect diagnosis was actually higher in the Comparator arm. As in the Applicant's analysis, the number of patients additionally rendered nonevaluable by the Medical Officer was fairly well distributed between treatment arms.

In addition, the Medical Officer changed 33 patients in the Applicant's clinically nonevaluable patient population from clinically nonevaluable to evaluable, as follows:

TABLE 3
MEDICAL OFFICER CHANGES TO APPLICANT'S CLINICALLY NONEVALUABLE POPULATION

	SYNERCID	COMPARATOR
Nonevaluable to failure by Medical Officer[1]	12	16
Nonevaluable to improve/cure by Medical Officer	0	5
TOTAL	12	21

[1]Many of the patients who were changed to failure had received antibiotics after the study drug was discontinued. If the antibiotics were given for continuation of therapy for the skin and skin structure infection for which the patient was entered in the study, the Medical Officer categorized them as clinical failures.

Medical Officer's Comment: A higher number of patients in the Comparator arm were rendered evaluable after the Medical Officer's Analysis compared with the Synercid arm. Most changes in each arm resulted in changes from nonevaluable to clinical failure (with slightly more in the Comparator arm), while 5 patients were changed to clinical successes in the Comparator arm and none in the Synercid arm. The net result of these changes is minimal, since 4 more failures in the Comparator arm and 5 more successes in the Comparator arm compared with the Synercid arm.

8.2.6.3. Bacteriologically Evaluable Patients - The following table contains a summary of the Applicant's and Medical Officer's determination of the bacteriological evaluability status in the clinically evaluable patient population divided by treatment arm. The Applicant's evaluability data are taken from Volume 1.249, page 63.

TABLE 4
BACTERIOLOGICALLY EVALUABLE PATIENTS[1]

	SYNERCID	COMPARATOR
Total Enrolled	229	221
Fully Evaluable per Medical Officer	62 (27.1%)	58 (26.2%)
Fully Evaluable per RPR	100 (43.7%)	79 (35.7%)

[1]of the clinically evaluable population

Medical Officer's Comment: The data in Table 4 demonstrate that approximately one quarter of the patients in each treatment arm were considered to be both bacteriologically and clinically evaluable by the Medical Officer's analysis. The diagnosis with the highest number of patients labeled "erysipelas" (which usually included patients with cellulitis) might be expected to have a relatively low bacteriological evaluability rate, since isolation of an etiologic pathogen may be more difficult than would be encountered in the next two most common diagnostic categories of traumatic and surgical wound infections.

Given below are the reasons for changes to the bacteriologically evaluable population from evaluable to nonevaluable made by the Medical Officer:

		SYNERCID	COMPARATOR
1.	Clinically Nonevaluable	33	22
2.	No Valid Baseline Pathogen	12	7
3.	No MIC's	4	3
	TOTAL	49	32

Medical Officer's Comment: More patients in the Synercid arm than in the Comparator arm were changed to nonevaluable. Most of these changes were the result of a change in clinical evaluability. The most frequent reason for rendering a patient nonevaluable due to no baseline pathogen was the presence of an organism such as *S. epidermidis* in a setting where is was not considered by the Medical Officer to be a pathogen.

In addition, the Medical Officer changed 22 patients in the Applicant's bacteriologically nonevaluable patient population from nonevaluable to evaluable, as follows:

TABLE 5
MEDICAL OFFICER CHANGES TO APPLICANT'S BACTERIOLOGICALLY NONEVALUABLE POPULATION

	SYNERCID	COMPARATOR
Nonevaluable to failure by Medical Officer	9	9
Nonevaluable to improve/cure by Medical Officer	2	2
TOTAL	11	11

Medical Officer's Comment: Equal numbers of patients were changed in each arm and each category resulting in a net increase in both treatment arms of seven failures.

Table 6 below gives an overall summary of changes made by the Medical Officer to the Applicant's evaluable patient populations:

TABLE 6
EVALUABILITY CHANGES BY MEDICAL OFFICER

	CLINICALLY EVALUABLE		BACTERIOLOGICALLY EVALUABLE	
NUMBER OF PATIENTS	SYNERCID	COMPARATOR	SYNERCID	COMPARATOR
Total enrolled	229	221	229	221
Evaluable per Applicant	136	120	100	79
Changed to nonevaluable by Medical Officer	43	35	49	32
Changed to evaluable by Medical Officer	12 (12 failures)	21 (16 failures)	11 (9 failures)	11 (9 failures)
Net change in evaluable patients	-31	-14	-38	-21
Evaluable per Medical Officer	105	106	62	58

8.2.6.4. Clinical Efficacy - The Medical Officer evaluated the case summaries of all patients. The primary efficacy endpoint was the clinical response in the clinically evaluable population determined at the test of cure assessment (between 7 and 30 days after completion of study drug) or when the patient discontinued therapy prior to the test of cure assessment. Table 7 below shows the clinical efficacy analysis using the Applicant's (Volume 1.249, page 75) and the Medical Officer's evaluability analysis.

TABLE 7
CLINICAL EFFICACY - STUDY JRV 304

SUCCESS[1]	SYNERCID	COMPARATOR	95% C.I. FOR DIFFERENCE
per Medical Officer	52/105 (49.5%)	55/106 (51.9%)	(-15.9%, 11.1%)
per Applicant	88/136 (64.7%)	82/120 (68.3%)	(-15.2%, 7.9%)

[1]Success is defined as Number of patients cured + improved/total number of patients clinically evaluable

Please see the statistician Dr. Li Ji Shen's review for details of the statistical analysis. Briefly, a confidence interval analysis was done to estimate the magnitude of the difference in satisfactory efficacy proportions among treatments and to determine whether treatments had equivalent efficacy. The Applicant followed the guidelines set forth in the "Points to Consider" document. The lower confidence limit had to be greater than or equal to the allowed lower boundary for the given efficacy range involved, and the value of zero had to be contained between the lower and upper confidence limits in order to establish equivalence between two treatment arms. For all statistical analyses performed, a p-value less than or equal to 0.05 was considered statistically significant.

Medical Officer's Comment: The results fulfill the criteria for demonstration of similarity between treatment arms. Success rates for each diagnostic category were fairly similar between treatment arms. The Applicant's analysis demonstrated a 3.6% higher success rate in the Comparator arm whereas a 2.4% higher efficacy rate in the comparator arm was found by the Medical Officer's analysis. Table 3 above demonstrates that the Medical Officer changed more patients in the comparator arm to clinical failures and Table 2 demonstrates that more patients in the Synercid arm were rendered unevaluable. This accounts for the decrease in efficacy rates in both treatment arms from the Applicant's to the Medical Officer's analysis, with a somewhat greater relative decrease in the comparator arm.

The clinical efficacy rates in this study of 49.5% in the Synercid arm and 51.9% in the Comparator arm are low when compared with recent Divisional approvals for this indication which have been in the range of 70%. In particular, examination of the data set did not provide an explanation for the relatively low clinical efficacy rate in the approved comparator arm of oxacillin or vancomycin.

8.2.6.5. Bacteriological Efficacy - In the following sections, bacteriological efficacy rates will be given by patient, by pathogen, and for monomicrobial versus polymicrobial infections. Additionally, data will be presented regarding efficacy of the study drugs in bacteremic patients, against methicillin-resistant *Staphylococcus aureus,* and against *Staphylococcus aureus* with MLSb constitutive resistance.

8.2.6.5.1. Bacteriological Efficacy by Patient - The following table gives the results of the analysis of the bacteriological efficacy rates by patient for the fully evaluable patient population at the test of cure visit:

TABLE 8
BACTERIOLOGICAL EFFICACY BY PATIENT

SUCCESS[1]	SYNERCID	COMPARATOR	95% C.I. FOR DIFFERENCE
per Medical Officer	29/62 (46.8%)	35/58 (60.3%)	(-31.3%, 4.1%)
per Applicant	63/100 (63.0%)	60/79 (75.9%)	(-26.3%, 0.4%)

[1]Success is defined as Number of patients with pathogens eradicated + presumed eradicated/total number of fully evaluable patients

Medical Officer's Comment: The efficacy rates for both treatment arms are lower in the Medical Officer's analysis than in the Applicant's analysis. As shown in Table 5, equal numbers of patients were changed from nonevaluable to fail by the Medical Officer, while more patients in the Synercid arm were changed to nonevaluable, as seen in Table 4.

8.2.6.5.2. Bacteriological Efficacy by Pathogen - The bacteriological efficacy rates by pathogen for the fully evaluable patient population at the test of cure visit are given in Table 9 on the following page. Bacterial pathogens included in the table are those aerobic gram-positive bacteria likely to be etiologic pathogens in complicated skin and skin-structure infections.

TABLE 9
BACTERIOLOGICAL EFFICACY BY PATHOGEN

	MEDICAL OFFICER		RPR	
ORGANISM	Synercid	Comparator	Synercid	Comparator
Staphylococcus aureus	16/33 (48.5%)	25/40 (62.5%)	32/52 (61.5%)	36/48 (75.0%)
Staphylococcus spp. including coagulase-negative[1]	4/6 (66.7%)	0/1 (0%)	29/36 (80.6%)	19/26 (73.1%)
Streptococcus agalactiae	0/2 (0%)	7/8 (87.5%)	5/5 (100%)	11/13 (84.6%)
Streptococcus pyogenes	6/9 (66.7%)	5/8 (62.5%)	9/14 (64.3%)	4/5 (80.0%)
Streptococcus dysgalactiae	1/1 (100%)	1/5 (20.0%)	2/4 (50.0%)	4/5 (80.0%)
Streptococcus spp.	3/4 (75.0%)	2/4 (50.0%)	12/15 (80.0%)	2/2 (50.0%)
Enterococcus spp. non-*faecium*[2]	0/4 (0%)	0/0 (0%)	4/10 (40.0%)	4/6 (66.7%)
TOTALS	30/59 (50.8%)	40/66 (60.6%)	93/136 (68.4%)	80/105 (76.2%)

[1]The Medical Officer accepted coagulase negative staphylococci as pathogens when the patient had a surgical site infection or an infected catheter site. In other infection types, it was regarded as a colonizer and not as a pathogen.
[2]No *Enterococcus faecium* were isolated from the fully evaluable patient population.

Medical Officer's Comment: As would be expected in a study of skin and skin-structure infections, the most commonly isolated pathogen in both treatment arms was *S. aureus*. The by pathogen bacteriological efficacy rate of 48.5% in the Synercid arm contrasts with the 62.5% found in the Comparator arm. *S. pyogenes* was the next most commonly isolated pathogen, and the bacteriological efficacy rates were 66.7% and 62.5% for the Synercid and Comparator arms, respectively. Other organisms were isolated in numbers too small for meaningful analysis, including *S. epidermidis* and *S. agalactiae* that are organisms requested for labeling by the Applicant.

8.2.6.5.3. Bacteriological efficacy in polymicrobial versus monomicrobial infections - A comparison of eradication rates by pathogen in patients with polymicrobial versus monomicrobial infection is given in the Table 10 below for the fully evaluable patient population. The populations compared are "monomicrobial" in which cultures grew a single strain of aerobic gram-positive bacteria, as detailed in Table 9 in the previous section, and "polymicrobial" in which cultures grew more than one of these bacteria.

TABLE 10
BACTERIOLOGICAL EFFICACY – POLYMICROBIAL VERSUS MONOMICROBIAL INFECTIONS

	MONOMICROBIAL		POLYMICROBIAL	
ERADICATION[1]	Synercid	Comparator	Synercid	Comparator
per Medical Officer	24/51 (47.0%)	28/48 (58.3%)	6/8 (75.0%)	12/18 (67.0%)
per Applicant	35/53 (66.0%)	38/48 (79.2%)	59/85 (69.4%)	43/58 (74.1%)

[1]Eradication = organisms eradicated + presumed eradicated/total organisms isolated

Medical Officer's Comment: The bacteriological eradication rate was lower in the Synercid arm than in the Comparator arm for patients with monomicrobial infections (47% versus 58%, respectively). Many of the patients classified by the Applicant as having a polymicrobial infection were eliminated from the clinically and bacteriologically evaluable patient population, since they should have been excluded according to the protocol. As a result, there was a slightly higher bacteriological eradication rate in the Synercid arm than in the Comparator arm (75% versus 67%), but the number of patients, especially in the Synercid arm, was small.

8.2.6.5.4. Bacteriological eradication in bacteremic patients - Table 11 on the following page demonstrates pathogen eradication rates (eradication + presumed eradication/total episodes of bacteremia) in study patients with bacteremia at baseline:

TABLE 11
BACTERIOLOGICAL ERADICATION IN BACTEREMIC PATIENTS

	MEDICAL OFFICER		APPLICANT	
Organism	**Synercid**	**Comparator**	**Synercid**	**Comparator**
Staphylococcus aureus	0/2 (0%)	2/2 (100%)	1/3 (33.3%)	2/2 (100%)
Staphylococcus epidermidis	1/1 (100%)	0/0 (0%)	1/2 (50.0%)	1/1 (100%)
Streptococcus spp.	1/1 (100%)	0/0 (0%)	3/3 (100%)	0/0 (0%)
TOTALS	2/4 (50.0%)	2/2 (100%)	5/8 (62.5%)	3/3 (100%)

Medical Officer's Comment: The number of patients with bacteremia caused by each organism is too small to allow definitive conclusions to be drawn regarding study drug efficacy against bacteremic episodes caused by a given bacterial pathogen.

8.2.6.5.5. Eradication rates for resistant pathogens - In the following two sections are given bacteriological eradication rates for two antibiotic resistant organisms which are potential isolates from patients with skin and skin-structure infections.

- Methicillin-resistant *Staphylococcus aureus*:

TABLE 12
BACTERIOLOGICAL ERADICATION RATES OF [redacted] RESISTANT *S. AUREUS*

	EVALUABLE		NONEVALUABLE	
CLINICAL RESPONSE	**Synercid**	**Comparator**	**Synercid**	**Comparator**
Clinical success (cure+improve)	2	2	2	3
Clinical failure	4	2	2	1
Success (%)	2/6 (33.3%)	2/4 (50.0%)	2/4 (50.0%)	3/4 (75.0%)
Indeterminate	NA	NA	6	3

- *Staphylococcus aureus* with MLSb constitutive resistance:

TABLE 13
BACTERIOLOGICAL ERADICATION RATES OF *S. AUREUS* WITH MLSb CONSTITUTIVE RESISTANCE

	EVALUABLE		NONEVALUABLE	
CLINICAL RESPONSE	**Synercid**	**Comparator**	**Synercid**	**Comparator**
Clinical success (cure+improve)	0	2	0	0
Clinical failure	3	1	1	1
Success (%)	0/3 (0%)	2/3 (66.7%)	0/1 (0%)	0/1 (0%)
Indeterminate	NA	NA	1	0

Medical Officer's Comment: Small numbers of each of these resistant pathogens were isolated from the patients in this study. In the Synercid arm, 2 of 6 (33.3%) methicillin-resistant *S. aureus* were eradicated, as were 2/4 organisms (50%) in the Comparator arm. Similarly, 0 of 3 *S. aureus* with MLSb constitutive resistance were eradicated, as were 2 of 3 organisms (66.7%) in the Comparator arm.

8.2.6.6. Safety -

8.2.6.6.1. Deaths: A total of seven patients died during this study, three in the Synercid arm and four in the comparator arm. All of the deaths were considered by the investigators to be unrelated to the study medication. The Medical Officer reviewed these cases and concurs that the deaths were unrelated to study medication.

8.2.6.6.2. **Most common non-venous adverse events:** Non-venous adverse events described by the investigators as either "probably" or "possibly" related to study drug occurred in 65 (28.4%) patients in the Synercid arm and 36 (16.3%) patients in the comparator arm. The most frequent study drug related adverse events were:

- Digestive System: 30 patients in the Synercid arm and 13 patients in the comparator arm experienced nausea, vomiting, dyspepsia, or constipation; each of these adverse events were approximately three times more common in the Synercid arm.
- Skin and Appendages: Pruritis or rash occurred in 10 and 7 Synercid patients, respectively; comparable figures for the comparator patients are 9 and 6, respectively.
- Body as a Whole: In the Synercid arm 20 patients experienced adverse events of this type, including 6 with headache and 9 with "pain". In the comparator arm, 7 patients experienced adverse events in this category, including 1 each with headache and "pain"; the remainder of these patients are not itemized.

Serious non-venous adverse events were reported by 30 (13.1%) of the patients in the Synercid arm and 25 (11.3%) in the comparator arm. The only two serious adverse events thought by the investigators to be related to the study drug occurred in the Synercid arm: one report of myopathy (muscle necrosis at site of infection) and one report of cellulitis.

8.2.6.6.3. **Venous adverse events:** Venous adverse events deemed by the investigator to be "possibly" or "probably" study drug related occurred in 160 (69.9%) of the patients in the Synercid arm and 73 (33.0%) of patients in the comparator arm. In patients with venous adverse events of moderate or severe severity, most commonly described were inflammation [28 (12.2%) Synercid and 8 (3.6%) comparator], edema [22 (9.6%) Synercid and 4 (1.8%) comparator] and "reaction" [11 (4.8%) Synercid and 5 (2.3%) comparator]. Two episodes of thrombus or thrombophlebitis occurred in the Synercid arm, one mild and one moderate in severity; none were noted in the comparator arm. Changes in infusion sites due to site irritation occurred in 62.0% (142/229) in the Synercid arm and in 35.7% (79/221) of the comparator arm. Serious venous adverse events considered by the investigator to be study drug related occurred in one patient in the Synercid arm (injection site inflammation) and one patient in the comparator arm (injection site inflammation and pain).

8.2.6.6.4. **Adverse events resulting in discontinuation:** Non-venous adverse events resulted in discontinuation of therapy in 27 (11.8%) patients in the Synercid arm and 11 (5%) in the comparator arm. Adverse venous events resulted in discontinuation of therapy in 26 (11.4%) patients in the Synercid arm and 5 patients (2.3%) in the comparator arm. One patient in the Synercid arm discontinued the study due to an adverse laboratory event. Multiple abnormalities were noted including elevations in BUN, total bilirubin, alkaline phosphatase, AST, and GGT, with decreases in total protein, albumin, and CO2, all considered to be possibly related to study drug.

8.2.6.6.5. **Bilirubin/Liver function tests** – This will be addressed in the integrated safety summary.

8.2.7. **Applicant's Summary and Conclusions** - The following information is taken from Volume 1.249, pages 3-5 and 132. The Applicant enrolled 450 patients with complicated skin and skin-structure infections in this study, of which 229 were treated with intravenous Synercid 7.5 mg/kg q 12 hours and 221 were treated with either oxacillin 2g q6 hours or vancomycin 1g q12 hours. More patients in the Synercid arm withdrew from the study without completing treatment, primarily for adverse clinical events. Slightly more patients in the Synercid group had baseline pathogens, but the types of baseline causative pathogens were similar between the two treatment groups, with staphylococci accounting for 40%-45% of all isolated pathogens. The duration of study drug therapy was 1.4 days shorter in the Synercid group, primarily due to shorter duration of therapy in patients who were prematurely discontinued from treatment.

Of those patients found to be clinically evaluable by the Applicant, 88/136 (64.7%) in the Synercid arm and 82/120 (68.3%) in the Comparator arm had a satisfactory clinical response at the Test of Cure visit, which is the primary efficacy parameter for this study. Comparable bacteriological efficacy rates for the fully evaluable population at the Test of Cure visit were 63/100 (63.0%) in the Synercid arm and 60/79 (75.9%) in the Comparator arm.

The Applicant concludes that Synercid given in a dose of 7.5 mg/kg intravenously every 12 hours was found to produce an equivalent clinical success rate to the Comparator arm in the study. The 95% confidence interval (-15.2, 7.9) showed that the clinical outcomes of the two treatment regimens were equivalent. The by-pathogen and by-patient bacteriologic success rates were lower in the Synercid group. This was due to lower bacteriologic success rates in patients with *S. aureus* as the baseline pathogen. The lower bacteriologic response in the Synercid group was due predominantly to a higher incidence of clinical failures due to discontinuation for an adverse event and receipt of new antibiotics. More patients in the Synercid group had mixed polymicrobial infections and resultant lower clinical and bacteriologic responses. The difference in by-patient bacteriologic success rate led to a lower overall (clinical + bacteriologic) success rate for Synercid. More superinfections were observed among Synercid-treated patients, as a result of more clinical failures due to premature discontinuations for an adverse event and receipt of non-study antibiotics.

8.2.8. **Medical Officer's Summary and Discussion** - The results of the clinical efficacy analysis in the clinically evaluable patient population for this study demonstrate equivalence of Synercid with comparator (oxacillin or vancomycin) in the treatment of complicated skin and skin-structure infections (49.5% versus 51.9%, respectively; 95% C.I. -15.9%, 11.1%). Issues to be considered in evaluation of the results of study JRV 304 include the following:

- The clinical evaluability rates in this study were relatively low, 45.9% in the Synercid arm and 48.0% in the comparator arm. The majority of patients were classified as nonevaluable because of violations of the protocol. These included violation of the entry criteria, with many patients found nonevaluable due to underlying skin and skin-structure infections typically caused by organisms which would not be expected to respond to Synercid. The most common examples were patients with extremity infections (often chronic) in patients with diabetes mellitus or ischemic peripheral vascular disease. Additionally, patients were found to be nonevaluable due to violations such as return outside the designated time frame for the test of cure visit.
- The overall success rates for both treatment arms in this study are low. Clinical efficacy rates in the range of 70% have been observed in trials for this indication. Clinical efficacy rates in the range of 70% would be more consistent with recently approved agents. The low clinical efficacy rate of the comparator arm (oxacillin or vancomycin) remains unexplained.
- The by patient bacteriological efficacy rate was lower in the Synercid arm than in the comparator arm (46.8% versus 60.3%, respectively; 95% C.I. –31.3%, 4.1%). In particular, bacteriological efficacy against *Staphylococcus aureus* was lower in patients who received Synercid.
- Adverse events considered by the investigator to be study drug related were approximately twice as common in the Synercid arm as in the comparator arm for both venous and non-venous adverse events; of particular note, 160 (69.9%) of the patients in the Synercid arm had study drug related adverse events. Study drug discontinuations due to adverse events occurred three times more frequently in the Synercid group.
- The number of patients with methicillin-resistant *Staphylococcus aureus* in this study was quite small. There were 17 isolates from nonevaluable patients and 10 from evaluable patients; 2/6 patients in the Synercid arm with [redacted] resistant *Staphylococcus aureus* had a successful outcome, whereas 2/4 in the comparator arm were successes. Similarly, the number of patients with cultures that grew *Staphylococcus aureus* with MLSb constitutive resistance was too small to draw definitive conclusions regarding study drug efficacy (6 evaluable, 3 nonevaluable).

8.2.9. **Medical Officer's Conclusions** - The results of Study JRV 304 demonstrate that the clinical efficacy of Synercid 7.5 mg/kg q 12 hrs in the treatment of complicated skin and skin-structure infections is similar to the approved comparator arm regimen of oxacillin or vancomycin. The bacteriological efficacy of this Synercid regimen was lower than that of the comparator arm. Study drug related adverse events were more frequent in the Synercid arm, as were discontinuations due to adverse events when compared with the comparator arm.

8.3. Complicated Skin and Skin Structure Infections - Protocol JRV 305 (Taken from Volume 1.252, pages 2-137 and Volume 1.253, pages 4-127, unless otherwise specified.) The protocol for this study is essentially identical to Protocol JRV-304 as outlined above in Section 8.2. Significant differences between the two protocols are listed below. Excluding these differences, the information that would be contained in Sections 8.3.1. through 8.3.4.7.2. should be assumed to be identical to that in the corresponding sections of 8.2. including objective/rationale, study details (includes patient population, inclusion criteria, exclusion criteria, endpoints (efficacy), study drug administration, study evaluations, safety consideration, and statistical analyses proposed. The title, study design, and a study summary are given below; included in the latter are significant differences between this protocol and that of JRV 304.

8.3.1. Title - Phase III Randomized Multicenter Comparative Study of Synercid (quinupristin/dalfopristin) versus Standard Therapy in the Treatment of Complicated Gram-positive Skin and Skin-structure Infections

8.3.3. Study Design – Study JRV 305 is an open-label, Phase 3, randomized comparative trial. In order to minimize potential bias, the Applicant constructed algorithms for evaluability (clinical and bacteriologic) and efficacy (clinical and bacteriologic) responses, and all patients were evaluated with these tools. In patients for whom this was not possible, a Steering Committee comprised of six physicians blinded to treatment assignment reviewed the data. This multicenter trial was conducted at 89 centers including 2 in Australia, 5 in Belgium, 2 in the Netherlands, 28 in France, 10 in Germany, 4 in Israel, 7 in Italy, 2 in South Africa, 1 in the United Kingdom, and 28 in the United States.

8.3.4. Study Details – Please see section 8.2.4. Appendix 2 contains a schedule of Study Procedures which is reproduced from Volume 1.253, page 8.

8.3.4.1. Study Summary - Study JRV 305 enrolled 443 patients age 18 or older with complicated skin and skin-structure infections between June of 1995 and July of 1996. Patients had a baseline evaluation performed, and 221 were randomized to receive Synercid (7.5 mg/kg q12 hrs) and 222 to receive a comparator. Patients randomized to the comparator arm received cefazolin sodium (1g q8 hrs). Vancomycin (1g q12 hrs) was substituted as the comparator if cefazolin could not be administered due to: a) suspected or confirmed [redacted] resistant staphylococcus or b) documented history of immediate hypersensitivity to penicillins, cephalosporins, or carbapenems. The vancomycin dose could be adjusted based on vancomycin blood levels. The duration of study drug treatment was up to 14 days. Patient assessments were scheduled at baseline (prior to initiation of study drug therapy), study day 4, within 24 hours after last study drug infusion (the "end of treatment" visit), and at 14 to 28 days post treatment (the "test of cure" visit). The primary efficacy parameter was the clinical response in the clinically evaluable population determined either at the test of cure assessment or when the patient discontinued therapy prior to the test of cure assessment.

Differences between protocols JRV 304 and JRV 305 include the following:

- In protocol JRV 305, patients with infections following clean surgical procedures are specifically excluded if the gastrointestinal, gynecological and respiratory tract have been entered.
- Patients with infections resulting from partial thickness burn wounds (less than 5% total body surface area) are included in JRV 304, but excluded from JRV 305.
- Patients with skin and skin-structure infections at foreign body sites are included in study JRV 305, but not specifically listed in JRV 304.
- There is no absolute requirement for purulent/seropurulent drainage in study JRV 305, as long as three of the other clinical signs/symptoms as listed above are present.
- Study JRV 304 lists "SSSI that would be likely to yield mixed pathogens (gram-positive and gram-negative or aerobic and anaerobic infections)" as a specific exclusion criteria, which Study JRV 305 does not. The latter study excludes "Baseline pathogen(s) presumed to be resistant to either Synercid or vancomycin prior to randomization".

8.3.5. Review of Curriculum Vitae for All Investigators -

Medical Officer's Comment: Review of the submitted curricula vitae demonstrates that the investigators who enrolled patients in this study are qualified by training and experience to conduct the study in Protocol JRV 305.

8.3.6. Study Results

8.3.6.1. Study Population - **Demographics and Primary Diagnosis of Infection** - The demographics of all patients in the intent-to-treat population and of the FDA clinically evaluable population are given in Table 14 below, divided by treatment group. The type of skin and skin-structure infection is also listed in the table.

TABLE 14
DEMOGRAPHICS AND DIAGNOSIS

	INTENT-TO-TREAT POPULATION		FDA'S CLINICALLY EVALUABLE POPULATION	
	Synercid	Comparator	Synercid	Comparator
Number of Patients	221	222	113	120
Age less than 65 yr. (Y/N)	135/86	145/77	64/49	81/39
Sex (M/F)	120/101	109/113	61/52	62/58
Race (Caucasian/Black/etc.)	175/31/15	187/20/15	(95/13/5)	(101/11/8)
Surgical intervention (Y/N)	60/161	70/152	30/83	42/78
Diagnosis				
Erysipelas + Other	9	10	7	8
Erysipelas	97	91	55	46
Infections following surgical procedure/Other	35	41	18	22
SSSI at CVC Insertion Site	4	3	3	2
SSSI at Foreign Body Site	2	3	1	2
Severe Carbunculosis/Other	11	13	4	9
Traumatic Wound Infections	46	42	22	24
Other	17	19	3	7

Medical Officer's Comment: The proportion of females was slightly higher in the Comparator arm in the Intent to Treat analysis; however, the demographics of the arms were comparable with respect to sex for the Medical Officer's clinically evaluable patient population. The demographics of the two treatment arms were otherwise comparable for the parameters of age, sex, and race in both the Medical Officer's clinically evaluable patient population and the intent-to-treat population. Additionally, similar numbers of patients of each presenting condition (erysipelas + other, erysipelas, infections following surgical procedure/other, infection at central venous catheter insertion site, SSSI at foreign body site, severe carbunculosis/other, traumatic wound infections, and "other") were enrolled in each treatment arm, and there was no difference between treatment arms in the occurrence of bacteremia.

8.3.6.2. **Clinically Evaluable Patients:** The total enrolled and the number of evaluable patients as determined by RPR and by the Medical Officer are given in Table 15 below.

TABLE 15
CLINICAL EVALUABILITY

	RPR		MEDICAL OFFICER	
	Synercid	Comparator	Synercid	Comparator
Total Enrolled	221	222	221	222
Clinically Evaluable	153 (69.2%)	153 (68.9%)	113 (51.1%)	120 (54.1%)

Medical Officer's Comment: The data in Table 15 demonstrate that the percentage of clinically evaluable patients in this study was just over 50% after analysis by the Medical Officer. A comparable number of patients were changed in each arm from evaluable by the Applicant to nonevaluable by the Medical Officer.

Given on the following page are the Applicant's reasons for exclusion of patients from the clinically evaluable population and the corresponding number of patients who were excluded for each reason:

		SYNERCID	COMPARATOR
1.	Missing Required Efficacy Data	38	38
2.	Efficacy Visit Too Early or Too Late	1	0
3.	Prohibited Antibiotic Prior to Study Drug	5	4
4.	Prohibited Antibiotic: Post-Study Drug	3	3
5.	Prohibited Concomitant Antibiotic	11	10
6.	Insufficient Baseline Criteria	6	7
7.	Poor Study Drug Compliance	3	3
8.	Insufficient Duration of Treatment	1	4
	TOTAL	68	69

Medical Officer's Comment: The most frequent reason for rendering a patient nonevaluable was "Missing required efficacy data", with approximately equal numbers of patients in each treatment arm; "missing required efficacy data" was also the most frequent reason for exclusion in Study JRV 304. This category largely encompassed patients who did not have a Test of Cure visit either because they were lost to follow-up or because the patient received non-study antibiotics. Overall, the numbers of patients excluded from the clinically evaluable patient population were similar between treatment arms.

The table below gives the reasons for changes to the Applicant's clinically evaluable patient population from evaluable to nonevaluable made by the Medical Officer. The numbers in parentheses represent the proportion of these subjects that were assessed as clinical successes by the Applicant.

		SYNERCID	COMPARATOR
1.	Incorrect Diagnosis[1]	23 (50%)	12 (83%)
2.	Infection Type[2]	4 (25%)	11 (36%)
3.	Missing Required Efficacy Data	11 (73%)	9 (100%)
4.	Efficacy Visit Too Early or Too Late[3]	6 (100%)	8 (100%)
5.	Condition Precluding Eval of Response	5 (60%)	1 (0%)
6.	Prohibited Antibiotic Prior to Study Drug	1 (100%)	0
7.	Prohibited Antibiotic: Post-Study Drug	1 (100%)	0
8.	Prohibited Concomitant Antibiotic	0	2 (100%)
9.	Protocol Design Violation	2 (100%)	0
10.	Treatment stop for a reason other than failure	1 (0%)	0
	TOTAL	54 (62%)	43 (77%)

[1]Category 1 "Incorrect Diagnosis" includes those patients deemed unevaluable by the Medical Officer due to their underlying condition falling outside the parameters defined as appropriate for inclusion in this study. Specifically, these patients had polymicrobial infections caused by pathogenic organisms other than gram-positives. The Medical Officer did not review these patients in detail.

[2]Patients in category 2 "Infection Type" had underlying conditions such as an infected foot lesion in a patient with diabetes mellitus or superinfection of a chronic lower extremity ulcer in a patient with ischemic vascular disease. Patients with these types of underlying conditions should not have been enrolled in the study according the protocol, since these lesions would be expected to yield mixed pathogens, including gram-negative and/or anaerobes.

[3] The Medical Officer accepted patients who returned between days 7 and 30 for the test of cure visit.

Medical Officer's Comment: Twice as many Synercid patients as Comparator patients were found nonevaluable due to an incorrect diagnosis by the Medical Officer. These patients largely account for the proportionally larger decrease in the clinically evaluable population in the Synercid arm. Of note, the percentage of clinical successes in those patients changed to nonevaluable by the Medical Officer due to an incorrect diagnosis was actually higher in the Comparator arm. As in the Applicant's analysis, the number of patients additionally rendered nonevaluable by the Medical Officer was fairly well distributed between treatment arms.

In addition, the Medical Officer changed 24 patients in the Applicant's nonevaluable patient population from clinically nonevaluable to evaluable, as follows:

TABLE 16
MEDICAL OFFICER CHANGES TO APPLICANT'S CLINICALLY NONEVALUABLE POPULATION

	SYNERCID	COMPARATOR
Nonevaluable to failure by Medical Officer[1]	12	7
Nonevaluable to improve/cure by Medical Officer	2	3
TOTAL	14	10

[1]Many of the patients who were changed to failure had received antibiotics after the study drug was discontinued. If the antibiotics were given for continuation of therapy for the skin and skin structure infection for which the patient was entered in the study, the Medical Officer categorized them as clinical failures.

Medical Officer's Comment: A higher number of patients in the Synercid arm were rendered evaluable after the Medical Officer's Analysis compared with the Comparator arm. Most changes in each arm resulted in changes from nonevaluable to clinical failure (with slightly more in the Synercid arm), while 3 patients were changed to clinical successes in the Comparator arm and 2 in the Synercid arm. The net result of these changes is 10 more failures in the Synercid arm and 4 more failures in the Comparator arm.

8.3.6.3. Bacteriologically Evaluable Patients - The following table contains a summary of the Applicant's and Medical Officer's determination of the bacteriological evaluability status in the clinically evaluable patient population divided by treatment arm. The Applicant's evaluability data are taken from Volume 1.252, page 74.

TABLE 17
BACTERIOLOGICALLY EVALUABLE PATIENTS[1]

	SYNERCID	COMPARATOR
Total Enrolled	221	222
Fully Evaluable per Medical Officer	46 (20.8%)	53 (23.9%)
Fully Evaluable per Applicant	90 (40.7%)	82 (36.9%)

[1]Of the clinically evaluable patient population

Medical Officer's Comment: The data in Table 17 demonstrate that approximately one quarter of the patients in each treatment arm were considered to be both bacteriologically and clinically evaluable by the Medical Officer's analysis. The diagnosis with the most patients labeled "erysipelas" (which on review of the individual cases, usually included patients with cellulitis) might be expected to have a lower bacteriological evaluability rate, since isolation of an etiologic pathogen may be more difficult than would be encountered in patients in the next two most common diagnostic categories of traumatic and surgical wound infections.

Given below are the reasons for changes to the Applicant's bacteriologically nonevaluable population from evaluable to nonevaluable which were made by the Medical Officer:

		SYNERCID	COMPARATOR
1.	Clinically Nonevaluable	29	21
2.	No Valid Baseline Pathogen	12	7
3.	No MIC's	10	9
	TOTAL	51	37

Medical Officer's Comment: More patients in the Synercid arm than in the Comparator arm were changed to nonevaluable. Most of these changes were the result of a change in clinical evaluability. The most frequent reason for rendering a patient nonevaluable due to no baseline pathogen was the presence of an organism such as *S. epidermidis* in a setting where is was not considered by the Medical Officer to be a pathogen.

In addition, the Medical Officer changed 15 patients in the Applicant's bacteriologically nonevaluable patient population from nonevaluable to evaluable, as follows:

TABLE 18
MEDICAL OFFICER CHANGES TO APPLICANT'S BACTERIOLOGICALLY NONEVALUABLE POPULATION

	SYNERCID	COMPARATOR
Nonevaluable to failure by Medical Officer	6	7
Nonevaluable to improve/cure by Medical Officer	1	1
TOTAL	7	8

Medical Officer's Comment: Approximately equal numbers of patients were changed in each arm and each category resulting in a net increase of 5 failures in the Synercid arm and 6 failures in the Comparator arm.

Table 19 below gives an overall summary of changes made by the Medical Officer to the Applicant's evaluable patient populations:

TABLE 19
EVALUABILITY CHANGES BY MEDICAL OFFICER

	CLINICALLY EVALUABLE		BACTERIOLOGICALLY EVALUABLE	
NUMBER OF PATIENTS	SYNERCID	COMPARATOR	SYNERCID	COMPARATOR
Total enrolled	221	222	221	222
Evaluable per RPR	153	153	90	82
Changed to nonevaluable by Medical Officer	54	43	51	37
Changed to evaluable by Medical Officer	14 (12 failures)	10 (7 failures)	7 (6 failures)	8 (7 failures)
Net change in evaluable patients	-40	-33	-44	-29
Evaluable per Medical Officer	113	120	46	53

8.3.6.4. Clinical Efficacy - The Medical Officer evaluated the case summaries of all patients. The primary efficacy endpoint was the clinical response in the clinically evaluable population determined at the test of cure assessment (between 7 and 30 days after completion of study drug) or when the patient discontinued therapy prior to the test of cure assessment. Table 20 below shows the clinical efficacy analysis using the Applicant's (Volume 1.252, page 75) and the Medical Officer's evaluability analysis.

TABLE 20
CLINICAL EFFICACY - STUDY JRV 305

SUCCESS[1]	SYNERCID	COMPARATOR	95% C.I. FOR DIFFERENCE
per Medical Officer	75/113 (66.4%)	77/120 (64.2%)	(-10.0%, 14.4%)
per RPR	109/153 (71.2%)	111/153 (72.5%)	(-11.4%, 8.8%)

[1]Success is defined as Number of patients cured + improved/total number of patients clinically evaluable

Please see Dr. Shen's review for details of the statistical analysis and section 8.2.6.4. above for a brief discussion of the confidence interval analysis.

Medical Officer's Comment: These results demonstrating 66.4% clinical efficacy by Synercid and 64.2% clinical efficacy by Comparator in the clinically evaluable population at the test of cure visit fulfill the criteria for demonstration of equivalence between treatment arms. The clinical efficacy of the two treatment arms is very similar by both the Medical Officer's and Applicant's analyses. Clinical efficacy

in the Synercid arm is 4.8% lower by the Medical Officer's analysis than by the Applicant's and 8.3% lower in the comparator arm. As described in section 8.3.6.2., the Medical Officer changed more patients in the Synercid arm to nonevaluable as well as changing more patients to clinical failures in the Comparator arm. This small difference (4.8% versus 8.3%) thus represents a relatively small net change in successful outcomes as a result of changes from evaluable to nonevaluable by the Medical Officer's analysis, in addition to the clinical failures added to both arms. The clinical efficacy of both treatment arms in study JRV 305 was somewhat higher than the 49.5% clinical efficacy in the Synercid arm and 51.9% in the Comparator arm noted in study JRV 304.

8.3.6.5. Bacteriological Efficacy - In the following sections, bacteriological efficacy rates will be given by patient, by pathogen, and for monomicrobial versus polymicrobial infections. Additionally, data will be presented regarding efficacy of the study drugs in bacteremic patients, against [redacted]-resistant *S. aureus*, and against *S. aureus* with MLSb constitutive resistance.

8.3.6.5.1. Bacteriological Efficacy by Patient - The following table gives the results of the analysis of the bacteriological efficacy rates by patient for the fully evaluable patient population at the test of cure visit:

TABLE 21
BACTERIOLOGICAL EFFICACY BY PATIENT

SUCCESS[1]	SYNERCID	COMPARATOR	95% C.I. FOR DIFFERENCE
per Medical Officer	31/46 (67.3%)	29/53 (54.7%)	(-6.4%, 31.7%)
per RPR	62/90 (68.9%)	57/82 (69.5%)	(-14.4%, 13.2%)

[1]Success is defined as Number of patients with pathogen(s) eradicated + presumed eradicated/total number of patients fully evaluable

Medical Officer's Comment: The efficacy rates for both treatment arms are lower in the Medical Officer's analysis than in the Applicant's (1.6% in the Synercid arm versus 14.8% in the Comparator arm). More patients in the Synercid arm than in the comparator arm were rendered nonevaluable (see Part 8.3.6.3.), while similar numbers of patients were changed from nonevaluable to clinical failures (Table 18).

8.3.6.5.2. Bacteriological Efficacy by Pathogen - Bacteriological efficacy rates by pathogen for the fully evaluable patient population at the test of cure visit are given in Table 22 below. Bacterial pathogens included in the table are those aerobic gram-positive bacteria likely to be etiologic pathogens in complicated skin and skin-structure infections.

TABLE 22
BACTERIOLOGICAL EFFICACY BY PATHOGEN

	MEDICAL OFFICER		RPR	
ORGANISM	Synercid	Comparator	Synercid	Comparator
Staphylococcus aureus	22/34 (64.7%)	19/37 (51.4%)	38/57 (66.7%)	39/52 (75.0%)
Staphylococcus spp. including coagulase-negative[1]	2/3 (66.7%)	3/5 (60.0%)	10/12 (83.3%)	11/14 (78.6%)
Streptococcus agalactiae	2/3 (66.7%)	1/1 (100%)	2/4 (50.0%)	2/2 (100%)
Streptococcus pyogenes	10/10 (100%)	3/8 (37.5%)	16/16 (100%)	6/8 (75.0%)
Streptococcus dysgalactiae	0/1 (0%)	3/5 (60.0%)	2/3 (33.3%)	5/8 (62.5%)
Streptococcus spp.	0/0 (0%)	1/3 (33.3%)	5/7 (71.4%)	4/7 (57.1%)
Enterococcus spp. non-*faecium*[2]	0/1 (0%)	1/1 (100%)	2/9 (22.2%)	3/6 (50.0%)
TOTALS	36/52 (69.2%)	31/60 (51.7%)	75/108 (69.4%)	70/97 (72.2%)

[1]The Medical Officer accepted coagulase-negative staphylococci as pathogens when the patient had a surgical site infection or an infected catheter site. In other infection types, it was regarded as a colonizer and not as a pathogen.
[2]No *Enterococcus faecium* were isolated from the fully evaluable patient population.

Medical Officer's Comment: As would be expected in a study of skin and skin-structure infections, the most commonly isolated pathogen in both treatment arms was *S. aureus*. The by pathogen bacteriological efficacy rate for *S. aureus* of 64.7% in the Synercid arm of this study was higher than the 51.4% found in the Comparator arm. Of note, this actually reverses the relative efficacy of the two

treatment arms against *S. aureus* that resulted from the Applicant's analysis. *S. pyogenes* was the next most commonly isolated pathogen, and the bacteriological efficacy rates were 100% and 37.5% for the Synercid and Comparator arms, respectively. Other organisms were isolated in numbers too small for meaningful analysis, including *S. epidermidis* and *S. agalactiae* that are organisms requested for labeling by the Applicant.

8.3.6.5.3. Bacteriological efficacy in polymicrobial versus monomicrobial infections - A comparison of eradication rates by pathogen in patients with polymicrobial versus monomicrobial infection is given in the Table 23 below for the fully evaluable patient population. The populations compared are "monomicrobial" in which cultures grew a single strain of aerobic gram-positive bacteria, as detailed in Table 22 in the previous section, and "polymicrobial" in which cultures grew more than one of these bacteria.

TABLE 23
BACTERIOLOGICAL EFFICACY - POLYMICROBIAL VERSUS MONOMICROBIAL INFECTIONS

	MONOMICROBIAL		POLYMICROBIAL	
ERADICATION[1]	Synercid	Comparator	Synercid	Comparator
per Medical Officer	25/36 (69.4%)	24/40 (60.0%)	11/16 (68.8%)	7/20 (35.0%)
per RPR	45/58 (77.6%)	36/57 (63.2%)	31/55 (56.4%)	35/41 (85.4%)

[1]Eradication = organisms eradicated + presumed eradicated/total organisms isolated

Medical Officer's Comment: The bacteriological eradication rate was higher in the Synercid arm than in the Comparator arm for patients with monomicrobial infections (69.4% versus 60.0%, respectively). Many of the patients classified by the Applicant as having a polymicrobial infection were eliminated from the clinically and bacteriologically evaluable patient population, since they should have been excluded according to the protocol. As a result, although there was a higher bacteriological eradication rate in the Synercid arm than in the Comparator arm (68.8% versus 35.0%), the number of patients was relatively small. As can be seen from the polymicrobial results in the table, there was a more pronounced effect on the Comparator group after the Medical Officer's analysis, with a resultant decrease in efficacy rate. Since the majority of these patients with polymicrobial infections were rendered nonevaluable based on their culture results without a detailed examination of the case report, it seems unlikely that systematic bias could account for these results.

8.3.6.5.4. Bacteriological eradication in bacteremic patients - Table 24 below demonstrates pathogen eradication rates (eradication + presumed eradication/total episodes of bacteremia) in study patients with bacteremia at baseline:

TABLE 24
BACTERIOLOGICAL ERADICATION IN BACTEREMIC PATIENTS

	MEDICAL OFFICER		RPR	
Organism	Synercid	Comparator	Synercid	Comparator
Staphylococcus aureus	1/3 (33.3%)	2/4 (50.0%)	1/3 (33.3%)	2/4 (50.0%)
Other-gm. neg rods	0/0 (0%)	0/0 (0%)	1/2 (50.0%)	0/0 (0%)
Streptococcus spp.	2/2 (50.0%)	1/2 (50.0%)	2/2 (100%)	1/2 (50.0%)
TOTALS	3/5 (60.0%)	3/6 (50.0%)	4/7 (57.0%)	3/6 (50.0%)

Medical Officer's Comment: Overall, a similar percentage of patients had their bacteremia eradicated in the Synercid and Comparator arms. However, the number of cases of bacteremia caused by specific bacteria is too small to allow any definitive conclusions regarding study drug efficacy.

8.3.6.5.5. Eradication rates for resistant pathogens - In the following two sections are given bacteriological eradication rates for two antibiotic resistant organisms which are potential isolates from patients with skin and skin-structure infections.

- [redacted]esistant *Staphylococcus aureus*:

TABLE 25
BACTERIOLOGICAL ERADICATION RATES OF [redacted] RESISTANT *S. AUREUS*

	EVALUABLE		NONEVALUABLE	
CLINICAL RESPONSE	Synercid	Comparator	Synercid	Comparator
Clinical success (cure+improve)	3	1	3	1
Clinical failure	0	1	0	0
Success (%)	3/3 (100%)	1/2 (50.0%)	3/3 (100%)	1/1 (100%)
Indeterminate	NA	NA	4	0

- *Staphylococcus aureus* with MLSb constitutive resistance:

TABLE 26
BACTERIOLOGICAL ERADICATION RATES OF *S. AUREUS* WITH MLSb CONSTITUTIVE RESISTANCE

	EVALUABLE		NONEVALUABLE	
CLINICAL RESPONSE	Synercid	Comparator	Synercid	Comparator
Clinical success (cure+improve)	3	1	2	0
Clinical failure	0	2	0	0
Success (%)	3/3 (100%)	1/3 (33.3%)	2/2 (100%)	-
Indeterminate	NA	NA	3	0

Medical Officer's Comment: Relatively small numbers of each of these resistant pathogens were isolated from the patients in this study, making it difficult to draw definitive conclusions regarding the efficacy of study drug in this setting. In the Synercid arm, 3 of 3 (100%) [redacted] resistant *S. aureus* were eradicated, as were 1 of 2 organisms (50%) in the Comparator arm. Similarly, 3 of 3 *S. aureus* with MLSb constitutive resistance were eradicated, as were 1 of 3 organisms (33.3%) in the Comparator arm.

8.3.6.6. Safety –

8.3.6.6.1. **Deaths** - A total of four patients died during the study, all in the Synercid arm. All of the deaths were considered by the investigators to be unrelated to the study medication. The Medical Officer has reviewed these cases and concurs that the deaths were unrelated to study medication.

8.3.6.6.2. **Most Common Non-venous Adverse Events** - Non-venous adverse events described by the investigators as either "probably" or "possibly" related to study drug occurred in 46 (20.9%) patients in the Synercid arm and 22 (9.9%) patients in the comparator arm. The most frequent study drug related adverse events were:

- Digestive System: 18 patients in the Synercid arm and 9 patients in the comparator arm experienced nausea or vomiting; vomiting occurred in 5 (2.3%) patients in the Synercid arm and 1 (0.5%) patient in the comparator arm.
- Skin and Appendages: In the Synercid arm, 13 patients experienced adverse events of this body system; 7 (3.2%) in the Synercid arm had a rash while none in the comparator arm had a rash.
- Body as a Whole: In the Synercid arm 16 (7.2%) patients experienced adverse events of this type, including 5 with "pain". In the comparator arm, 10 (4.5%) patients experienced adverse events in this category, which were not further itemized.

Serious non-venous adverse events were reported by 34/221 (15.4%) of the patients in the Synercid arm and 22/222 (9.9%) in the comparator arm. Of the 16 serious adverse events thought by the investigators to be related to the study drug, 13 occurred in the Synercid arm: one report each of anaphylactoid reaction, cellulitis, fever, infection, "aggravation reaction", "vascular anomaly", diarrhea, gastrointestinal hemorrhage, hemolytic anemia, leg cramps, paresthesia, rash, and skin ulcer. There were three reports of serious non-venous adverse events in the comparator group, all "infection".

8.3.6.6.3. **Venous Adverse Events** - Venous adverse events deemed by the investigator to be "possibly" or "probably" study drug related occurred in 146 (66.1%) of the patients in the Synercid arm and 72 (32.4%) of patients in the comparator arm. In patients with venous adverse events of moderate or severe severity, most commonly described were inflammation [52 (23.5%) Synercid and 11 (5.0%) comparator], edema [11 (5.0%) Synercid and 2 (1.0%) comparator] and "reaction" [8 (4.8%) Synercid and 1 (<1.0%) comparator]. Six episodes of thrombus or thrombophlebitis occurred in the Synercid arm, two moderate ~~in severity and four severe; none were~~ noted in the comparator arm. Changes in infusion sites due to site irritation occurred in 133/ 221 (60.2%) in the Synercid arm and in 60/222 (27.0%) of the comparator arm. Serious venous adverse events ~~considered~~ to be study drug related occurred in one patient in the Synercid arm (injection site inflammation) and no patients in the comparator arm.

8.3.6.6.4. **Adverse Events Resulting in Discontinuation** - Non-venous adverse events resulted in discontinuation of therapy in 26 (11.8%) patients in the Synercid arm and 7 (3.2%) in the comparator arm. Adverse venous events resulted in discontinuation of therapy in 28 (12.7%) patients in the Synercid arm and 4 patients (1.8%) in the comparator arm. Eight patients in the Synercid arm and one comparator-treated patient discontinued the study due to adverse laboratory events. Synercid treated patients had treatment discontinued due to hematologic abnormalities (3 patients), liver function abnormalities (3 patients), glucosuria (1 patient), and multiple laboratory abnormalities (1 patient).

8.3.6.6.5. **Bilirubin/Liver function tests** – This will be addressed in the integrated safety summary.

8.3.7. **Applicant's Summary and Conclusions** - The following information is taken from Volume 1.252, pages 3-7 and 134. The Applicant enrolled 443 patients with complicated skin and skin-structure infections in this study, of which 221 were treated with intravenous Synercid 7.5 mg/kg q 12 hours and 222 were treated with either cefazolin 1g q8 hours or vancomycin 1g q12 hours. Approximately one-third of the patients were enrolled and treated in France and one-third in the United States, with the remainder divided among the other eight countries. A similar number of patients in each group withdrew from the study without completing treatment, primarily for adverse clinical events in the Synercid group and for test drug ineffectiveness in the Comparator group. An identical number of patients in each group were Clinically Evaluable, with similar reasons for exclusion from the Clinically Evaluable Population in each treatment group. Demographic characteristics were similar for the two treatment groups, as was the number and type of causative baseline pathogens. The duration of study drug therapy was one day shorter in the Synercid group, primarily due to shorter durations in patients who were prematurely discontinued from treatment.

Of those patients found to be clinically evaluable by the Applicant, 109/153 (71.2%) in the Synercid arm and 111/153 (72.5%) in the Comparator arm had a satisfactory clinical response at the Test of Cure visit, which is the primary efficacy parameter for this study. Comparable bacteriological efficacy rates for the fully evaluable population at the Test of Cure visit were 62/90 (68.9%) in the Synercid arm and 57/82 (69.5%) in the Comparator arm.

The Applicant concludes that Synercid given in a dose of 7.5 mg/kg intravenously every 12 hours was found to be statistically equivalent to standard therapy (cefazolin or vancomycin) with regard to clinical response for the treatment of hospitalized patients with complicated skin and skin-structure infections. The by-pathogen and by-patient bacteriologic success rates were equivalent in the bacteriologically evaluable population. The overall incidence of related adverse events, especially adverse venous events, was greater among Synercid-treated patients, and this led to more frequent premature discontinuation of therapy for this group. The Synercid recipients had a somewhat higher incidence of nausea and/or vomiting that was reported as related to study drug treatment. The incidences of laboratory test abnormalities were comparable between the two treatment groups with elevations of liver function tests reported more frequently in Synercid-treated patients and increases in BUN and decreases in hemoglobin reported more frequently for the Comparator agents.

8.3.8. **Medical Officer's Summary and Discussion** - The results of the clinical efficacy analysis in the clinically evaluable patient population for this study demonstrate similarity of Synercid with comparator (cefazolin or vancomycin) in the treatment of complicated skin and skin-structure infections (66.4% versus 64.2%; 95% C.I. -10.0%, 14.4%). Issues to be considered in evaluation of the results of study JRV 305 include the following:

- The clinical evaluability rates in this study were relatively low, 51.1% in the Synercid arm and 54.1% in the comparator arm. The majority of unevaluable patients were classified as nonevaluable because of violations of the protocol. These included violation of the entry criteria, with many patients found nonevaluable due to underlying skin and skin-structure infections typically caused by organisms which would not be expected to respond to Synercid. The most common example being extremity infections (often chronic) in patients with diabetes mellitus or ischemic peripheral vascular disease. Additionally, patients were found to be nonevaluable due to violations such as return outside the designated time frame for the test of cure visit.
- The 66.4% clinical efficacy rate of Synercid in the treatment of complicated skin and skin structure infections is somewhat low; however, similarity with the comparator arm is demonstrated. Clinical efficacy rates in the range of 70% have been observed in trials for this indication. The low clinical efficacy rate of the comparator arm (cefazolin or vancomycin) remains unexplained.
- The incidence of drug-related adverse events was higher in the Synercid group than in the comparator group; non-venous adverse events were approximately twice as common in the Synercid arm and venous events were approximately three times as common in the Synercid arm. Study drug discontinuation due to adverse events was approximately five times more common in the Synercid group. In addition, nausea and vomiting were twice as frequent in the Synercid group, and elevations of liver function tests were slightly more common in the Synercid group.
- The number of patients with methicillin-resistant *Staphylococcus aureus* in this study was quite small. There were 8 isolates from nonevaluable patients and 5 from evaluable patients; 3/3 patients in the Synercid arm with [redacted] resistant *Staphylococcus aureus* had a successful outcome, whereas 1/2 in the comparator arm were successes. Similarly, the number of patients with cultures that grew *Staphylococcus aureus* with MLSb constitutive resistance was too small to draw definitive conclusions regarding study drug efficacy (6 evaluable and 5 nonevaluable).

8.3.9. **Medical Officer's Conclusions** - The results of Study JRV 305 demonstrate that the clinical efficacy of Synercid 7.5 mg/kg q 12 hrs in the treatment of complicated skin and skin-structure infections is equivalent to the approved comparator arm regimen of cefazolin or vancomycin. Study drug related adverse events were more frequent in the Synercid arm, as were discontinuations due to adverse events when compared with the comparator arm.

9. **Overall Efficacy**

9.1. **Summary** - The submission for this indication consists of two studies submitted as independent, adequate, and well-controlled studies to support the proposed labeling for use of Synercid in the treatment of complicated skin and skin-structure infections. The primary efficacy parameter in these studies is the clinical response in the clinically evaluable population determined at the test of cure assessment, which took place between 7 and 30 days after completion of study drug, or when the patient discontinued therapy prior to the test of cure assessment. Table 27 below shows the results of the Medical Officer's clinical efficacy analysis with the corresponding 95% confidence intervals.

TABLE 27
OVERALL CLINICAL EFFICACY ANALYSIS

Study	Satisfactory outcome % (n)[1] Synercid	Satisfactory outcome % (n)[1] Comparator	95% Confidence interval lower limit (actual/allowed)
JRV 304	49.5% (52/105)	51.9% (55/106)	(-15.9%, 11.1%)
JRV 305	66.4% (75/113)	64.2% (77/120)	(-10.0%, 14.4%)

[1]n=cure+improve (clinically evaluable)/ total clinically evaluable

Pairwise comparisons of the clinically evaluable patients with a satisfactory clinical outcome reveal that both JRV 304 and JRV 305 fulfill the Points to Consider criteria for equivalence. The point estimate of efficacy of the Synercid regimen was very close to that of the comparator regimen in both studies; in JRV 304 the point estimate of Synercid's efficacy was slightly lower and in JRV 305, it was slightly higher than the comparator regimen.

Table 28 shows the results of the bacteriological efficacy analysis for Synercid and the comparator regimens in both studies. These results are based on those patients deemed evaluable by the Medical Officer.

TABLE 28
OVERALL BACTERIOLOGICAL EFFICACY ANALYSIS

Study	Satisfactory outcome % (n)[1] Synercid	Satisfactory outcome % (n)[1] Comparator	95% Confidence interval lower limit (actual/allowed)
JRV 304	46.8% (29/62)	60.3% (35/58)	(-31.3%, 4.1%)
JRV 305	67.3% (31/46)	54.7% (29/53)	(-6.4%, 31.7%)

[1]n=number of patients with pathogen(s) eradicated + presumed eradicated (bacteriologically evaluable)/ total number of patients fully evaluable

Pairwise comparisons of the fully evaluable patients with a satisfactory bacteriological outcome reveals that study JRV 304 does not fulfill the Points to Consider criteria for equivalence, while study JRV 305 does satisfy this requirement. In parallel to the results of the clinical efficacy analysis, the point estimate of bacteriological efficacy of the Synercid regimen was lower than the comparator regimen in study JRV 304, while the opposite was true in study JRV 305.

9.2. **Medical Officer's Discussion** - Analysis of the two studies submitted by the Applicant in support of the request for labeling for Synercid in the indication of complicated skin and skin structure infections demonstrates that Synercid was equivalent to the comparator regimens used, as defined by the criteria outlined in the DAIDP's Points to Consider. In addition to the statistical demonstration of equivalence of the treatment regimens studied, the Points to Consider require "One statistically adequate and well-controlled multicenter trial establishing equivalence or superiority to an approved product. . ." for complicated skin and skin and skin-structure infections. Therefore, consideration of the overall approvability of this submission for the complicated skin and skin-structure indication requires that the supportive studies be adequate in the sense of incorporating optimal clinical trial design and management, primary effectiveness variables and endpoints, and evaluability criteria, as well as optimal statistical analysis (Points to Consider, Introduction to Issues). A detailed patient by patient review of the submitted studies raises two significant concerns regarding the adequacy of the two submitted studies.

The first and most important issue relevant to the discussion of the adequacy of the submitted studies is the low percentage of patients who were clinically evaluable in both of these studies. As previously noted, the primary efficacy variable in these studies was the clinical response in the clinically evaluable population determined at the test of cure assessment which was to take place between study days 14 and 28. (This interval was later widened by the Applicant to between days 4 and 30, and the Medical Officer accepted those who returned between days 7 and 30). By the Applicant's analysis, 59% and 54% of the patients were clinically evaluable in the Synercid and Comparator arms, respectively, in study JRV 304; comparable figures were 69% for both arms in study JRV 305. The most common reason for clinical nonevaluability by the Applicant's analysis was "missing required efficacy data"; many of these patients did not have a test of cure visit performed. After the Medical Officer's analysis, the resulting percentages of clinically evaluable patients were 46% and 48% in the Synercid and comparator arms, respectively, in study JRV 304; the comparable figures were 51% and 54%, respectively, in study JRV 305. There were two major categories of patients whose clinical evaluability status was changed by the Medical Officer. First, as discussed in detail in the text of this document, patients with infections which would *a priori* be expected to be caused by bacteria not included in Synercid's antimicrobial spectrum of activity were excluded from the clinically evaluable patient population by the Medical Officer; the most common examples of this type of patient were diabetics with infections of the lower extremities. These patients should not have been included in these studies based on the protocol as submitted by the Applicant. Additionally, lesser numbers of patients were excluded from the clinically evaluable patient population due to absence of culture data,

prior or simultaneous non-study antibiotics, or return for the test of cure visit outside the appropriate window. Again, these changes were the result of protocol violations, rather than disagreements by the Medical Officer with the protocol. The second major category of patients whose clinical evaluability was changed by the Medical Officer with a resultant effect on overall study outcome was patients whose clinical evaluability was changed from nonevaluable to clinical failure. These patients were usually classified by the Applicant as discontinuations due to adverse events, changes to oral antibiotics, or continuation of non-study intravenous antibiotics; all of these patients were treated as clinical failures by the Medical Officer, unless further antibiotics were administered for a clearly non-study-related reason. Overall, then, the fact that approximately half of the patients in these studies were nonevaluable raises serious concerns regarding the adequacy of study conduct and the general applicability of the results.

A second area of concern in evaluating the results of these studies is the low efficacy rates seen for both Synercid and the comparator arms, especially in study JRV 304. Although no anticipated cure rates are given in the IDSA guidelines, the recent clinical efficacy rates of approved drugs in the Division for the indication of complicated skin and skin-structure infections are more typically in the range seen for Zosyn (75% versus 74% for comparator) and Alatrofloxacin/Trovafloxacin (73% versus 77% for Zosyn/Vantin). In studies JRV 304 and JRV 305, both Synercid and the comparator arm have lower clinical efficacy rates than would be expected from examination of the above approval rates. It remains unclear, however, why the "gold standard" antimicrobial therapy (cefazolin or oxacillin/vancomycin) demonstrated such low efficacy rates. Patients with complicated skin and skin-structure infections caused by organisms other than gram-positive bacteria (and thus, resistant to Synercid and the comparators) would be expected to be excluded from this analysis based on the Medical Officer's inclusion and exclusion criteria. When the above information was presented to the DAIDP Advisory Committee on February 19, 1998, the Committee recommended approval based on the statistical demonstration of equivalence, and the opinion was expressed that the low clinical efficacy rate of Synercid could not be directly compared to that seen in other studies, since the study design and conduct may differ significantly.

The final concern regarding the Synercid submission for use in complicated skin and skin-structure infections is the safety profile of this product. Drug related adverse events were approximately two times more common in the Synercid arm than in the comparator arm in both studies. Venous adverse events occurred in 69.9% of Synercid patients in study JRV 304 and 66.1% in study JRV 305; this was approximately twice the rate in the comparator arm. These adverse events consisted of such phenomena as inflammation, edema, thrombus, and thrombophlebitis. One patient in each study in the Synercid arm had a venous adverse event considered to be serious. Of note were the discontinuation rates in the Synercid arm in both studies 23.2% in JRV 304 and 24.5% in JRV 305, compared with 7.3% and 5%, respectively, in the comparator arm. Approximately half of the discontinuations in the Synercid arm were due to venous adverse events. In the event of approval of the complicated skin and skin structure indication, the only bacterial pathogens with sufficient numbers to be included in the label are [redacted] susceptible *S. aureus* and *S. pyogenes*; other antimicrobial agents with better risk/benefit ratios are available with activity against these organisms.

The Medical Officer has detailed above concerns regarding the adequacy of these two studies of the use of Synercid in complicated skin and skin-structure infections. The result of these deficiencies is a failure to establish with confidence that a true beneficial effect of the drug has been demonstrated, despite the statistical demonstration of equivalence. In addition, the safety profile of Synercid makes its approval for this indication quite problematic, given the very high frequency of side effects including venous intolerance and the current availability of suitable alternative antimicrobials for this indication. Therefore, in consideration of the study conduct deficiencies including low clinical evaluability rates, the low efficacy rates for this clinical indication, and the high adverse event profile, the Medical Officer judges this indication to be nonapprovable.

10. **Medical Officer's Recommendation** - It is the Medical Officer's recommendation that Synercid should be Not Approved for the indication of complicated skin and skin-structure infections.

/S/

Susan D. Thompson, M.D.

Concurrence Only:
HFD-520/DivDir/Chikami /S/ 8/11/98
HFD-520/TLMO/Roberts NR 7/25/98

cc:
HFD-520
HFD-520/MO/Thompson
HFD-520/DepDir/Gavrilovich
HFD-520/MO/Rakowsky
HFD-520/Micro/Marsik
HFD-520/Chem/Timper
HFD-725/Stats/Shen
HFD-520/PharmTox/Seethaler
HFD-520/CSO/Dillon-Parker

APPENDIX 1

JRU 304

STUDY PROCEDURES:

Study Procedures	Day 1 (Bsln)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	End of Treat	Test of Cure
Info Cons	X															
Med/Hist Demograph	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Max Temp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X			X											X	X
Clinical Signs/Symp	X			X											X	X
Tolerance (site of Iv)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gram's Stn	X															
Site cultrs Aero/Anaer	X			X*	*If material is available for culture										X*	X*
Blood cultr	X			X**	**If positive at baseline or if clinical signs/symptoms of bacteremia										X**	X**
Bld chem	X			X											X	X
LFT panel	X			X			X			X			X		X	X
Urinalysis	X			X											X	X
Creat Clear	X			X											X	X
Hematol	X			X											X	X
Vanco level	Perform as clinically indicated to assess vancomycin dosing															
Preg test	X															
Prior/Conc Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Surg Interv	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

APPENDIX 2

JRU 305

STUDY PROCEDURES:

Study Procedures	Day 1 (Bsln)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	End of Treat	Test of Cure
Info Const	X															
Med/Hist Demograph	X															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Max Temp	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X			X											X	X
Clinical Signs/Symp	X			X											X	X
Tolerance (site of iv)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gram's Stn	X[1]															
Site cultures Aero/Anaer	X			X[2]											X[2]	X[2]
Blood cultr	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[1]	X[1]
Bld chem	X			X											X	X
LFT panel	X			X			X			X			X		X	X
Urinalysis	X			X											X	X
Creat Clear	X			X											X	X
Hematology	X			X											X	X
Vanco level	Perform as clinically indicated to assess vancomycin dosing															
Pregcy test	X[4]															
Prior/Conc Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adv Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] If available.
[2] If material is available for culture.
[3] If positive cultures at previous assessment or as clinically appropriate.
[4] If applicable.

61 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

CLINICAL REVIEW OF COMPARATIVE STUDY SAFETY INFORMATION

NDA 50-748

Date of Submission: The original NDA was submitted on September 5, 1997, and it contained safety data through January 8, 1996. The safety update report was submitted on January 5, 1998, and it contains safety data through October 31, 1997. An amendment was submitted on April 14, 1998, and includes information on hepatic toxicity which was requested in the March 5, 1998 approvable letter for NDA 50-747.

Date of Safety Review Initiation: February 2, 1998

Date Review to Supervisor: June 18, 1998

Drug: Synercid (quinupristin/dalfopristin) IV

Applicant: Rhone-Poulenc Rorer Pharmaceuticals, Inc.
Collegeville, PA 19426

Proposed Indications: Approval for Synercid is requested for the following indications: complicated skin and skin structure infections; [redacted] infections due to Vancomycin-resistant *Enterococcus faecium;* and infections caused by *Staphylococcus aureus* [redacted]

Proposed Dosage and Administration: The recommended dose is 7.5 mg/kg. Frequency of dosing varies by indication, as follows:

A. Complicated skin and skin structure infections [redacted] every 12 hours for 7 days.

B. [redacted] infections due to Vancomycin-resistant *Enterococcus faecium,* and infections caused by *Staphylococcus aureus* every 8 hours for 10 days for [redacted] and duration as required for the other infections.

Material Reviewed: The applicant has divided the adverse event reports by Phase 1, 2 and 3 results, as well as separated the data into venous events and non-venous events. The safety update (January 5, 1998) almost exclusively concerns emergency use patients. Review of the safety data for emergency use patients is contained in a separate review of NDA 50-747 dated March 2, 1998. This review will consist of the following sections:

1. Overview of studies

2. Review of Phase 1 clinical safety data

3. Review of Phase 2 clinical safety data

4. Review of Phase 3 clinical safety data

5. Review of hepatic toxicity

6. Conclusions

It should be noted that the most relevant safety results are in the Phase 3 comparative use studies. The Phase 1 and 2 data will be briefly summarized.

1. Overview of studies:

There were 4175 healthy volunteers and patients in the safety data base for this NDA. These were divided as follows:

A. Synercid patients in non-emergency use studies
   i. 515 in 25 Phase 1 studies
   ii. 143 in 4 Phase 2 studies
   iii. 1099 in 5 Phase 3 studies

B. Placebo subjects and comparative patients in non-emergency use studies
   i. 58 received placebo (all healthy subjects)
   ii. 1161 received a comparator drug

C. Synercid patients in emergency-use studies: 1199. Please see separate review of these patients dated March 2, 1998.

The comparator drugs used in Phase 3 studies were as follows:

A. Skin and skin structure: cefazolin, oxacillin, vancomycin

[redacted]

2. Review of Phase 1 clinical safety data

The following table represents the exposure of the 515 patients exposed to Synercid in Phase 1.

	n	Dosage
Single dose of Synercid	310	1.4-29.4 mg/kg
Multiple doses of Synercid	178	5.0-15.0 mg/kg
Multiple doses of Synercid combined with other med	27	7.5 mg/kg

The following table, which is identical to table 11 on p. 88 of volume 124 of the NDA summarizes the exposure to the drug in the multiple dose studies.

Summary of Extent of Exposure By Dose, Repeated-dose Studies

Treatment Group / Dose Level (mg/kg)	Number of Subjects (N = 236)	Daily Dose (mg/kg)	Days Treated		
			Mean +/- SD	Min	Max
Synercid monotherapy					
5 mg/kg q12h	19	10	6.00 ± 2.73	1.00	10.00
7.5-8 mg/kg q12h	36	15-16	4.68 ±0.68	2.50	6.00
7.5 mg/kg q8h [a]	68	22.5	2.60 ±0.81	1.00	3.33
10 mg/kg q12h	12	20	7.00 ±2.57	1.00	10.00
15 mg/kg q12h	43	30	3.20 ±1.49	1.00	5.00
Total Synercid monotherapy:	178				
Synercid in combination					
7.5 mg/kg q8h	27	22.5	1.44 ±0.51	1.00	2.00
Placebo	31		5.35 ±2.53	1.00	10.00

[a] Including 25 subjects who received a single dose of cyclosporine during treatment with repeated-doses of Synercid

A. Single-dose studies

The most frequent non-venous events reported in the Synercid single-dose group were headache (10%), nausea (3.9%), dizziness (2.9%) and vomiting (2.6%).

The placebo group in these studies was small (27) so the precision of the observations in this group is poor. The total percentages of subjects reporting non-venous events in the single-dose studies were 28.1% for Synercid and 40.7% for placebo.

There were venous events reported in 27.7% of the Synercid single-dose patients, predominately injection site inflammation (16.1%) and/or injection site pain (18.7%). The placebo group reported venous events in 11.1% of subjects.

B. Multiple-dose studies

The most frequent non-venous events reported in the Synercid multiple-dose group were headache (13.6%), nausea (9.7%), and abdominal pain, dizziness and rash (3.4% each). Once again, the placebo group was quite small (31). The total percentages of subjects reporting non-venous events in multiple-dose studies were 44.3% for Synercid and 29.0% for placebo.

There were venous events reported in 85.8% of the Synercid multiple-dose subjects, predominantly injection site inflammation (73.0%) and/or injection site pain (64.0%). There were also significant rates of injection site reaction (30.3%) and edema (21.3%). The placebo group reported venous reactions in 41.9% of patients, mostly pain (32.3%) and inflammation (22.6%).

C. Discontinuations and serious events

In all Phase 1 studies, 9.9% of Synercid patients were discontinued due to adverse events. No such discontinuations were necessary in the placebo group. There were two serious adverse events in the Synercid group which required discontinuation. (An adverse event was considered serious if it required hospitalization). One was an extensive erythematous and pruritic eruption

with lymphadenopathy, and the other was an allergic reaction (facial edema, rash, paresthesia, nausea and vomiting).

Reviewer's Comment: The percentages above represent all reported reactions, whether considered to be related to study medication or not. The great majority of the reactions seen were felt to be possibly or probably related to drug therapy.

3. Review of Phase 2 clinical safety data

The following table represents the exposure of the 143 patients exposed to Synercid in Phase 2.

	n	Dosage
Non-comparative studies	24	3.0-9.0 mg/kg
Comparative study (203)	93	5.0 or 7.5 mg/kg q 12 h
Comparative study (204)	26	5.0 or 7.5 mg/kg q 8 h

The following tables, which are identical to Tables 35 and 36 on pp. 113 and 114 of volume 124 of the NDA, summarizes the exposure to the drug in the comparative studies (203 and 204).

Summary of Study Drug Treatment Duration and Number of Infusions by Treatment Group - Study 203

	Synercid 5.0 mg/kg q12h	Synercid 7.5 mg/kg q12h	Ceftriaxone 1g qd
	n = 48	n = 45	n = 54
Treatment Duration (days)			
Mean ± SEM	6.1 ± 0.4	6.1 ± 0.3	7.2 ± 0.4
Range			
Median	6.0	6.0	7.0
Number of Infusions[a]			
Mean ± SEM	16.0 ± 1.1	16.4 ± 1.0	19.3 ± 1.2
Range			
Median	15.0	15.0	18.0

a: Number of infusions includes placebo administration
Data Source: Final Study Report 203, Table 31.

Summary of Study Drug Treatment Duration and Number of Infusions by Treatment Group - Study 204

	Synercid 5.0 mg/kg q8h	Synercid 7.5 mg/kg q8h	Vancomycin 1 g q12h
	N = 11	N = 15	N = 13
Treatment Duration (days)			
Mean ± SEM	7.5 ± 1.1	7.7 ± 1.1	4.7 ± 0.8
Range			
Median	7.0	7.0	4.0
Number of Infusions			
Mean ± SEM	19.4 ± 3.4	20.1 ± 3.1	7.7 ± 1.5
Range			
Median	18.0	19.0	6.0

Data Source: Final Study Report 204, Table 18

A. Frequency of events

The most frequent non-venous events reported in the Synercid patients were diarrhea (6.9%), abdominal pain (6.3%) and insomnia and pain (undefined) (4.1% each). The comparator drugs used in Phase 2 were ceftriaxone and vancomycin. The most common adverse event in the ceftriaxone group was nausea in 7.4% of patients, while in the vancomycin group, chest pain was noted in 2/13 patients (15.4%).

Venous events were reported in 70.5% of Synercid patients, predominantly noted as "local reaction". Venous event rates in the comparator drugs were 51.9% for ceftriaxone and 23.1% for vancomycin.

The following tables, which are identical to Tables 47 and 48 on pp. 121 and 122 of volume 124 of the NDA, present the adverse venous events thought to be related to treatment in the comparative studies.

Summary of Related (Possible or Probable) Adverse Venous Events - Study 203

	Number (%) of Patients		
Adverse Venous Events at Injection Site	Synercid 5.0 mg/kg n = 48	Synercid 7.5 mg/kg n = 45	Ceftriaxone 1g n = 54
Patients with Related Adverse Venous Events	31 (64.6)	37 (82.2)	20 (37.0)
Edema	3 (6.2)	3 (6.7)	0
Hypersensitivity	0	1 (2.2)	0
Inflammation	7 (14.6)	13 (28.9)	6 (11.1)
Local reaction	19 (39.6)	22 (48.9)	14 (25.9)
Mass [a]	2 (4.2)	1 (2.2)	0
Pain	9 (18.8)	12 (26.7)	2 (3.7)

[a] Thrombosis or Thrombophlebitis

Summary of Related (Possible or Probable) Adverse Venous Events - Study 204

	Number (%) of Patients		
Adverse Venous Events at Injection Site	Synercid 5.0 mg/kg n = 11	Synercid 7.5 mg/kg n = 15	Vancomycin 1g n = 13
Patients with Related Adverse Venous Events	3 (27.3)	4 (26.7)	3 (23.1)
Inflammation	0	2	0
Local reaction	1	2	1
Pain	1	1	0

Reviewer's Comment: **The applicant did not draw any conclusions concerning a relationship between the dose (mg/kg) and the frequency of venous adverse events. The results from Study 203 are suggestive of a dose relationship, though the number of patients is too small to permit a definitive conclusion.**

B. Discontinuations and serious events (including deaths)

A total of 18 (12.5%) Synercid patients discontinued therapy in Phase 2 studies due to non-venous adverse events, while 2 (2.9%) patients in the comparator drug groups discontinued due to non-venous events. A total of 11 (7.6%) Synercid patients discontinued due to venous events, while no patient discontinued in the comparator group due to venous events. Thus, the

overall totals for discontinuations due to adverse events are 20.2% for the Synercid group vs. 2.9% for the comparator group.

Serious adverse events in the Synercid group included one report each of cardiac decompensation, lung disorder (COPD), embolus, heart arrest, cachexia, osteomyelitis and pyogenic arthritis; none were felt to be drug related. Serious adverse effects which were felt to be possibly or probably related to Synercid therapy were reported in 2 patients. These events were dyspnea, hypoxia and fever in one patient, and systolic heart murmur, endocarditis, fever and pyogenic arthritis in a second patient.

In the ceftriaxone group, there was one serious adverse event [redacted] which was not drug related. Finally, there are two reports of thrombophlebitis - one severe in the Synercid group which was not felt to be drug related, and one moderate in the vancomycin group which was felt to be drug related. It is not clear how this distinction was made.

Eight Synercid patients died during Phase 2 studies, in addition to two ceftriaxone patients and one vancomycin patient. Two of the Synercid deaths were felt to be possibly related to drug therapy (apnea, embolus). The other Synercid deaths were due to pneumonia, neoplasm, cardiorespiratory arrest, AIDS, sepsis and multiorgan failure. None of the deaths in the comparator drugs were felt to be drug related. They were identified as respiratory arrest, heart failure, hepatic decompensation.

4. Review of Phase 3 clinical safety data

The following table, which is identical to Table 77 on p. 146 of volume 124 of the NDA, presents the daily exposure of the 1099 patients exposed to Synercid in Phase 3. Nearly all patients received a dose of 7.5 mg/kg.

Summary of Extent of Exposure to Synercid Treatment by Relative Mean Daily Dose and by Dose Frequency - Phase III Comparative Studies

Dose Frequency	q8h			q12h		
Dose	N	Range (Days)	Median (Days)	N	Range (Days)	Median (Days)
Relative Mean Daily Dose						
<12 mg/kg	2	1-2	1.5	97	1-15	2.0
12-15 mg/kg	0	0	0	390	1-27	7.0
15-18 mg/kg	2	6-14	10.0	450	1-16	6.0
18-22.5 mg/kg	69	3-21	11.0	9	3-9	4.0
>=22.5 mg/kg	77	3-17	9.0	2	3-5	4.0
Missing	0	0	0	1	6-6	6.0
Total Number of Patients	150			949		

Data Source Appendix II, Table 2.10

A. Complicated skin and skin structure infections.

The following material is taken from summaries prepared by Dr. Susan Thompson.

i. Study 304 (Synercid vs. oxacillin-vancomycin)

a. **Deaths:** A total of seven patients died during the study, three in the Synercid arm and four in the comparator arm. All of the deaths were considered by the investigators to be unrelated to the study medication.

b. **Most common non-venous adverse events:** Non-venous adverse events described by the investigators as either "probably" or "possibly" related to study drug occurred in 65 (28.4%) patients in the Synercid arm and 36 (16.3%) patients in the comparator arm. The most frequent study drug related adverse events were:

   i. Digestive System: 30 patients in the Synercid arm and 13 patients in the comparator arm experienced nausea, vomiting, dyspepsia, or constipation; each of these adverse events were approximately three times more common in the Synercid arm.

   ii. Skin and Appendages: Pruritus or rash occurred in 10 and 7 Synercid patients, respectively; comparable figures for the comparator patients are 9 and 6, respectively.

   iii. Body as a Whole: In the Synercid arm 20 patients experienced adverse events of this type, including 6 with headache and 9 with "pain". In the comparator arm, 7 patients experienced adverse events in this category, including 1 each with headache and "pain"; the remainder of these patients are not itemized.

   Serious non-venous adverse events were reported by 30 (13.1%) of the patients in the Synercid arm and 25 (11.3%) in the comparator arm. The only two serious adverse events thought by the investigators to be related to the study drug occurred in the Synercid arm: one report of myopathy (muscle necrosis at site of infection) and one report of cellulitis.

c. **Venous adverse events:** Venous adverse events deemed by the investigator to be "possibly" study related occurred in 160 (69.5%) of the patients in the Synercid arm and 73 (33.0%) of patients in the comparator arm. In patients with venous adverse events of moderate or severe severity, most commonly described were inflammation [28 (12.2%) Synercid and 8 (3.6%) comparator], edema [22 (9.6%) Synercid and 4 (1.8%) comparator] and "reaction" [11 (4.8%) Synercid and 5 (2.3%) comparator]. Two episodes of thrombus or thrombophlebitis occurred in the Synercid arm, one mild and one moderate in severity; none were noted in the comparator arm. Changes in infusion sites due to site irritation occurred in 62.0% (142/229) in the Synercid arm and in 35.7% (79/221) of the comparator arm. Serious venous adverse events considered by the investigator to be study drug related occurred in one patient in the Synercid arm (injection site inflammation) and one patient in the comparator arm (injection site inflammation and pain).

d. **Adverse events resulting in discontinuation:** Non-venous adverse events resulted in discontinuation of therapy in 27 (11.8%) patients in the Synercid arm and 11 (5%) in the comparator arm. Adverse venous events resulted in discontinuation of therapy in 26 (11.5%) patients in the Synercid arm and 5 patients (2.3%) in the comparator arm. One patient in the Synercid arm discontinued the study due to an adverse laboratory event. Multiple abnormalities were noted including elevations in BUN, total bilirubin, alkaline phosphatase, AST, and GGT, with decreases in total protein, albumin, and CO2, all considered to be possibly related to study drug.

ii. Study 305 (Synercid vs. cefazolin-vancomycin)

a. **Deaths:** A total of four patients died during the study, all in Synercid arm. All of the deaths were considered by the investigators to be unrelated to the study medication.

b. **Most common non-venous adverse events:** Non-venous adverse events described by the investigators as either "probably" or "possibly" related to study drug occurred in 46 (20.9%) patients in the Synercid arm and 22 (9.9%) patients in the comparator arm. The most frequent study drug related adverse events were:

   i. Digestive System: 18 patients in the Synercid arm and 9 patients in the comparator arm experienced nausea or vomiting; vomiting occurred in 5 (2.3%) patients in the Synercid arm and 1 (0.5%) patient in the comparator arm.

   ii. Skin and Appendages: In the Synercid arm, 13 patients experienced adverse events of this body system; 7 (3.2%) in the Synercid arm had a rash while none in the comparator arm had a rash.

   iii. Body as a Whole: In the Synercid arm 16 (7.2%) patients experienced adverse events of this type, including 5 with "pain". In the comparator arm, 10 (4.5%) patients experienced adverse events in this category, which were not further itemized.

   Serious non-venous adverse events were reported by 34/221 (15.4%) of the patients in the Synercid arm and 22/222 (9.9%) in the comparator arm. Of the 16 serious adverse events thought by the investigators to be related to the study drug, 13 occurred in the Synercid arm: one report each of anaphylactoid reaction, cellulitis, fever, infection, "aggravation reaction", "vascular anomaly", diarrhea, gastrointestinal hemorrhage, hemolytic anemia, leg cramps, paresthesia, rash, and skin ulcer. There were three reports of serious non-venous adverse events in the comparator group, all "infection".

c. **Venous adverse events:** Venous adverse events deemed by the investigator to be "possibly" or "probably" study related occurred in 146 (66.1%) of the patients in the Synercid arm and 72 (32.4%) of patients in the comparator arm. In patients with venous adverse events of moderate or severe severity, most commonly described were inflammation [52 (23.5%) Synercid and 11 (5.0%) comparator], edema [11 (5.0%) Synercid arm 2 (1.0%) comparator] and "reaction" [8 (4.8%) Synercid and 1 (<1.0%) comparator]. Six episodes of thrombus or thrombophlebitis occurred in the Synercid arm , two moderate in severity and four severe; none were noted in the comparator arm. Changes in infusion sites due to site irritation occurred in 133/221 (60.2%) in the Synercid arm and in 60/222 (27.0%) of the comparator arm. Serious venous adverse events considered to be study drug related occurred in one patient in the Synercid arm (injection site inflammation) and no patients in the comparator arm.

d. **Adverse events resulting in discontinuation:** Non-venous adverse events resulted in discontinuation of therapy in 26 (11.8%) patients in the Synercid arm and 7 (3.2%) in the comparator arm. Adverse venous events resulted in discontinuation of therapy in 28 (12.7%) patients in the Synercid arm and 4 patients (1.8%) in the comparator arm. Eight patients in the Synercid arm and one comparator-treated patient discontinued the study due to adverse laboratory events. Synercid treated patients had treatment discontinued due to hematologic abnormalities (high WBCs in 2 patients and low hematocrit and hemoglobin in 1 patient), liver function abnormalities (high alkaline phosphatase and GGT in 2 patients, high AST in 1 patient), glucosuria (1 patient), and multiple laboratory abnormalities (1 patient).

In summary, the following comparisons are notable (the results of both studies have been combined in this presentation):

	% of Total Patients Enrolled	
	Synercid	Comparator
Related Non-Venous Events	24.6	13.0
Related Serious Non-Venous Events	3.3	0.7
Related Venous Events	68.0	32.7
Discontinuations (All Causes)	25.7	6.3
Discontinuations (Venous Events)	12.0	2.0
Discontinuations (Non-Venous Events)	11.8	4.0

Reviewer's Comment: The percentage of patients experiencing adverse events and discontinuations were consistently higher (2 - 6 times) for Synercid vs. Comparator-treated patients.

2 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Summary of Clinical Safety Data

More adverse events were reported for Synercid compared to the control drugs used in the comparative clinical trials. In general, patients discontinued therapy while on Synercid more often than while on comparator drugs due to adverse effects. This observation is especially noticeable when Synercid is administered by peripheral infusion due to venous toxicity, but is

generally true for venous and non-venous reactions alike. In the controlled clinical studies (i.e., skin and skin structure infections, [redacted] the following comparisons may be made:

	Synercid	Comparator
% with related non-venous AE's	23.2	20.7
% with related venous AE's	62.6	41.8
% discontinuing due to non-venous AE's	9.6	4.3
% discontinuing due to venous AE's	9.2	2.0

Thus, approximately 19% of Synercid patients discontinued therapy due to related adverse events during the controlled studies, as compared to 6.3 % in the comparator arms. This is a threefold difference.

No unusual toxicity patterns were noted with Synercid administration. A decision to approve the drug for these indications should take into consideration the potential benefits and risk to the patient population to be treated. If approved, the labeling for the drug should reflect the adverse event profile for Synercid as compared to standard therapies.

5. Review of hepatic toxicity:
(Taken from the White Paper on Hepatoxicity prepared by the applicant and submitted to NDA 50-747. Letter date for submission was April 14, 1998.)

In the phase 1 studies with Synercid, mild changes in liver function tests {LFTs} i.e., primarily ALT/AST abnormalities, were noted. In response to this observation RPR established the Synercid Liver Safety Board composed of physicians from academic institutions from Europe and the US. The Safety Board was requested to (1) characterize the liver safety profile of Synercid, and (2) advise on precautions for the conduct of the subsequent clinical trials.

The safety Board initially met in June 1993, and after review of the phase 1 data and early phase 2 study data characterized the liver toxicity finding as "a mild, rapid onset cytolytic phenomenon." They concluded this finding did not preclude further clinical development of Synercid. The Safety Board recommended the following:

a) patients with ALT/AST increases up to 3 X the Upper Limit of Normal (ULN) could be included in future studies;
b) patients with ALT/AST increases up to 5 X ULN should be excluded from future studies;
c) prothrombin time should be monitored during treatment;
d) patients with ALT/AST abnormalities should be followed until the test values return to normal; and
e) study the effects of Synercid on the elderly, patients with abnormal LFTs and normal subjects given repeated administration.

These recommendations were followed by RPR in the design of the phase 2 studies.

The second meeting of the Safety Board was in June 1994. The data from the phase 2 studies were reviewed along with a few case reports from the Emergency-use program. The board confirmed their initial characterization of the liver toxicity findings, i.e., "a mild rapid onset cytolytic phenomenon, as opposed to having a component of cholestasis." They concluded that RPR could continue development into phase 3 with a Synercid dose of 7.5 mg/kg q 8h or q 12h. Additionally, they made the following recommendations:

a) exclude from Phase 3 studies patients with ALT/AST or conjugated bilirubin >5x ULN;
b) monitor liver function tests (LFT) twice a week throughout the treatment period; and
c) discontinue patients with LFT>5x ULN on treatment if baseline was <3x ULN or with doubling of baseline LFT on treatment if baseline value was >3x ULN.

The parameters that were assessed to evaluate hepatic safety were ALT, AST, total bilirubin, conjugated bilirubin, lactic dehydrogenase, alkaline phosphatase, GGT, albumin and total protein.

A. Combined comparative studies

Analysis of the data from the parameters analyzed above indicates that significant differences between the Synercid and comparator groups exist only in the ALT, AST, total bilirubin and conjugated bilirubin categories.

The following table presents, in broad categories, the changes for bilirubin:

Patients with On-Treatment Bilirubin Increases

	Synercid (%)	Comparator (%)
Any increase in total bilirubin	45.0	22.0
Any increase in conjugated bilirubin	46.8	26.2

The sponsor-defined criteria for "clinically significant" and "critically abnormal" values are as follows:

	ALT/AST	Total bili/conjugated bili
Clinically significant elevation*	>5 ULN	>3ULN
Critically abnormal level*	>10 ULN	>5 ULN

*These definitions are used throughout the subsequent tables. It is to be noted that patients included in the "Critical" column are not represented in the corresponding "Significant" column.

The following table summarizes the differences in these sponsor-defined criteria for the combined phase 3 comparative studies. This table is derived from Table 1 in the April 14, 1998 submission.

Table 2 - Number and % of Patients with Abnormal Liver Function Values (Selected Tests)

		Number (%) of Patients			
		Treatment			
		Synercid		Comparator	
Parameter	Phase	Significant	Critical	Significant	Critical
AST	On-treatment	11 (1.1)	9 (0.9)	23 (2.3)	2 (0.2)
	Post-treatment	7 (0.8)	7 (0.8)	1 (0.1)	3 (0.3)
ALT	On-treatment	15 (1.5)	4 (0.4)	35 (3.5)	4 (0.4)
	Post-treatment	15 (1.7)	7 (0.8)	12 (1.3)	1 (0.1)
Total Bilirubin	On-treatment	6 (0.6)	9 (0.9)	5 (0.5)	2 (0.2)
	Post-treatment	1 (0.1)	4 (0.4)	0	2 (0.2)
Conjugated Bilirubin	On-treatment	24 (2.5)	29 (3.6)	8 (0.8)	3 (1.6)
	Post-treatment	12 (1.4)	15 (2.1)	5 (0.6)	5 (0.7)

B. Individual comparative studies

The following presentations follow the same format as Table 2 above, with the data presented by indication. This table is identical to Table 3 in the April 14, 1998 submission.

Table 3 - Number and % of Patients with Abnormal Liver Function Values by Indication

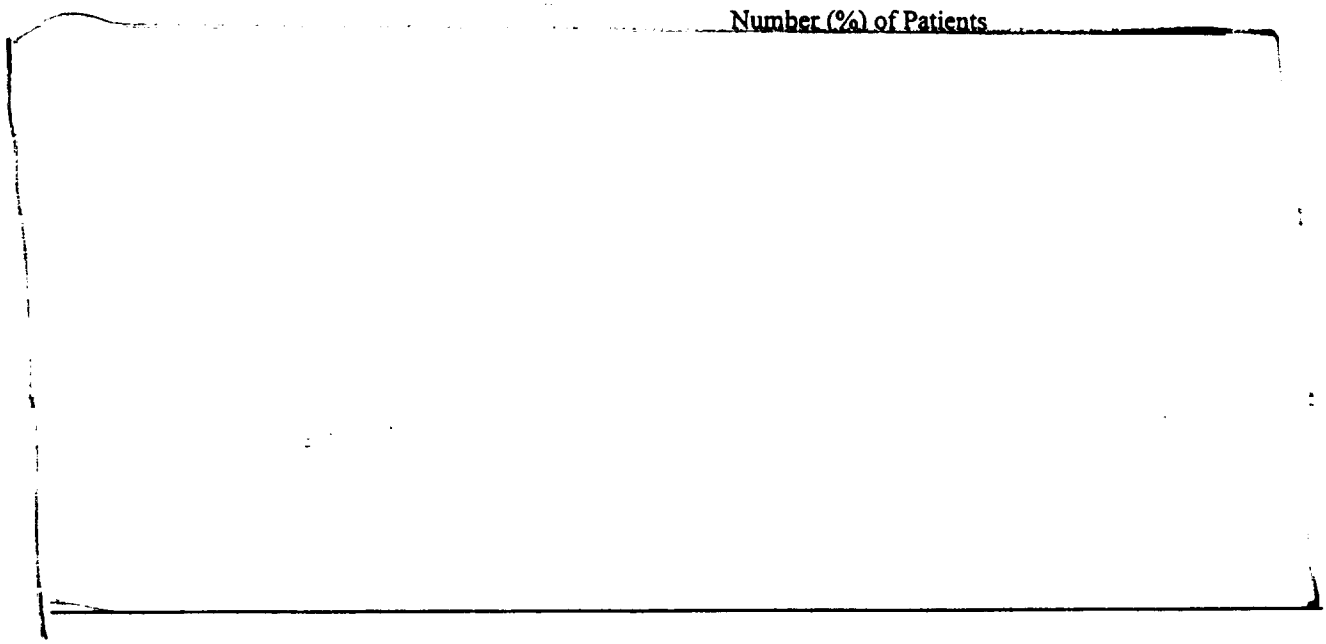


Table 3 continued.

		Skin and Skin-Structure Infections			
		Synercid		Oxacillin or cefazolin + vancomycin	
Parameter	Phase	Significant	Critical	Significant	Critical
AST	On-treatment	1 (0.3)	4 (1.1)	5 (1.3)	0
	Post-treatment	4 (1.2)	0	0	2 (0.6)
ALT	On-treatment	2 (0.5)	0	3 (0.8)	0
	Post-treatment	5 (1.5)	0	3 (0.9)	0
Total Bilirubin	On-treatment	1 (0.3)	3 (0.8)	0	1 (0.3)
	Post-treatment	0	1 (0.3)	0	1 (0.3)
Conjugated Bilirubin	On-treatment	4 (1.2)	4 (1.2)	0	1 (0.3)
	Post-treatment	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)

Reviewer's Comment: **More patients in the Synercid group exhibited high levels of total and conjugated bilirubin. This was especially true for conjugated bilirubin. The [redacted] studies were notable both for higher AST/ALT values in the comparator group (ceftriaxone/erythromycin) and higher bilirubin in the Synercid group. Abnormal values (as defined) were less frequent in the skin and skin structure patients.**

C. Discontinuations due to abnormal liver function values.

The following table is identical to Table 7 in the April 14, 1998 submission.

Table 4 - Patients Discontinued from Comparative Studies due to Abnormal Liver Function Values

Body System Adverse Event (COSTART term)	Number (%) of Patients	
	Synercid n = 1099	Comparator n = 1094
Number of Patients with Adverse Events	5 (0.5)	6 (0.5)
Total Protein	1 (0.1)	0 (0.0)
Total Bilirubin	3 (0.3)	0 (0.0)
Alkaline Phosphatase	2 (0.2)	0 (0.0)
AST	4 (0.4)	3 (0.3)
ALT	3 (0.3)	4 (0.4)
GGT	3 (0.3)	2 (0.2)
Conjugated Bilirubin	2 (0.2)	0
Lactate Dehydrogenase	0 (0.0)	1 (0.1)

Reviewer's Comment: Discontinuations due to abnormal laboratory values were comparable in the Synercid and comparator groups. Although data concerning the mechanism of bilirubin abnormalities and reversibility of these abnormalities are sparse, there do not appear to be striking differences between the two groups in these parameters.

D. Mechanism of bilirubin abnormality/reversal of abnormality.

An analysis was performed by the applicant to determine whether bilirubin abnormalities were isolated or associated with other liver function test (LFT) abnormalities. Patients were considered to be evaluable if they had conjugated bilirubin values equal to or above 2 times ULN. They were not evaluable if no on-treatment conjugated bilirubin data were available. The following rules were applied to the evaluable cases:

LFT abnormalities were classified as cytolytic if ALT and/or AST values were equal to or above 2 times the ULN.

LFT abnormalities were classified as cholestatic if Alkaline Phosphatase values were equal to or above 2 times the ULN.

LFT abnormalities were classified as mixed if both ALT and/or AST and Alkaline Phosphatase values equal to or above 2 times the ULN were observed.

Bilirubin abnormalities were classified as isolated if other LFT data did not meet the definitions of cytolytic, cholestatic, or mixed.

The following table, which is identical to Table 12 in the April 14, 1998 submission, presents the results of this analysis:

Table 5 - Characterization of Significant Bilirubin Abnormalities-All Comparative Studies

	Isolated	Cytolytic	Cholestatic	Mixed
Synercid (n = 69)	41 59.4%	11 15.9%	8 11.6%	9 13.0%
Comparator (n = 24)	7 29.2%	4 16.7%	6 26.0%	7 29.2%

Reviewer's Comment: **These data do not suggest a defined mechanism of hepatic toxicity. The applicant theorizes that Synercid may interfere with the transport of conjugated bilirubin by competitive inhibition related to the infectious process. Two mechanisms are proposed: first, Synercid may competitively inhibit the excretion of conjugated bilirubin into the bile by its carrier protein. Second, the glutathione - conjugated metabolite of quinupristin may lose its GSH moiety in the bile caniculus, releasing methylene quinupristin which is known to be a reactive intermediate. Methylene quinupristin could impair transporters by direct or indirect mechanisms. More studies in this area are needed.**

E. Adverse Events/Mortality

The applicant analyzed adverse event reports in patients with underlying hepatic insufficiency to determine whether a relationship exists. In the comparative studies, the incidence of non-venous events was higher in patients with chronic liver disease (81.3%) than in patients without chronic liver disease (68.3%). This tabulation includes patients in both the Synercid and comparator groups. When only related non-venous adverse events were considered, the incidence was comparable (18.8% for patients with liver disease and 23.5% for patients without liver disease).

The applicant also analyzed the patients with on-treatment conjugated bilirubin elevations to determine whether they were reversible. There were only 46 patients (Synercid n=35; comparator n=11) with complete data sets (i.e., pre-treatment, on-treatment and post-treatment), so statistical trends could not be determined. The rate of reversibility was somewhat lower in the Synercid group. However, it should be noted that most patients who had on-treatment conjugated bilirubin abnormalities also had abnormal readings pre-treatment. Thus, 77% of Synercid patients and 67% (6/9) of comparator patients who had abnormal pre-treatment readings also had abnormal on-treatment readings. Post-treatment conjugated bilirubin readings were in the normal range in 62% of Synercid patients and 75% (6/8) of comparator patients. Once again, no conclusions should be drawn from these results.

In a separate analysis of conjugated bilirubin levels, baseline concentrations were categorized as normal, moderately elevated (greater than ULN to 2x ULN) and greater than 2x ULN. The incidence of adverse non-venous events was highest among the 2x ULN group (73.4%). These rates for the normal group and moderately elevated group were 58.2% and 60.2%, respectively. However, when only related non-venous events were considered, the