NDA 50-747 **September 21, 1999**
NDA 50-748

Rhone-Poulenc Rorer Pharmaceuticals
Attention: John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs
500 Arcola Road
Collegeville, PA 19426-0107

Dear Dr. Savarese:

Please refer to your new drug applications (NDA's) dated September 5, 1997, received September 5, 1997, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for SYNERCID (quinupristin/dalfopristin) I.V. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of the following submissions:

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March 5, 11, and 19; April 3, 14, 15, and 24; May 5, 20, 25, and 26; June 2, 4, 8, 9, 18, 21, and 30; July 8, 23, 28, and 31; August 12; September 16; October 19, and 22; November 23; December 11, 17 and 18, 1998; January 15, 25, and 26; March 26; April 27; May 20, and 26; June 4; July 8, 23, and 28; August 10, 17, 18, and 30; September 2, 1999.

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September 11; October 19; December 16, 17, and 18, 1998; January 26; March 26; April 27; May 20, and 25; June 4, 18, and 21; July 23, and 28; August 10, 17, 18, and 30; September 2, 1999.

Your submission(s) of July 23, 1999 constituted a complete response to our March 5, 1998 (NDA 50-747) and September 4, 1998, (NDA 50-748) action letters.

This new drug application provides for the use of SYNERCID (quinupristin/dalfopristin) I.V. for the treatment of vancomycin resistant *Enterococcus faecium* (Subpart H, NDA 50-747) and for the treatment of complicated skin and skin structure infections (NDA 50-748).

We have completed the review of application **NDA 50-747**, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve SYNERCID (quinupristin/dalfopristin) I.V. for use as recommended in the submitted final printed labeling (package insert submitted August 17, 1999, immediate container and carton labels submitted August 10, 1999). Accordingly, the application is approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

Specifically, this approval is granted based on your agreement to comply with the conditions of Accelerated Approval (Subpart H; 21 CFR 314.500) and to conduct the confirmatory clinical study as required under 21 CFR 314.510. The final VREF Confirmatory Protocol was agreed to and submitted December 21, 1998 (revised protocol submitted July 8, 1999). We remind you that semi-annual reports on the progress of the study must be submitted to the Agency. These reports should include information on the number of investigative sites and the number of subjects enrolled. Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

Additionally, we have completed the review of application **NDA 50-748**, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted August 17, 1999, immediate container and carton labels submitted August 10, 1999). Accordingly, the application is approved effective on the date of this letter.

In addition, we note your following Phase 4 commitments, specified in your submissions dated January 15, 1999 (NDA 50-747) and December 16, 1998 (NDA 50-748), that are not a condition of accelerated approval. These commitments include:

<u>Clinical</u>

1. To conduct a pharmacokinetic study(ies) in the pediatric population (0-16 years).

2. To collect surveillance data on the development of resistance to Synercid (especially among vancomycin-resistant *Enterococcus faecium* strains) and the impact of this resistance on clinical outcomes. These data will be collected in the confirmatory study.

Biopharmaceutics

1. To submit the results of the *in vitro* protein binding study in human plasma using a analytical assay method, as well as, the results of an *in vivo* study.

2. To conduct and submit the results of open randomized parallel group pharmacokinetic and safety study of the interaction between repeated administration of rifampin and Synercid.

3. To submit data from all ongoing human pharmacokinetic studies:

    a. Population Pharmacokinetic Study;

    b. Lung tissue penetration data which will be collected as part of your ongoing drug development program;

    c. Pharmacokinetics in patients with renal impairment.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to these NDAs. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to these NDAs as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report(s) to these NDAs. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval (NDA 50-747), you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55, however, we acknowledge receipt of your submission containing your pediatric plan and proposed pediatric study (See Clinical #1 above). We are deferring submission of your completed pediatric studies until December 2, 2000.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Maureen Dillon-Parker, Project Manager, at (301) 827-2125.

Sincerely,

Sandra Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research