CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-747

50-748

ADMINISTRATIVE DOCUMENTS

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

New Drug Application #50-748
Form FDA 356h
Item 1

Synercid®
(quinupristin/dalfopristin)

Item 13: *Patent Information*

Patent Information for the Synercid® (quinupristin/dalfopristin) original New Drug Application is found on the following pages.

Item 13 -Patent/Exclusivity Information

1)	Active Ingredient(s):	quinupristin/dalfopristin
2)	Strength(s):	7.5 mg/kg
3)	Trademark:	SYNERCID®
4)	Dosage Form (Route of Administration):	i.v.
5)	Application Firm Name:	Rhône-Poulenc Rorer Pharmaceuticals Inc.
6)	IND Number:	[redacted]
7)	NDA Number:	50-748 and 50-747
8)	Approval Date:	N/A
9)	Exclusivity – date first ANDA could be submitted or approved and length of exclusivity period:	Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 5 years after the date of approval of this application.
10)	Applicable patent numbers and expiration date of each:	4,668,669, Expiration January 10, 2006 4,798,827, Expiration May 21, 2007

11) To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached. We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application. The reasons that these studies or reports are insufficient are presented in the attachment as well.

Item 13. Patent Information

1)	Patent number	4,798,827
2)	Date of expiration	May 21, 2007
3)	Type of patent	drug substance; drug product
4)	Name of patent owner	Rhône-Poulenc Rorer S.A.
5)	U.S. representative	Rhône-Poulenc Rorer Pharmaceuticals Inc.

The undersigned declares that Patent No. 4,798,827 covers the formulation, composition, and/or method of use of Applicant's Synercid® (quinupristin/dalfopristin) product. This product is the subject of this application for which approval is being sought.

Signed:
Name: Ross J. Oehler
Title: Assistant General Counsel, Patents and Trademarks
Rhône-Poulenc Rorer Pharmaceuticals Inc.

Date: 9/4/97

50-747

EXCLUSIVITY SUMMARY for NDA # 50-748 SUPPL # —

Trade Name SYNERCID IV **Generic Name** Quinupristin/dalfopristin
Applicant Name Rhone Poulenc Rorer **HFD-**520.

Approval Date Sept 21, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

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

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # JRV304 } skin/skin structure

Investigation #2, Study # JRV305 }

Investigation #3, Study # 301, 398, 398B, 399 } VREF indication

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_/
Investigation #2	YES /___/	NO /_/
Investigation #3 All (4)	YES /___/	NO /_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_/
Investigation #2	YES /___/	NO /_/
Investigation #3 All (4)	YES /___/	NO /_/

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

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # QRV304

Investigation #2, Study # QRV305

Investigation #3, Study # 301, 398, 398B, 399

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [ ] YES /X/ ! NO /__/ Explain: ____

Investigation #3 [ ] YES X

Investigation #2

IND # [ ] YES /X/ ! NO /__/ Explain: ____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ ! NO /X/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /X/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

/S/ 9-15-99

Signature Date

Title: Prog Mgr.

/S/ 9/17/99

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	50747	**Trade Name:**	SYNERCID(DALFOPRISTIN/QUINUPRISTIN)IV 50
Supplement Number:		**Generic Name:**	DALFOPRISTIN/QUINUPRISTIN
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	Synercid is indicated for the treatment of patients with serious or life-threatening infections associated with vancomycin-resistant Enterococcus faecium (VREF) bacteremia. Synercid has been approved for marketing in the US for this indication under FDAs accelerated approval regulations.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication, but is inadequate to support pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

See comments on NDA 50-748. (9-15-99) Synercid was used in a limited number of pediatric patients under emergency use conditions at a dose of 7.5 mg/kg q8h or q12h. However, safety and effectiveness of Synercid in patients under 16 years of age has not been established.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN DILLON-PARKER

/S/ 9-15-99

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	50748	**Trade Name:**	SYNERCID (DALFOPRISTIN/QUINUPRISTIN)IV 5
Supplement Number:		**Generic Name:**	DALFOPRISTIN/QUINUPRISTIN
Supplement Type:		**Dosage Form:**	
Regulatory Action:	AP	**Proposed Indication:**	Complicated skin and skin structure infe

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

This application is approved for the skin and skin structure indication. The indications l [redacted] infections caused by Staphylococcus aureus were submitted for review and found not approvable in the AE letter. The indication, which also will appear in the labeling, Vancomycin-resistant Enterococcus faecium, was found approvable under N50-747 on 3/5/98. Pediatric studies have not been conducted with Synercid. Studies are part of the Phase 4 approval action and will be further discussed with the sponsor. A new chemistry manufacturing site has been found acceptable which allows for the approval of this application at this time.

Will discuss pediatric studies with sponsor as application progresses, Currently under a withhold approval due to a failed CMC inspection.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN DILLON-PARKER

Signature /S/ — Date 9-15-99

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: March 5, 1998

TO: Murray M. Lumpkin, M.D.
Acting Director, Office of Drug Evaluation IV
Center for Drug Evaluation and Research

FROM: Gary K. Chikami, M.D. /S/
Director, Division of Anti-Infective Drug Products

SUBJECT: NDA 50-747 SYNERCID I.V. (quinupristin/dalfopristin)

ASSESSMENT

Rhone-Poulenc Rorer Pharmaceuticals Inc. has submitted NDA 50-747, an original new drug application for SYNERCID I.V. (quinupristin/dalfopristin), a fixed combination of two semisynthetic streptogramin antibiotics, for intravenous administration in the treatment of infections due to vancomycin-resistant Entercoccus faecium.

CMC

There are several outstanding issues that were identified in the Establishment Inspection Report for [redacted] the facility that manufactures the final drug product. The facility was inspected by the [redacted] and significant CGMP deficiencies that were noted included:

[redacted]

On the basis of these and other CGMP deficiencies, the District has forwarded a recommendation to withhold approval of NDA 50-747 and the related NDA 50-748. The Division of Manufacturing and Product Quality concurs with the recommendation from the District.

PHARMACOLOGY

Acute, subacute and chronic (up to six months) toxicology studies have been conducted in mice, rats and monkeys with SYNERCID. The principle toxicities that were observed included reactions at the injection site, including phlebitis, ulceration and necrosis, liver toxicity, renal toxicity and bone marrow toxicity. The injection site reactions were related to the concentration of the solution and the duration of the infusion. The toxicities appeared to be reversible after discontinuation of dosing.

Dalphopristin was associated with increased chromosome abnormalities in Chinese hamster ovary cells. Quinupristin and SYNERCID produced ambiguous results. The compounds were not clastogenic or mutagenic in four other genotoxicity assays. Long term carcinogenicity assays have not been conducted.

Segment I , segment II and segment III reproductive toxicity studies have been conducted with SYNERCID. No treatment-related adverse reproductive or teratogenic effects were observed. A small number of abnormalities occurred in both treated and control groups and because some of the abnormalities had been observed in historical control animals from previous studies, it was concluded that the abnormalities seen could not be attributed to drug treatment. On the basis of these results, Pregnancy Category B has been recommended in the package insert.

MICROBIOLOGY

SYNERCID is a combination of two semisynthetic streptogramin antibiotics. The mechanism of action is inhibition of protein synthesis. The two components have different binding sites at the bacterial ribosome, and the two components show synergistic activity. The spectrum of activity of the product is limited to gram positive organisms. This activity may be bacteriocidal or bacteriostatic, depending on the organism. The product does exhibit a post-antibiotic effect, the length of which may vary depending upon the dose and target organism. Organisms may show intrinsic resistance (e.g., Enterococcus faecalis) or may acquire resistance through either chromosomal or extra-chromosomal mechanisms.

BIOPHARMACEUTICS

SYNERCID is a combination of quinupristin and dalfopristin, both of which are converted in vivo to active metabolites. Fecal excretion constitutes the major elimination route for both compounds and their metabolites. The pharmacokinetics of the components and their metabolites are complex and are extensively reviewed in the Biopharmaceutics Review.

There are several outstanding issues in regard to Biopharmaceutics.

1. Adequate pharmacokinetic information is not available for pediatric patients. Phase 4 studies should be conducted to define the pharmacokinetics in pediatric patients.
2. While the effect of hepatic impairment on the pharmacokinetics of SYNERCID has been studied, adequate data on the dose adjustment in this patient population are not available. Therefore no recommendation can be made in regard to dose adjustment in this patient population. This issue should be addressed in phase 4 studies.
3. The product is an inhibitor of CYP3A4. Drug interaction studies have been conducted in vitro and in vivo for cyclosporine. On the basis of these results a recommendation for monitoring of cyclosporine levels and dose reduction has been made in the package insert. For other drugs metabolized by CYP3A4 and for which there is a potential interaction, no clinical studies have been conducted. A precaution statement has been included in the package insert on this potential interaction. The applicant should systematically study this issue as part of their phase 4 development of the product.

CLINICAL

The applicant has submitted the results from four treatment use studies in support of the safety and efficacy of SYNERCID for the treatment of infections due to vancomycin- resistant Enterococcus faecium. The studies were non-comparative. There are no currently approved agents for the treatment of infections due to this organism and there is no universally accepted standard of care regimen. The applicant has submitted a review of the scientific literature on the epidemiology and treatment of this infection, however, because of differences in study design, quality of information collected and patient populations studied, clinical response rates, including estimates of mortality, with which to make valid comparisons to the data collected in the SYNERCID studies could not be constructed.

In the clinical studies there were a large number of subjects who did not fulfill the inclusion/exclusion criteria and the criteria for evaluability. In addition, because of the nature of the patient population (most subjects had underlying illness that contributed significant co-morbidity and contributed to the overall mortality) a large number of subjects died during therapy. These factors made estimation of the clinical response rate difficult. This uncertainty and the lack of a concurrent control made it difficult to draw any conclusion regarding the efficacy of SYNERCID. The overall assessment is that substantial evidence to support the effectiveness of SYNERCID has not been provided by these studies.

The studies do provide evidence that treatment with SYNERCID does have an effect on clearance of bacteremia in patients with or without an identified source of infection. Patents with bacteremia are at highest risk and represent the population for whom there is the most need of a therapeutic agent. For infections clinical benefit is demonstrated by cure of the site of infection as demonstrated by resolution on appropriate follow-up or a decrease in mortality. Clearance of bacteremia, however, may be considered to be a surrogate endpoint that is likely to predict clinical benefit. Given the life-threatening nature of this infection, the need for effective therapy

and the demonstrated effect on the surrogate endpoint (clearance of bacteremia), consideration for approval under the Accelerated Approval Regulations is recommended by the division. As part of such an approval, the applicant would be required to conduct studies to confirm the clinical benefit of treatment with SYNERCID. The confirmatory study must be conducted with due diligence and should be underway at the time of approval.

On February 19, 1998, this application was discussed at a meeting of the Anti-Infective Drug Products Advisory Committee. The committee concluded (by a vote of 10 to 0) that the data did not support conclusion that safety and efficacy had been demonstrated, however, because of life-threatening nature of the condition, lack of alternatives and the effect on clearance of bacteremia, they felt that the product should be available and recommended (by a vote of 9 to 1) that the application for the treatment of vancomycin-resistant E. faecium should be approved.

Other issues that should be addressed in phase 4 studies include safety and efficacy in pediatric patients and the systematic collection of information on the emergence of resistance to SYNERCID.

ACKNOWLEDGMENT

I would like to acknowledge the outstanding work of the review team on priority New Drug Application. Through their dedication and hard work, they have been able to complete the review of this complex application, including presentation to the Anti-Infective Drug Products Advisory Committee, within six months. The reviewers on this application are: Mr. James Timper, Dr. David Katague, Dr. Ken Seethaler, Dr. Robert Osterberg, Dr. Fred Marsik, Dr. Al Sheldon, Dr. He Sun, Dr. Frank Pelsor, Dr. Liji Shen, Dr. Daphne Lin, Dr. Alex Rakowsky, Dr. Susan Thompson, Mr. David Bostwick and Dr. Rosemary Roberts. The project managers, Ms. Maureen Dillon-Parker and Ms. Kim Roche and their supervisor Mr. Jim Bona and to be especially acknowledged for their outstanding management of this complex application to its completion within the six month review period.

893

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: DAN Boring, Ph.D.

FROM: Division of Anti-Infectives HFD- 520
Attention: JIM TIMPER Phone 827-2193

DATE: 10-7-97

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Synercid NDA/~~ANDA~~# 50-748

Company Name: Rhone-Poulenc Rorer Pharmaceuticals, Inc

Established name, including dosage form: quinupristin/dalfopristin 500 mg/vial Lyophilized

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Complicated skin & skin structure infections;

Initial comments from the submitter: (concerns, observations, etc.)
This is 1-P drug.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

Consult #893 (HFD-520)

SYNERCID quinupristin/dalfopristin for injection

The Committee noted sound-alike/look-alike conflicts with the following marketed products: SYNEREL, SYNEMOL and SYNTHROID. The committee felt there was a low potential for mix-up with these products since they are different dosage forms, strengths and therapeutic classes. There were no misleading aspects found.

The Committee has no reason to find the proposed proprietary name unacceptable.

/S/ , Chair

CDER Labeling and Nomenclature Committee

M E M O R A N D U M

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

DATE: February 2, 1998

FROM: Microbiology Staff
Office of New Drug Chemistry

SUBJECT: Synercid (quinupristin/dalfopristin) I.V.
NDA 50-747
NDA 50-748

TO: Gary Chikami, MD
Director
Division of Anti-Infective Drug Products HFD-520

Based on the discussions held at the internal meeting on January 29, 1998, we have the following understandings:

1) The NDA 50-748, classified as 1P, is indicated for the treatment of complicated skin and skin structure infections,

2) The subject combination drug may offer therapeutic benefit in cases where no other drug(s) do, and where progression of the disease condition can lead to serious medical consequences including death.

3) There is a treatment IND in effect for the subject drug for the above indications.

The Microbiology Staff, ONDC concurs that the application not be approved based on the recommendations of the CHI-DO and CDER's Office of Compliance. Reference is made to our January 27, 1998 E-mail and to Dr. Uratani's Addendum to Microbiology Review dated February 2, 1998.

We feel that the drug can be made available under the Treatment IND in cases where other therapy in inappropriate if specific labelling and instructions state that the reconstituted product must be passed through a prior to administration to the patient. The following rationale is applied to this conclusion:

[redacted](150 mg of quinupristin and 350 mg dalfopristin) and is therefore unlikely to support microbial growth as a dry dosage form.

2) The inspection observations indicate that the manufacturing process does not seem to be in a state of control, and may result in the introduction of non-sterile equipment into the process. We feel that the level of contamination introduced into the process, and perhaps the product, would be low. That is, the number of microorganisms introduced into any product container would be expected to be [redacted] is unlikely to support growth, the number or microorganisms in any vial at the time of reconstitution would likely also be low.

[redacted]

/S/ 2/2/98

Peter H, Cooney, PhD
Chief, Microbiology Staff
Office of New Drug Chemistry

/S/ 2/2/98

Brenda Uratani, PhD
Review Microbiologist
Microbiology Staff

cc:
HFD-520/Timper
HFD-520/Roberts
HFD-520/Roche
HFD-520/Dillon-Parker
HFD-830/Chen

Application: NDA 50747/000
Stamp: 05-SEP-1997
Regulatory Due: 07-DEC-1999
Applicant: RHONE POULENC RORER
500 ARCOLA RD
COLLEGEVILLE, PA 194260800
Priority: 1P
Org Code: 520

Action Goal:
District Goal: 13-JUN-1998
Brand Name: SYNERCID(DALFOPRISTIN/QUINUPRISTIN)IV 50
Estab. Name:
Generic Name: DALFOPRISTIN/QUINUPRISTIN

Dosage Form: (FOR INJECTION)
Strength: 500 MG./INJ

Application Comment: THIS IS REINSPECTION REQUEST FOR THE [redacted] DRUG PRODUCT.
CAN'T REMOVE THE FRENCH SITE TO THIS REQUEST. (on 28-MAY-1998 by J. TIMPER JR (HFD-520) 301-827-2193)

FDA Contacts: M. DILLON PARKER (HFD-520) 301-827-2125 , Project Manager
J. TIMPER JR (HFD-520) 301-827-2193 , Review Chemist
D. KATAGUE (HFD-520) 301-827-2174 , Team Leader

Overall Recommendation: WITHHOLD on 27-FEB-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 10-SEP-1999 by S. FERGUSON (HFD-324) 301-827-0062
WITHHOLD on 03-SEP-1999 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 01-SEP-1998 by J. SINGER (HFC-240) 301-827-0388

Establishment: 1018495
CATALYTICA PHARMACEUTICALS INC
US HWY 264/US HWY 11
GREENVILLE, NC

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: SVL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-JUN-1999				
SUBMITTED TO DO	23-JUN-1999	PS			
ASSIGNED INSPECTION	07-JUL-1999	PS			
INSPECTION SCHEDULED	29-JUL-1999				
INSPECTION PERFORMED	03-SEP-1999		03-SEP-1999		
DO RECOMMENDATION	03-SEP-1999			ACCEPTABLE	[redacted]
OC RECOMMENDATION	03-SEP-1999			INSPECTION ACCEPTABLE	
				DISTRICT RECOMMENDATION	

Establishment: [redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: SVL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				
SUBMITTED TO DO	28-OCT-1997	PS			
ASSIGNED INSPECTION	28-OCT-1997	PS			
INSPECTION PERFORMED	25-NOV-1997		24-NOV-1997		[redacted]

[redacted]

THE ISSUES FOUND IN THE INSPECTION.

DO RECOMMENDATION	25-NOV-1997		WITHHOLD [redacted] PREVIOUS DEVIATIONS PERSIST [redacted]
EIR RECEIVED BY OC	07-JAN-1998		
OC RECOMMENDATION	21-JAN-1998		WITHHOLD [redacted] EIR REVIEW-CONCUR W/DISTRICT
SUBMITTED TO OC	28-MAY-1998		[redacted]
SUBMITTED TO DO	29-MAY-1998 PS		
ASSIGNED INSPECTION	29-MAY-1998 PS		
INSPECTION SCHEDULED	06-JUL-1998	10-JUL-1998	
INSPECTION SCHEDULED	06-JUL-1998	10-JUL-1998	
INSPECTION PERFORMED	14-JUL-1998	10-JUL-1998	
			[redacted]
DO RECOMMENDATION	14-JUL-1998		WITHHOLD [redacted] PREVIOUS DEVIATIONS PERSIST

EI OF 5/11-7/10/98 REVEALED OBJECTIONS AS NOTED IN THE INSPECTION CONDUCTED MILESTONE.

EIR RECEIVED BY OC	14-AUG-1998	
OC RECOMMENDATION	01-SEP-1998	WITHHOLD [redacted] EIR REVIEW-CONCUR W/DISTRICT
OC RECOMMENDATION	10-SEP-1999	WITHHOLD [redacted] FACILITY (FIRM) WITHDRAWN

PER EMAIL DTD 9/9/99 FROM DAVID KATAGUE.

Establishment: [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				
OC RECOMMENDATION	28-OCT-1997			ACCEPTABLE BASED ON PROFILE	[redacted]

Establishment: 9610119
RHONE POULENC RORER
9 QUAI JULES GUESDE
VITRY-SUR-SEINE, CEDEX, FR

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: ANTIBIOTIC POTENCY TESTING (on 28-OCT-1997 by M. EGAS (HFD-322)

301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				
SUBMITTED TO DO	28-OCT-1997	GMP			
ASSIGNED INSPECTION	29-OCT-1997	GMP			
INSPECTION PERFORMED	28-JAN-1998		16-JAN-1998		
DO RECOMMENDATION	27-FEB-1998			ACCEPTABLE	
OC RECOMMENDATION	27-FEB-1998			INSPECTION ACCEPTABLE	
				DISTRICT RECOMMENDATION	

Establishment: 9615688
RHONE POULENC RORER
24 AVENUE JEAN JAURES
DECINES CHARPIEU, CEDEX, FR
DMF No: AADA:
Responsibilities: INTERMEDIATE MANUFACTURER
Profile: CRU OAI Status: NONE
Estab. Comment: FERMENTATION OF RP 74502 PRODUCT (on 28-OCT-1997 by M. EGAS (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				
SUBMITTED TO DO	28-OCT-1997	GMP			
ASSIGNED INSPECTION	29-OCT-1997	GMP			
INSPECTION PERFORMED	28-JAN-1998		07-JAN-1998		
DO RECOMMENDATION	27-FEB-1998			ACCEPTABLE	
OC RECOMMENDATION	27-FEB-1998			INSPECTION ACCEPTABLE	
				DISTRICT RECOMMENDATION	

Establishment: 9610113
RHONE POULENC RORER INC
35 AVE JEAN JAURES
VILLENVEUVE LA GARENNE, CEDEX, FR
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment: SYNTHESIS (on 28-OCT-1997 by M. EGAS (HFD-322) 301-594-0095)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				
SUBMITTED TO DO	28-OCT-1997	GMP			
ASSIGNED INSPECTION	29-OCT-1997	GMP			
INSPECTION PERFORMED	28-JAN-1998		21-JAN-1998		
DO RECOMMENDATION	27-FEB-1998			ACCEPTABLE	
OC RECOMMENDATION	27-FEB-1998			INSPECTION ACCEPTABLE	
				DISTRICT RECOMMENDATION	

Establishment:
DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

Profile: CRU OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-OCT-1997				[redacted]
SUBMITTED TO DO	28-OCT-1997	GMP			
ASSIGNED INSPECTION	29-OCT-1997	GMP			
INSPECTION PERFORMED	28-JAN-1998		13-JAN-1998		
DO RECOMMENDATION	27-FEB-1998			ACCEPTABLE	
OC RECOMMENDATION	27-FEB-1998			INSPECTION ACCEPTABLE	
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 50748/000**
Stamp: **05-SEP-1997** Regulatory Due: **07-DEC-1999**
Applicant: **RHONE POULENC RORER**
500 ARCOLA RD
COLLEGEVILLE, PA 194260800

Priority: **1S** Org Code: **520**
Action Goal: District Goal: **05-AUG-1998**
Brand Name: **SYNERCID**
(QUINUPRISTIN/DALFOPRISTIN) IV
Established Name:
Generic Name: **QUINUPRISTIN/DALOPRISTIN**
Dosage Form: **INJ (INJECTION)**
Strength: **350MG/150MG IN 10ML**

FDA Contacts: ID = , **Project Manager**
J. TIMPER JR **(HFD-520)** **301-827-2193** , **Review Chemist**
D. KATAGUE **(HFD-520)** **301-827-2174** , **Team Leader**

Overall Recommendation:

WITHHOLD on 03-SEP-1999 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 01-SEP-1998 by J. SINGER (HFC-240) 301-827-0388
WITHHOLD on 27-FEB-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1018495**
CATALYTICA PHARMACEUTICALS
US HWY 264/US HWY 11
GREENVILLE, NC
DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **03-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **01-SEP-1998**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRIC**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **18-SEP-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**
DRUG SUBSTANCE STERILITY TESTER

Establishment: **9610119**
RHONE POULENC RORER
9 QUAI JULES GUESDE
VITRY-SUR-SEINE, CEDEX, FR

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE OTHER TESTER**

Establishment: **9615688**
RHONE POULENC RORER
24 AVENUE JEAN JAURES
DECINES CHARPIEU, CEDEX, FR

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **INTERMEDIATE MANUFACTURER**

Establishment: **9610113**
RHONE POULENC RORER INC
35 AVE JEAN JAURES
VILLENVEUVE LA GARENNE, CEDE

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**

Responsibilities: **INTERMEDIATE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-FEB-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved : OMB No. 0910-0014
Expiration Date: December 31, 1999
See OMB Statement on Reverse

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect.(21 CFR 312.40).

1. NAME OF SPONSOR
Rhône-Poulenc Rorer Pharmaceuticals, Inc.

2. DATE OF SUBMISSION
30-Aug-99

3. ADDRESS (Number, Street, City, State and Zip Code)
500 Arcola Road
Collegeville, PA 19426

4. TELEPHONE NUMBER (Include Area Code)
(610) 454- 5471

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)
Synercid (quinupristin/dalfopristin)

6. IND NUMBER (If previously assigned)

7. INDICATION(S) (Covered by this Submission)
Treatment of Vancomycin-Resistant Enterococcus Faecium (VREF) Infections

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

TRIP
N(210)GC

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

Serial Number
210

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☒ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW, REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP

DDR RECEIPT STAMP

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 31 1999
MEGA DOC RM

DIVISION ASSIGNMENT:

IND NUMBER ASSIGNED:

12. CONTENTS OF APPLICATION

This application contains the following items: (check all that apply)

☒ 1. Form FDA 1571 [21 CFR 312.23 (a) (1)]

☐ 2. Table of Contents [21 CFR 312.23 (a) (2)]

☐ 3. Introductory statement [21 CFR 312.23 (a) (3)]

☐ 4. General investigational plan [21 CFR 312.23 (a) (3)]

☐ 5. Investigator's brochure [21 CFR 312.23 (a) (5)

☐ 6. Protocol(s) [21 CFR 312.23 (a) (6)]

- ☐ a. Study protocol(s) [21 CFR 312.23 (a) (6)]
- ☐ b. Investigator data [21 CFR 312.23 (a)(6)(iii)(b)] or completed Form(s) FDA 1572
- ☐ c. Facilities data [21 CFR 312.23 (a) (6)(iii(b)] or completed Form(s) FDA 1572
- ☐ d. Institutional Review Board data [21 CFR 312.23 (a) (6)(iii)(b)] or completed Form(s) FDA 1572

☐ 7. Chemistry, manufacturing, and control data [21 CFR 312.23 (a) (7)]

- ☐ Environmental assessment or claim for exclusion [21 CFR 312.23 (a) (7)(iv)(e)]

☐ 8. Pharmacology and toxicology data [21 CFR 312.23 (a) (8)]

☐ 9. Previous human experience [21 CFR 312.23 (a) (9)]

☐ 10. Additional information [21 CFR 312.23 (a) (10)]

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ Yes ☐ No

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION ☐ Yes ☐ No

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Phillipe Prokocimer, M.D. — Vice President, Anti-Infectives

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Philip Chaikin, Pharm.D., M.D. — Vice President, Clinical Research and Development

Marc S. Bonnefoi, DVM, Ph.D. — Vice President, Non-Clinical Safety Assessment

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that compiles with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

John J. Savarese, M.D., Ph.D.

Director, Regulatory Affairs

17. SIGNATURE OF SPONSOR'S AUTHORIZED REPRESENTATIVE

18. ADDRESS (Number,Street,City,State and Zip Code

500 Arcola Road - P.O. Box 1200

Collegeville, PA 19426-0107

19. TELEPHONE NUMBER (Include Area Code)

(610) 454- 5471

20. DATE

30-Aug-99

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001

MEMORANDUM

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

DATE: May 21, 1998

FROM: Maureen P. Dillon-Parker
Project Manager, HFD-520

SUBJECT: NDA 50-747 - Synercid IV

TO: NDA 50-747/File

An informal teleconference was held with the Sponsor, Rhone Poulenc Rorer (RPR), on May 5, 1998. The attendees from FDA were: Rosemary Roberts, Susan Thompson, Alex Rakowsky and Maureen Dillon-Parker; the attendees from RPR were Jack Savarese, Mark Learn, Mary Elicone, and George Talbot. The purpose of this discussion was to explore additional options for a clinical confirmatory trial. Specifically, the Division would like to see an active comparative study in lieu of or in addition to a dose response study to support approval under the Subpart H regulations.

The Division proposed comparing Synercid to a panel of possible drug combinations, depending on the patient's organism susceptibility. The three drug combinations suggested were as follows:

a. High dose ampicillin + an aminoglycoside
b. Doxycycline + chloramphenicol
c. Rifampin +ciprofloxacin + gentamicin

The Divison had a long discussion with the sponsor and requested that they consider a study of this type and/or prepare a counter proposal for discussion with the Division.

cc:
Orig NDA 50-747
HFD-520/Div File
HFD-520/TLMO/Roberts
HFD-520/MO/Rakowsky
HFD-520/MO/Thompson
HFD-520/PMS/Dillonparker/5-26-98

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved : OMB No. 0910-0014
Expiration Date: December 31, 1999
See OMB Statement on Reverse

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Rhône-Poulenc Rorer Pharmaceuticals, Inc.

2. DATE OF SUBMISSION
23-Nov-98

3. ADDRESS (Number, Street, City, State and Zip Code)
500 Arcola Road
Collegeville, PA 19426

4. TELEPHONE NUMBER (Include Area Code)
(610) 454- 5471

5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)
Synercid (quinupristin/dalfopristin)

6. IND NUMBER (if previously assigned)

7. INDICATION(S) (Covered by this Submission)
Treatment of Vancomycin-Resistant Enterococcus Faecium (VREF) Infections

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

Serial Number
172

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that appl

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND
☐ RESPONSE TO CLINICAL HOL

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOG
☐ PHARMACOLOGY/TOXICOLOG
☐ CLINICAL

IND SAFETY REPORT(S)
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATIO
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENC
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW, REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b)
☐ TREATMENT PROTOCOL 21 CFR 312.35(a)
☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
50-747 / 50-748

APPLICATION INFORMATION

NAME OF APPLICANT Rhone-Poulenc Rorer	DATE OF SUBMISSION July 29, 1999
TELEPHONE NO. (*Include Area Code*) 610-454-5471	FACSIMILE (FAX) Number (*Include Area Code*) 610-454-5779
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*): 500 Arcola Road MS H-19 Collegeville, PA 19426	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 50-748

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*) N/A	PROPRIETARY NAME (*trade name*) IF ANY Synercid®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) quinupristin = C53H67N9O10S /dalfopristin = C34H50N4O9S	CODE NAME (*If any*) RP59500 (RP 57669/RP 54476)
DOSAGE FORM: ,	STRENGTHS: 500mg per vial
	ROUTE OF ADMINISTRATION: Intravenous

(PROPOSED) INDICATION(S) FOR USE: Complicated skin and skin structure infections; nosocomial pneumonia; community-acquired pneumonia

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Manufacturing site for drug product 6 month stability update for Catalytica. Withdrawal of Centeon LLC as a manufacturing site.

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

	This application contains the following items: (*Check all that apply*)
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3 Summary (21 CFR 314.50 (c))
	4 Chemistry section
X	A Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314 50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e g 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8 Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15 Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314 71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowlegde are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
for: John J Savarese	John J. Savarese, M.D., Ph.D. Sr. Director, Regulatory Affairs	July 29, 1999

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
500 Arcola Road, Collegeville, PA 19426	(610) 454-5471

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MEMORANDUM OF TELECONFERENCE

DATE: February 26, 1998

APPLICATION NUMBER: NDA 50-747; SYNERCID (quinupristin/dalfopristin)

BETWEEN: **Representatives from Rhône Poulenc Rorer Pharmaceuticals**

Name: Phil Chaikin, M.D., Vice President, Clinical
Max Talbott, M.D., Vice President, Regulatory Affairs
Carol Jablonski, Regulatory Affairs
Mark Learn, Regulatory Affairs
Harriett Nadler, Ph.D., Microbiology (Clinical)
A. Rodgers, Biostatistics
Ray Zhu, Ph.D., Biostatistics

AND

Representatives from the Division of Anti-Infective Drug Products, HFD-520

Name: Murray M. Lumpkin, M.D., Deputy Center Director for Review Mgmt
Diane Murphy, M.D., Office Director, ODE IV
Gary K. Chikami, M.D., Division Director
Rosemary Roberts, M.D., Medical Team Leader
Alexander Rakowsky, M.D., Medical Officer
Susan Thompson, M.D., Medical Officer
David Bostwick, Clinical Reviewer
Fred Marsik, Ph.D., Microbiologist
Frank Pelsor, Ph.D., Team Leader, Biopharmaceutics
Albert Sheldon, Ph.D., Team Leader, Microbiology
Liji Shen, Ph.D., Statistical Reviewer
Daphne Lin, Ph.D., Team Leader, Statistics
Kim Roche, Project Manager
Maureen P. Dillon-Parker, Regulatory Health Project Manager

SUBJECT: To discuss the March 5th Action for this application

DISCUSSION POINTS:

- Division would like to take an approvable action on the application next Thursday (March 5, 1998).
- It was agreed that due to the outstanding chemistry issues the application could not be approved.
- The Advisory Committee did not find that the data from the clinical studies demonstrated that Synercid is safe and effective for the treatment of VREF infections. They did feel that there is an unmet need for the product and that there was evidence of activity and, therefore, recommended that it be approved.

- The application will be approved under the accelerated approval regulations (21 CFR 314, Subpart H), and, thus, clinical confirmatory study(ies) will be required.

- It was felt that Synercid had demonstrated an effect on the surrogate endpoint of clearance of bacteremia. The clinical benefit of Synercid must be shown in the clinical confirmatory trial. RPR may want to use resolution of the infection at the site of infection as a measurement of clinical benefit.

- The design of the clinical confirmatory trial will have to be discussed further. A draft of the trial will be needed prior to next Thursday's action. The trial must be ongoing at the time of approval. RPR commited to complete the outline of the trial by next Wednesday (March 4, 1998).

- A randomized, prospective trial would be better than historical data.

- The appropriate outcome and comparator (possibly doxycycline and chloramphenicol) regimen for the trial will have to be discussed further.

- Because there is no regimen approved for this indication, the question arises whether an equivalence vs a superiority trial would provide adequate data to confirm the clinical benefit of Synercid. If designed as a superiority trial and Synercid is superior to the comparator this would provide confirmation of the clinical benefit. If designed as an equivalence trial and Synercid is found equivalent, then additional data would be required to show that the control regimen is safe and effective (i.e., through the literature).

- RPR should focus on keeping the study blinded. They should consider regimens that can be blinded to the investigator.

- Once approved Synercid would become the standard for other regimens seeking the same claim.

- Study 301 could be used as a model in developing the clinical confirmatory trial. Patients who are failing all other treatments would not necessarily be enrolled in this trial.

- A mortality benefit would be the easiest to measure, however, a prospective study with tightly defined clinical endpoints (resolution of infection at the infection site) is also a consideration.

- If the clinical confirmatory trial demonstrates equivalence, a dose response study could be conducted to provide supportive information. However, it was noted that dose-response designs have not been used much in phase III trials for anti-infective agents.

- Clearly RPR would like to have a superiority outcome. RPR will research further the combination of doxycycline/chloramphenicol.

- According to RPR, at the 10 mg/kg dose of Synercid a transaminase effect was seen, therefore, RPR went back to the 7.5 mg/kg dosing.

  RPR will look into the literature and come up with some proposals.

- A March 5th action will be taken on NDA 50-747. This action will include draft labeling for the VREF indication only. FDA will address any issues with the other indications (nosocomial pneumonia and skin and skin structure infections), NDA 50-748, following action on this application.

- Mr. Learn will contact Ms. Dillon-Parker to follow-up on Monday or Tuesday of next week.

/S/

Maureen P. Dillon-Parker
Project Manager

MEMORANDUM OF TELECONFERENCE

DATE: April 2, 1998

APPLICATION NUMBER: NDA 50-747; SYNERCID (quinupristin/dalfopristin)

BETWEEN: **Representatives from Rhône Poulenc Rorer Pharmaceuticals**

Name: Jack Savarese, M.D., Regulatory Affairs
Mark Learn, Regulatory Affairs
George Talbott, M.D., Clinical Research

AND

Representatives from the Division of Anti-Infective Drug Products, HFD-520

Name: Diane Murphy, M.D., Office Director, ODE IV
Gary K. Chikami, M.D., Division Director
Rosemary Roberts, M.D., Medical Team Leader
Alexander Rakowsky, M.D., Medical Officer
Susan Thompson, M.D., Medical Officer
David Bostwick, Clinical Reviewer
Liji Shen, Ph.D., Statistical Reviewer
Daphne Lin, Ph.D., Team Leader, Statistics
Maureen P. Dillon-Parker, Regulatory Health Project Manager

SUBJECT: To discuss the proposed clinical confirmatory trial

DISCUSSION POINTS: (See attachment which was provided to RPR following the meeting)

Note: RPR has proposed the following arms in the dose response study which is the subject of this teleconference:

Regimen A = 7.5 mg/kg IV Synercid q 8 hours
Regimen B = 7.5 mg/kg IV Synercid q 12 hours plus ampicillin 2 gm IV q 6 hours
Regimen C = 7.5 mg/kg IV Synercid q 8 hours plus ampicillin 2 gm IV q 6 hours

- FDA stated that a dose response trial would be acceptable.
- However, the ability to demonstrate a dose response is of concern for the following reasons:

  a. The proposed doses of Synercid may not be sufficiently different. The study as proposed may not be able to show a difference between arm B and arm C.

b. Due to the uncertainty in the pK/pD relationship, it may be hard to show a dose response. Demonstrating a detectable difference in success versus failure as the measured outcomes may be difficult.

- The Division originally proposed that a comparative study would be performed with a dose-response trial providing supportive data.

- The Division expressed concerns that if the trial as proposed fails, then the clinical benefit of treatment with Synercid for VREF will not have been verified.

- The Division reviewed the proposed dosing regimens and asked whether there was any evidence from previous trials (phase 2 trials) that there are differences in clinical response rates in the proposed dosing regimens of Synercid. RPR stated that due to the various study designs, this aspect was not addressed and that *a priori* they cannot determine this.

The Division stated that in general the dose response trial can provide data to verify the clinical benefit of Synercid. Some caveats were pointed out:

a. A dose response trial may be more complex in design. Pharmacokinetic/pharmacodynamic data would be important in the design of the trial.

b. The proposal to use a combination (i.e., Synercid and Ampicillin) raises some issues.

c. The accelerated approval (Subpart H) for Synercid is for monotherapy, while in the proposed trial combination therapy is used. The indication would have to be revised to reflect combination therapy if the data support this.

- RPR stated that there is a feasibility problem with using a standard-of-care (SOC) control arm that may differ at each center. RPR prefers to use a dose response approach (as outlined in their facsimile of March 4, 1998) and would look to improve the design.

- The Division stated that the confirmatory study should provide a definitive answer with regard to the clinical benefit of Synercid. A trial that demonstrates superiority would provide the clearest demonstration of benefit.

- If C beats A & B, then there is the combination issue. If A & C beat B, then a dose response may not have been demonstrated. If all three do the same, then the question becomes what does Synercid contribute. The Division feels that this trial design is risky.

- RPR stated that for the analysis of the results if 2 dose regimens are evaluated, then superiority must be demonstrated; if 3 dose regimens are evaluated, then a trend must be demonstrated.

- RPR would like to design a dose response trial with monotherapy. RPR may select 2-3 dose regimens to see if there is a pD difference because selecting a non-dichotomous parameter is difficult. The Division suggested that RPR choose a low, medium and high dose, and select an appropriate patient population. RPR might select 7.5 mg/kg q 12 hours as the low dose, 7.5 mg/kg q 8 hours and 10 mg/kg q 8 hours, however, the 10 mg/kg q 8 hours dosing has a poor adverse reaction profile.

- RPR noted that since the study would be blinded, the investigator could discontinue therapy at the blinded (10 mg/kg) dose and continue with the labeled dose.

- The Division reminded RPR that for a superiority trial the analysis will be performed on Intent-to-Treat (ITT) population with strict inclusion/exclusion criteria. In addition, patients lost to ADR's would be considered failures.

- RPR felt that an external safety monitoring board could be set up to handle safety issues.

- RPR had spoken with several infectious disease physicians (i.e., consultants to RPR) to get their input into possible study drug choices. RPR found that most of their consultants would use Synercid, however, if this was not an option, then they would use the combination chloramphenicol/ doxycycline (C/D). However, some consultants were not enthusiastic about using C/D because they felt that the utility may already be reduced due to *in-vitro* resistance. Most felt that a cell wall active drug was a better choice.

- The Division stated that there was no disagreement over the scientific issues, however, they questioned what would physicians use if Synercid was not available. If the study doesn't provide clinical confirmation of effectiveness, then it is possible that the claim could be removed from the product. RPR felt that if Synercid was not available then ethically C/D would be considered.

- RPR stated that they would like to move forward with the dose response study. The Division stated that they should take the caveats under consideration and also provide a rationale for the dosing selections. RPR should collect additional information from Phase 2 and the retrospective Phase 3 emergency use study and any other studies provide a rationale for the proposed doses (7.5 q 8 hour and 7.5 q 12 hour doses). Toxicity information should be provided on the 10 mg/kg dosing.

- The Division stated that RPR should address the following: the analysis of the 3-arm study and multiple pair wise comparisons vs trend analysis.

- The Division noted to RPR that a 3-arm (3 doses of Synercid) study is desirable and a larger population may be needed. With a 2 arm (2 doses of Synercid) study, statistical superiority must be demonstrated. The primary analysis will be performed on the ITT population. All three inclusion criteria as outlined must be met for the ITT analysis. These must be prospectively defined.

- RPR should provide a strict definition of Clinical Bacterial infection.

- The Division will be meeting to finalize an Agenda for the Nosocomial pneumonia and skin and skin structure indications teleconference.

- RPR should provide the Division with a timeline for when they anticipate the study starting and ending. RPR estimates that enrollment will take over a year.

- The Division reminded RPR that there are several outstanding issues regarding the chemistry portion of the application that must be resolved prior to taking a final action on the applications.

- RPR stated that the revised labeling will be submitted shortly and that the information requested on bilirubin will be provided on April 10th.

/S/

Maureen P. Dillon-Parker
Project Manager

/S/

Gary K. Chikami, M.D.
Division Director

MEMORANDUM OF TELECONFERENCE

DATE: May 19, 1998

APPLICATION NUMBER: NDA 50-748; SYNERCID (quinupristin/dalfopristin)

BETWEEN: **Representatives from Rhône Poulenc Rorer Pharmaceuticals**

Name: J. Savarese, Director, Regulatory Affairs
G. Talbot, Director, Clinical Development
M. Learn, Senior Manager, Regulatory Affairs
H. Nadler, Director, Clinical Developent
R. Zhu, Director, Biostatistics
A. Acusta, Manager, Biostatistics
K. Agar, Sr. Manager, Regulatory Affairs
T. Bekele, Director, Clinical Development
MB Dorr, Associate Director, Clinical Development
R. Livesay, Strategic Marketing
K. Poulos, Director, Strategic Marketing
P. Prokocimer, Vice President, Anti-Infective Clinical

AND

Representatives from the Division of Anti-Infective Drug Products, HFD-520

Name: A. Rakowsky, Medical Officer
D. Bostwick, Clinical Reviewer
M. Dillon-Parker, Regulatory Health Project Manager

SUBJECT: To discuss the Phase 3 Protocols (Study 309/Central Catheter-related infections; Study 312/Chronic Osteomylitis; Study 313/Prosthetic joints)

DISCUSSION POINTS:

Study 309 - Central Catheter-related infections

To discuss the addendum submitted March 4, 1998 (protocol dated 11/18/97), which provides for a revised study protocol. The protocol is for the study of Synercid versus vancomycin or nafcillin in the treatment of patients with central catheter-related infections.

The following points were conveyed to RPR:

- TWO positive blood cultures or two positive cultures of any type are needed to be enrolled into the study. Two positive cultures for coagulase-negative *Staphylococcus* or two positive cultures for *Staphylococcus aureus* are required.

- The catheter tip must grow the SAME organism as the blood culture, not a SIMILAR organism as proposed.

- Patients without at least two positive cultures should be excluded.

- Molecular typing is not required. Susceptibility patterns are acceptable.

- Anti-fungal as well as anti-bacterial use should be listed in the concomitant medications section. Collecting this information on the non-antibacterial page is acceptable.

- "Oral relay therapy" is discouraged. If it is used, then strict switch criteria and a strict list of "acceptable" oral agents must be provided. If there is a good evaluation at the time of the switch and the switch criteria is met, then the switch is acceptable. The follow-up evaluation must be at the time when all antibiotics have been discontinued.

Study 312 - Chronic Osteomylitis

This study will compare Synercid versus standard therapy in the treatment of patients with chronic osteomyelitis.

The following points were conveyed to RPR:

- The study is designed with a comparator arm, although it is an open-label study. While a comparator arm may be used to see why efficacy rates overall are low, approval cannot be granted based on an unpowered comparison of Synercid to comparator. The way the current study protocol is designed, the 70% efficacy rate (noted in the Points-to-Consider document) would have to be met and failure to demonstrate this would lead to non-approval, regardless of what the comparator arm shows.

- Any available data regarding the penetration of Synercid into bone and joint fluid (i.e., pK/pD information) should be submitted. If no data is available then a study proposal should be submitted.

- The Points-to-Consider (PTC) document suggests that pK/pD data be available. If the efficacy rates are in mid to high 60's and there is no pK/pD data, then it would be difficult to be lenient about the 70% criteria.

- The test-of-cure (TOC) visit must be one year post-therapy as reflected in the PTC and IDSA Guidances. The current protocol uses 4-6 months.

- Regarding to concomitant therapy:

  a. Clearly state which drugs (like aztreonam) are allowed and at what doses.

  b. In situations where NO gram positive pathogens are found, the patient will be considered not fully evaluable. The study should be powered for patients where the effect of Synercid or comparator can be seen.

  c. Due to the small number of patients, either oral relay or i.v. should be selected for all patients. Splitting into various subgroups may underpower this study. If some patients are switched to oral, there must be good switch criteria and the switch must be well documented.

  d. The study allows for use of gram-positive active oral agents for other illnesses in the post-therapy period. The 10-day limit for any one course is acceptable, however the number of courses should be limited. It was suggested that 1 course every quarter (i.e., 3 months) is acceptable for osteomylitis.

- The Division would like to see the algorithms that will be used by the Steering Committee prior to the study being completed. Requested that the potentially evaluable patients in question that are sent to the Steering Committee also be sent to the Division.

- Submit an "interim analysis" plan and the Division will review and comment. Include any proposed penalty for the look or a rationale as to why no penalty should be imposed. The interim look would be to check the evaluability rate and possibly to increase the sample size. If the protocol design or the conduct of the study changes after the interim look, then the patients enrolled are not as valuable as the new patients being enrolled. If the interim analysis is conducted and the evaluability rates are lower than expected and the sample size is increased without changing the protocol then there is no problem. It should be clearly stated in the protocol how this will be handled.

- All isolates should be tested for MLSb constitutive resistance.

- The quality of life questionnaire cannot be used to support a labeling change.

Study 313 - Prosthetic joints

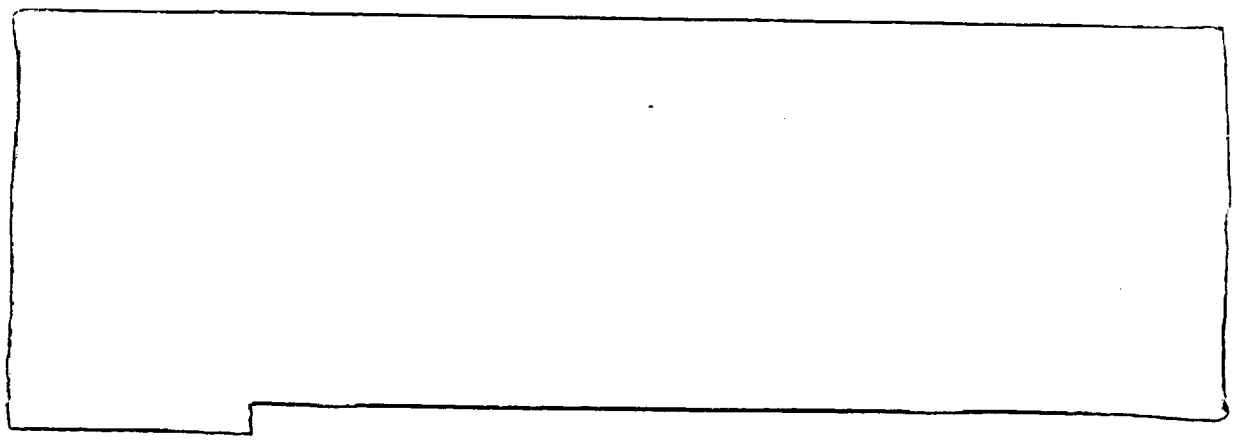
This study would compare Synercid to standard therapy in the treatment of patients with infected prosthetic joints.

The following points were conveyed to RPR:

- As currently written, a 90% efficacy rate will be the standard that the Synercid arm must reach, regardless of results from the comparator arm. If the comparator arm is used to demonstrate equivalence, then the study must be powered appropriately.

- The endpoint should be longer then "at least one week post-therapy..." The IDSA guidelines state that 10-14 weeks post-therapy is more appropriate. The minimum is 10-weeks for pathogen re-accumulation. RPR should put in writing why the endpoint chosen is different than that recommended by IDSA. It was decided that further discussions about the appropriate timing of the TOC visit are needed.

- Regarding concomitant therapy:

  a. 

  b. If "oral relay therapy" is done, then all patients should be allowed to do so, and there should be strict switch criteria.

  c. Any use of antibacterial agents should be discouraged in the post-antibiotic period unless they are narrow spectrum and have no staphylococcus coverage. Use of such agents, especially if they have good staphylococcus coverage, could lead to patients being found unevaluable.

- All isolates should be tested for MLSb constitutive resistance.

- Regarding the interim analysis, RPR should either propose what penalty they will pay for this, or provide a rationale for why one is not necessary.

- Again, the quality of life questionnaire cannot be used to support a labeling change.

GENERAL PROTOCOL COMMENT:

- The sponsor states that "additional information" will be gathered on patients who develop arthralgias and/or myalgias. RPR stated that the case report forms still just being designed. FDA stated that they would like to see them and would plan to submit them to the Rheumotology Division for comment.

/S/

Maureen P. Dillon-Parker
Project Manager

/S/

Alexander Rakowsky, M.D.
Medical Officer

MEMORANDUM OF TELECONFERENCE

DATE: October 8, 1998

APPLICATION NUMBER: NDA 50-747; SYNERCID (quinupristin/dalfopristin)

BETWEEN: **Representatives from Rhône Poulenc Rorer Pharmaceuticals**

Name: Jack Savarese, M.D., Regulatory Affairs
Mary Elicone, Regulatory Affairs
George Talbott, M.D., Clinical Development
Lisa Goldberg, Study Manager
Ray Zhu, Ph.D., Biostatistics

AND

Representatives from the Division of Anti-Infective Drug Products, HFD-520

Name: Rosemary Roberts, M.D., Medical Team Leader
Alexander Rakowsky, M.D., Medical Officer
Susan Thompson, M.D., Medical Officer
David Bostwick, Clinical Reviewer
Fred Marsik, Ph.D., Microbiologist
Daphne Lin, Ph.D., Team Leader, Statistics
Erica Brittain, Ph.D., Statistical Reviewer
Maureen P. Dillon-Parker, Regulatory Health Project Manager

SUBJECT: To discuss the Statistical issues for the vancomycin-resistant *Enterococcus faecium* (VREF) Clinical Confirmatory Protocol.

DISCUSSION POINTS:

- The interim analysis is a good tool for stopping a study or if safety is a concern. It is not acceptable to use the analyses for re-estimating the sample size because there may be an introduction of bias. Suggested that RPR start with a larger study and if there is a great efficacy response then the study could be stopped early.

- At this time the Division does not support the decision to use sample size re-estimation based on an interim observed treatment difference. The use of new methodology cannot be endorsed unless it has appeared in a peer-reviewed journal, and, additionally, reached some level of acceptance in the community.

- RPR stated that this is a severe disease and recruitment is slow. There is concern that the delta may be missed. FDA stated that adaptive sample size re-estimation based on the treatment effect is not recommended.

- Regarding the statistical analysis, FDA will review all 3 points (5, 7.5 and 10mg/kg). A relationship between the points (ADR's, physiological) must be demonstrated.

- Each patient should be linked to the physiological outcome. The investigator should determine the subjects that are clinical failures versus those that failed due to an adverse event.

- A positive is not required at each point (5, 7.5 and 10mg/kg). For example, if 10 mg/kg < 7.5 mg/kg and this is due to the number of withdrawals and not efficacy, then this may be acceptable.

- Multiple comparisons adjustment to the alpha level could be set at .025 (i.e., .05/2 rather than .05/3 used in the current protocol). This is the same level of adjustment typically used in the situation where there are two simultaneous comparisons.

  There is no easy way to agree on the win situations. The process for determining a win is as follows:
  - a paired comparison that reaches this standard of statistical significance (alpha = .025, two-sided)
  - a pattern of results in the three dose levels that provides support for efficacy.

- The Case Report Form should be revised to allow for the investigator to state the reason for a failure. This is for the ITT.

- The study is an ITT study. Therefore, all patients enrolled must be analyzed. RPR will review the CRF and separate the efficacy from the safety as a reason for withdrawal.

NCCLS PRESENTATION

- The slides which Dr. Nadler plans to present look fine. RPR should also look at the Advisory Committee Presentation slides, as some of the slides presented might also be useful. Some of the slides alluded to the difficulties in conducting these studies.

CHEMISTRY MANUFACTURING FACILITIES

- Estimated time for cleaning up the chemistry deficiencies at the [redacted] manufacturing facility was briefly discussed. RPR stated that FDA compliance and RPR would be discussing issues today or tomorrow. The estimated time before [redacted] would be ready for a reinspection was not known.

GENERAL

- FDA stated that the Division reviewers would be solely concentrating on revising the Clinical Confirmatory trial (CCT). There was acknowledgment of several other issues which would need to be discussed, however, it was agreed that the CCT must be brought to closure before further discussions on additional issues can take place.

- Once agreement is reached on the CCT, the IRB will need to review the final protocol.

- An investigators meeting is scheduled for January 28-29, 1999 with an anticipated CCT start date in early February.

- A letter responding to the approvable letter will be submitted next week and a revised package insert submitted in approximately 1 month.

/S/

Maureen P. Dillon-Parker
Project Manager

MTD-3601 DILLON PARKER

TELECONFERENCE MINUTES

Meeting Date: December 8, 1998

Time: 11:00 a.m.- 12:15 p.m.

NDA# and Drug Name: NDA 50-747 - Synercid

External Participant: Rhone Poulenc Rorer Pharmaceuticals

Type of Telecon: Discussion of November 23, 1998, clinical confirmatory protocol.

Meeting Chair: Alexander Rakowsky, Clinical Reviewer

External Participant Lead: Mary Elicone, Regulatory Affairs

Meeting Recorder: Maureen Dillon-Parker, Project Manager

FDA Division of Anti-Infective Drug Products Attendees:
Gary Chikami, Division Director
Rosemary Roberts, Clinical Team Leader
Alexander Rakowsky, Medical Officer
David Bostwick, Clinical Reviewer
Maureen Dillon-Parker, Project Manager
Daphne Lin, Statistical Team Leader
Erica Brittain, Statistical Reviewer

External Attendees:

Representatives from Rhône Poulenc Rorer Pharmaceuticals

Mary Elicone, Regulatory Affairs
George Talbott, Clinical Development
Shelley Fayocavitz, Study Leader
Sharon Grey, Study Manager
Ray Zhu, Biostatistics
Sasha Zheng, Biostatistics

A. Meeting Objectives:

To discuss the November 23, 1998, revised final clinical confirmatory trial.

B. Discussion Points:

1. Requested a copy of the new and revised Case Report Form (CRF).

2. a. Requested that RPR test for MLSb constitutive resistance on all strains at a central lab. RPR stated that this would be done.

   b. The cephalosporins, when used with Synercid, appear to be synergistic in an animal MRSA model. RPR representatives believed that there was no synergy against VREF with the cephalosporins, but would consult with their microbiology staff and get back to the Division on this issue.

3. Pharmacokinetics/Pharmacodynamics: The proposed pharmacokinetic substudy (found on pages 57-58 and 72-73) has been submitted to the pharmacokinetics reviewer for comment. If there are comments, the Division will communicate these to RPR.

4. Statistical Issues:

   a. The Division stated that the assumed difference between efficacy rates of 20% may be overly optimistic. If the overall difference in efficacy rates between the low and high dosing regimens is less than 20% then the number of patients to be enrolled will be inadequate to show an effect (i.e., an underpowered study). Performing the study with the 20% assumed difference, RPR runs the risk of completing this study without showing the desired effect. RPR believes that the postulated 20% difference in efficacy rates is achievable; this is based on the homogenous population to be studied and the past data. RPR acknowledged the risk that the trial may fail if the postulated difference is not observed.

b. Stratifying: Per page 63, there will be 20 cells into which patients will be stratified (the 4 dosing regimens with the 5 indications). Agreed that stratification would be based on infection type and that there would not be stratification per study center. However, RPR discussed their consideration of a dynamic allocation scheme to avoid large imbalances at the center level. The Division expressed reservations about dynamic allocation, and stated that the analyses should reflect the study designs. RPR agreed to discuss this issue internally and to submit more details about these analyses to the Division.

c. Interim Analysis: The first look is for safety at 1/4 of the way through the trial. At the first look there is no efficacy analysis. The second look, at the middle of the study, will consider safety and efficacy. [redacted] stopping rules will be applied to the second interim look and written into the protocol.

Wording in Section 9.2.4 of page 63 on the interim analysis should be re-written by RPR to clearly outline the details about the two interim analyses. Additionally, the consequences of each look should be clearly outlined [i.e., describe what happens to the multiple comparisons if an arm is dropped for safety or futility].

Independent Safety Monitoring Board (ISMB) is the only group to get unblinded information. This Board presents its conclusion to the Steering Committee. This Committee is the liaison between the ISMB and RPR.

RPR will fax to the Division the Charter document that defines the roles and responsibilities of the ISMB, as well as, a paragraph defining the stopping rules and consequences of each look.

d. Deaths/Adverse Events: Agree that the paragraphs on page 65 dealing with these issues are acceptable. However, the Division stressed the need for the investigator to adequately document the cases showing that VREF was NOT a factor in the death of a patient, otherwise the patient will be considered a failure.

e. Primary analysis: If no apparent interaction based on informal examination, then the Mantel-Haenszel test stratified on the basis of the 5 indications will be completed. This was acceptable to the Division because there would be little power to detect an interaction.

5. **Clinical:**

a. For UTI: This is a dose response study and, thus, clean infections are necessary. Therefore, the Division proposes that only pure growth of VREF be seen as consistent with true infection. RPR agreed to make this change.

- RPR stated that this study has become quite complex and that enrollment may be difficult, due to this select group of patients. FDA understood RPR's comment but noted that although RPR would like rapid enrollment, they must consider that various doses are being evaluated and treating patients with the true disease entity is most critical. RPR will keep FDA apprised of the study enrollment numbers. Open communication throughout the study is critical.

b. Skin and Skin Structure: Dr. Rakowsky conducted a literature search and found that pure growth of VREF is not 100% necessary. However, gram stains must be added and must show presence of WBCs. RPR will modify the protocol to reflect this.

c. Central-catheter:

1. Signs and symptoms must be followed in these patients and there should be specific signs and symptoms needed for enrollment (as is the case with the bacteremia of unknown origin (BUO) patients). RPR should add the signs and symptoms to the inclusion criteria.

2. More detail is needed in regard to what combination of culture results would lead to enrollment. Agreed that bacteriological diagnosis would be based on a positive semi-quantitative catheter tip culture (growth of VREF as a sole pathogen at >15 cfu/mL) and a positive peripheral blood culture (pure growth of VREF) obtained close together [on same day] and close to the time of the study drug initiation. If collected on the same day, it was agreed that strain typing would not be necessary.

3. Repeat blood cultures must be done at least 5 days after completion of therapy to verify clearance. The protocol currently reads 2 days. This will be modified to reflect 5 days.

d. Bacteria of Unknown Origin (BUO): Again (page 32) the timing of the cultures should be closer together. The CRF should allow for detailing what work up was done to rule out a possible source.

Also, pure growth of VREF in 2 or more cultures is required.

5. Miscellaneous:

a. Test-of-Cure (TOC) should be defined as at least 5 days after completion of therapy and all TOC cultures should be done at this time, and not earlier (as presently allowed in the protocol). If there is a late TOC (beyond day 21) and documentation that there has been no antimicrobial therapy, then these patients would be acceptable.

b. On page 60 (8.1.6), failure of therapy should not be listed as an AE. If it is, the Division recommended that it be listed as "probably" related to study drug and not as "not related". Per RPR, it is Corporate policy to list these as "not related" so as to clearly separate out the lack of efficacy from the true drug-related AEs in the analyses. The Division agreed to allow it to remain as written due to RPR's Corporate policy.

6. Conclusions:

a. RPR agreed to rewrite the statistical plan and provide more detail regarding the analyses addressing the many points discussed in the telecon.

b. A development timeline will be provided to the Division.

c. A revised label will be provided for the Divisions review. A telecon to discuss the labeling will be scheduled for after the first of the new year.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

cc:
Division File
HFD-520/DivDir/Chikami/init
HFD-520/MO/Bostwick/init
HFD-520/TLMed/Roberts/init
HFD-520/MO/Rakowsky/init
HFD-725/Stat/Lin/init
HFD-725/Stat/Brittain/init
HFD-520/PMS/Dillonparker/tc\N50747.128
rd/December 8, 1998
ft/January 11, 1999

TELECONFERENCE MINUTES

Meeting Date: December 21, 1998

Time: 11:00 - 11:10 a.m.

NDA# and Drug Name: NDA 50-747 - Synercid

External Participant: Rhone Poulenc Rorer Pharmaceuticals

Type of Telecon: Discussion of December 11, 1998 submission concerning statistical issues for final Synercid Clinical Confirmatory Protocol (#396).

Meeting Chair: Alexander Rakowsky, Clinical Reviewer

External Participant Lead: Jack Savarese, Regulatory Affairs

Meeting Recorder: Maureen Dillon-Parker, Project Manager

FDA Division of Anti-Infective Drug Products Attendees:
Gary Chikami, Division Director
Rosemary Roberts, Clinical Team Leader
Alexander Rakowsky, Clinical Reviewer
Susan Thompson, Clinical Reviewer
Paul Flyer, Statistical Team Leader, DOB III, HFD-725
Mohammad Huque, Statistical Team Leader, DOB II, HFD-715
Erica Brittain, Statistical Reviewer
Maureen Dillon-Parker, Project Manager

External Attendees:
Representatives from Rhône Poulenc Rorer Pharmaceuticals
Jack Savarese, Regulatory Affairs
George Talbott, Clinical Development
Shelley Fayocavitz, Study Leader
Ray Zhu, Biostatistics
Carol Jablonski, Clinical Development
Sherry Liu, Biostatistics

A. Meeting Objectives:

To discuss the December 11, 1998, revised final clinical confirmatory trial statistical issues.

B. CONCLUSIONS:

1. It was agreed that dynamic allocation would not be used in the randomization of this trial.

2. It was agreed that the protocol should reflect the intention to use formal stopping rules to stop the trial, or to drop an arm. The specifics of the rules will be reported in an updated protocol or other document after the next DSMB meeting, prior to study initiation.

3. It was agreed that the subset analysis that excludes central catheter-related infection patients is a key secondary analysis. Approval might be considered if ALL these apply: 1) The primary efficacy analysis, using all patients, shows a dose response that is almost statistically significant; 2) The subset analysis that excludes central catheter-related infection patients results in a statistically sigificant dose-response; AND 3) the difference in results of the two analyses is apparently due to high success in central catheter-related infection patients, regardless of treatment group.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

cc: Orig NDA 50-747
Division File
HFD-520/DivDir/Chikami/init 1/21/99
HFD-520/TLMed/Roberts/init 1/21/99
HFD-520/MO/Rakowsky ATR 1/19/99
HFD-520/MO/Thompson/init
HFD-725/Stat/Lin/init 1/20/99
HFD-725/Stat/Brittain/init EB 1/13/99
HFD-715/TLStat/Huque/init
HFD-725/Stat/Flyer/init 1/21/99
HFD-520/PMS/Dillonparker/tc\N50747.dec
rd/January 4, 1999 ft/January 11, 1999

FDA-RPR Teleconference
3:00 p.m., Wednesday, February 3, 1999
Synercid® (quinupristin/dalfopristin) I.V.
NDA 50-747/748
Alternate Drug Product Manufacturing Site - Catalytica Pharmaceuticals Inc.

FDA Participants:
Maureen Dillon Parker, Project Manager
Susan Thompson, MD - Medical Officer
David Bostick - Medical Officer
Alex Rakowsky, MD - Medical Officer
Gary Chikami, MD - Division Director
Roberta Roberts, MD - Medical Team Leader
???, Supervisory Chemist
James Timper, Reviewing Chemist

RPR Participants:
Bob Barwick, Senior Director, Worldwide Quality Assurance
Mary Elicone, Manager, Regulatory Affairs
Donald Esherick, Senior Manager, CMC Liaison, Regulatory Affairs
Bob Felt, PhD, Manager, Industrialization US
Greg Sam, Director, Qualification and Validation
John J. Savarese, MD, PhD, Senior Director, Regulatory Affairs
Liuda Shtohryn, PharmD, Senior Director, Worldwide CMC Regulatory Affairs

Issues from the Briefing Package:

4.1 Filing Requirements

RPR has manufactured three full-scale production batches of drug product at Catalytica in December 1998. RPR proposes to provide batch-release data for these three batches at the time of submission of the NDA Amendment to include Catalytica as an alternate manufacturing site for the drug product, Synercid. Does FDA agree that the NDA amendment can be submitted with batch release data, and stability data can be provided to the FDA during the review of the amendment?

FDA requires 3 months accelerated stability data and 3 months non-stressed data to be submitted in the NDA Amendment. In addition, the CMC section should contain the microbiological validation package.

4.2 Expiry Dating

The current expiry dating for the drug product is 24 months when stored at refrigerated conditions (5°C ±3°C). Because the minor changes at the alternate drug product manufacturing site are believed to have no impact on the stability of the drug product, RPR wishes to retain this same expiry dating for product manufactured at the Catalytica site. Does the FDA agree that the 24 month expiry dating applies to product manufactured at Catalytica?

FDA requests that 6 months stability data be submitted as soon as it is available, during the review process. Based on 6 months data, if the data look good, the FDA will grant 24-month expiry dating. Based on 3 months data, the FDA will only grant 18-month expiry dating. FDA stressed that the Agency will review the 6 month data quickly, in order to grant the requested 24-month expiry dating.

General IND/NDA Amendment Issues:

The IND Amendment for the Catalytica site should contain batch release data on the three full-scale production batches which have already been manufactured. In addition, the IND Amendment should contain 1 month accelerated data (i.e., stability data from the first test station). Also, RPR must verify that the Catalytica site is in compliance with cGMPs., this could be done by a written statement from Catalytica.

The NDA Amendment should contain the stability data as listed above, the microbiological validation report, and Catalytica must be inspection-ready at the time of submission. In addition, FDA requested that statistical analyses be performed on the stability data, using the FDA program. FDA stated that the Agency would not inspect Catalytica at the IND stage, that they would rely on the certification provided, but the Agency would request an inspection at the time of the NDA Amendment submission.

Synercid [redacted] Clinical Hold:

1) If removal of the clinical hold is not achieved for [redacted] manufactured supplies before RPR submits an IND amendment to introduce Catalytica as an alternate manufacturing site (Mar 99), does FDA agree that RPR can restart the clinical trials immediately (without a 30-day review by FDA as stated in the clinical hold letter)?

FDA will not grant a waiver of the 30-day review time. However, FDA will review the IND Amendment as quickly as possible.

2) Will FDA provide a letter to RPR to document the removal of the clinical hold if a) [redacted] supplies are used to resume clinical trials and b) if Catalytica supplies are used to resume clinical trials? Such a letter is anticipated to be necessary for submission to other regulatory agencies prior to restart of studies.

FDA will provide, in writing, the Agency's decision to remove the clinical hold.

RPR asked if the Reviewing Division had received any feedback from the Compliance Division, regarding the potential to use the supplies manufactured at [redacted] to raise the clinical hold and restart the clinical trials. RPR stated that [redacted] had been in contact with [redacted] to resolve this issue, since most of the batches manufactured at [redacted] had undergone the required third party review and additional LAL testing. Maureen Dillon Parker stated that she was in contact with Tracy Roberts, her counterpart, and the Compliance Division was addressing this issue but it had not yet been resolved.

RPR requested confirmation that when the NDA Amendment was submitted, with the 3 month stability data as requested, the Agency would give the Amendment expedited review. The Division confirmed that it would give expedited review.

TELECONFERENCE MINUTES

Meeting Date: June 7, 1999

Time: 10:30 - 11:30 a.m.

NDA# and Drug Name: NDA 50-747/748 - Synercid I.V.

External Participant: Rhône-Poulenc Rorer Pharmaceuticals

Type of Telecon: Follow-up discussion of the negative stopping rules for the Vancomycin-Resistant *Enterococcus faecium* (VREF) protocol [JRV-396].

Meeting Chair: Alexander Rakowsky, Clinical Reviewer

External Participant Lead: Mary Elicone, Regulatory Affairs

Meeting Recorder: Maureen Dillon-Parker, Project Manager

FDA Division of Anti-Infective Drug Products Attendees:
Alexander Rakowsky, Clinical Reviewer
Daphne Lin, Statistical Team Leader
Erica Brittain, Statistical Reviewer
Maureen Dillon-Parker, Project Manager

External Attendees:
Representatives from Rhône-Poulenc Rorer Pharmaceuticals
Ray Zhu, Biostatistics [#609-897-7897]
Mary Elicone, Regulatory Affairs
Lisa Goldberg, Clinical Research Associate
Shelly Fayocavitz, Senior Clinical Research Associate
William Geary, Senior Clinical Research Associate

A. Meeting Objectives:

Discussion of Amendment #1 dated May 26, 1999, concerning the negative stopping rules for the VREF-Confirmatory protocol (#JRV-396).

B. DISCUSSION:

GENERAL COMMENTS

1. [redacted]

2. Submission of May 20, 1999 [N-480], which provides for information supporting the addition of [redacted] to the labeling, is acceptable.

3. Submission of March 2, 1999, [N-468], which provides for a catheter-related bacteremia protocol (JRV-309), will need to be discussed via a teleconference in the next few weeks.

4. Submission of May 26, 1999, [General Correspondence (Synercid VREF Confirmatory Protocol #396 - Amendment #1) protocol changes are acceptable, however, Dr. He Sun, biopharmaceutical reviewer, has some wording revisions. These will be provided to RPR shortly.

5. Submission of May 25, 1999 [General Correspondence: Chemistry, Manufacturing and Controls] - Notification of particulate matter in the product manufactured at the Catalytica facility. This facility will be inspected once the submission requesting the addition of this manufacturing facility is made to the NDA.

[redacted]

7. Requested follow-up information on pediatric patient treated intrathecally on Friday, June 4, 1999.

NEGATIVE STOPPING RULES

After a lengthy discussion, the submission of May 26, 1999, was found acceptable. Highlights of the discussion are as follows:

- When looking at mortality as an endpoint, high dose vs low dose must be distinguished. If high mortality is seen in the high dose, then this arm of the study should be dropped. This would be an ad hoc decision. If there is high mortality seen in the low dose, then this is an efficacy issue.

- Having a formal allocation rule for the spending of alpha for clinical success and mortality was discussed. However, this was viewed as impractical because the DSMB would view a substantial mortality difference as unacceptable, and would feel it is unethical to wait until a stringent boundary is crossed.

- The clinical endpoint, regardless of mortality, will be RPR's focus. Mortality will be used as a guide for stopping the study, not for determining a win. It was decided that there should be no formal negative stopping rules.

- If there is no clinical efficacy difference seen by [redacted] but the Independent Safety Monitoring Board (ISMB) recommends that the trial should stop secondary to safety/mortality reasons, then RPR and FDA should telecon to discuss.

- If mortality rate differences between arms are substantial, it may be hard not to make a claim for this. The approval of the drug [redacted] was mentioned, where mortality was not an endpoint in the study, however, once a mortality effect was seen, a claim was made for it and the approval of the drug was based on this. In the RPR trial, mortality is viewed as a reason to stop the trial for safety and will not be used for a claim of demonstrated efficacy, since no alpha has been spent on the mortality endpoint.

CONCLUSION

- The Confirmatory Protocol submitted May 26, 1999, will remain as written. If the committee recommends termination of the study for any reason, the FDA and RPR will discuss via teleconference. FDA will be notified if the low dose is dropped or if any major changes are made to the protocol. If clinical success [redacted] is satisfied and RPR stops the trial, they take a risk on the adequacy of the data when it is reviewed. Agreed that all changes should be mutual RPR/FDA decisions.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/ 7-1-99

cc: Orig NDA 50-747/748
Division File
HFD-520/TLMO/Rakowsky/init 6/17/99 AT 07-1-99
HFD-725/TLStat/Lin/init 6/23/99
HFD-725/Stat/Brittain/init 6/22/99
HFD-520/PMS/Dillonparker/synercid\N50748.607
rd/June 16, 1999
ft/June 28, 1999

AGENDA

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING (63rd)

Food and Drug Administration
Hilton Hotel, Gaithersburg, MD

Thursday, February 19, 1998

OPEN SESSION

8:00 a.m.	Call to Order	Barth Reller, M.D., Acting Chair
8:05	Conflict of Interest Statement	Ermona McGoodwin Executive Secretary

Issue: NDAs 50-747 & 50-748 quinupristin/dalfopristin (Synercid®, Rhône-Poulenc Rorer Pharmaceuticals) for treatment of vancomycin-resistant *Enterococcus faecium* (VREF) infections, complicated skin and skin structure infections, [redacted] and for use in the treatment of infections caused by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains).

8:10	Introduction	Gary Chikami, M.D., Director Division of Anti-Infective Drug Products
8:15-8:45	Background	Barbara Murray, M.D. FDA Consultant
8:45-10:15	SPONSOR PRESENTATIONS - Rhône-Poulenc Rorer	
	Introduction	John Savarese, M.D., Ph.D.
	Epidemiology of Serious Gram-Positive Infections	Michael Edmond, M.D. MPH
	Medical Need	David Gilbert, M.D.
	Microbiology Profile	Harriette Nadler, Ph.D.
	Clinical Pharmacology	Gerald Rhodes, Ph.D.
	Clinical Trial Data	George Talbot, M.D.
10:15-10:30	**BREAK**	

10:30-11:00	FDA PRESENTATIONS:	
	Microbiology	Frederic Marsik, Ph.D. Microbiologist
	Biopharmaceutics	He Sun, Ph.D. Biopharmaceutist
11:00-12:00	[redacted]	Alexander Rakowsky, M.D. Medical Officer
	Skin & Skin Structure Infections/ [redacted] Safety	Susan Thompson, M.D. Medical Officer
12:00-1:30	**LUNCH**	
1:30-2:30	**OPEN PUBLIC HEARING**	
2:30-5:00	Committee Discussion, Questions and Vote	
5:00 p.m.	**ADJOURN**	

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✓ = in attendance

JANUARY 1998

Anti-Infective Drugs Advisory Committee Meeting (63rd)
February 19, 1998

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