NDA 50-687/S-004, S-007, S-008, S-009, S-010, S-011, S-012
NDA 50-688/S-006, S-008, S-009, S-010, S-011, S-012, S-013

Sankyo Pharma Inc.
Attention: John R. Short, R.Ph.
Senior Director, Regulatory Affairs
780 Third Avenue, 47th Floor
New York, NY 10017

Dear Mr. Short:

Please refer to your supplemental new drug applications dated February 26, 1999 (50-687/S-004 and 50-688/S-006), April 9, 1999 (50-687/S-007 and 50-688/S-008), April 16, 1999 (50-687/S-008 and 50-688/S-009), April 23, 1999 (50-687/S-009 and 50-688/S-010), April 26, 1999 (50-687/S-010 and 50-688/S-011), April 27, 1999 (50-687/S-011 and 50-688/S-012), and May 5, 1999 (50-687/S-012 and 50-688/S-013), received March 2, 1999 (50-687/S-004 and 50-688/S-006), April 12, 1999 (50-687/S-007 and 50-688/S-008), April 19, 1999 (50-687/S-008 and 50-688/S-009), April 26, 1999 (50-687/S-009 and 50-688/S-010), April 28, 1999 (50-687/S-010 and 50-688/S-011), April 29, 1999 (50-687/S-011 and 50-688/S-012), and May 6, 1999 (50-687/S-012 and 50-688/S-013), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Banan® (cefpodoxime proxetil) Tablets and Banan® (cefpodoxime proxetil) Granules for Oral Suspension. We note that these applications are 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 your submissions dated February 25, 1999, and January 19, 2000.

These supplemental new drug applications provide for the following revisions:

50-687/S-004 and 50-688/S-006:

1. In the **Geriatric Use** subsection of the **PRECAUTIONS** section, the number of patients in multiple-dose clinical studies of cefpodoxime proxetil film-coated tablets and the numbers of patients aged 65 and over and 75 and over have been updated. These new numbers include the patients that were reviewed to support the addition of the **Acute Exacerbations of Chronic Bronchitis** indication, approved December 22, 1997, in NDAs 50-687/S-001 and 50-688/S-001.

2. Under **Film-coated Tablets (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, the numbers of patients experiencing adverse events

and the incidence rates for diarrhea and vaginal fungal infections have been updated. These new numbers include the patients that were reviewed to support the addition of the **Acute Exacerbations of Chronic Bronchitis** indication, approved December 22, 1997,in NDAs 50-687/S-001 and 50-688/S-001.

3. Under **Film-coated Tablets (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, "tinnitus" has been added to the *Special Senses* category under **Incidence less than 1%**.

4. Under **Cephalosporin Class Labeling** in the **ADVERSE REACTIONS** section, the paragraph describing *Adverse reactions and Abnormal Laboratory Tests* was revised as follows:

"Allergic reactions including Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, agranulocytosis, and pancytopenia."

50-687/S-007 and 50-688/S-008:

5. In the **INDICATIONS AND USAGE** section, the **Community-acquired pneumonia** indication was revised to include beta lactamase-producing strains of *H. influenzae*.

50-687/S-008 and 50-688/S-009:

6. In the **ADVERSE REACTIONS** section, "allergic reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme" have been moved from the **Cephalosporin Class Labeling** subsection to the **Post-marketing Experience** subsection. With the subsequent addition of "serum sickness-like reaction", the resulting paragraph describing *Adverse reactions and Abnormal Laboratory Tests* under **Cephalosporin Class Labeling** now reads (see #4 above):

"Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, and pancytopenia."

7. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, the text in the **Preparation of Suspension** subsection was reformatted in tabular form.

50-687/S-009 and 50-688/S-010:

8. In the **ADVERSE REACTIONS** section, "serum sickness-like reactions" has been added

to the **Post-marketing Experience** subsection such that it follows "erythema multiforme".

50-687/S-010 and 50-688/S-011:

9. Under **Pharmacokinetics of Cefpodoxime Proxetil Suspension** in the **CLINICAL PHARMACOLOGY** section, the number and age range of pediatric patients have been updated.

10. Under **Pharmacokinetics of Cefpodoxime Proxetil Suspension** in the **CLINICAL PHARMACOLOGY** section, the cefpodoxime plasma levels in fasted patients after suspension administration have been updated for all time periods in the table.

11. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, the number of patients in multiple-dose clinical studies of cefpodoxime proxetil granules for oral suspension has been updated to N = 1586.

12. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, the numbers of patients experiencing adverse events have been updated. In addition, "vomiting" has been added as a primary reason for discontinued medication in multiple-dose clinical studies of cefpodoxime proxetil granules for oral suspension.

13. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, the subsection under **Incidence greater than 1%** has been revised as follows:

"Diarrhea 5.7%
The incidence of diarrhea in infants and toddlers (age 6 months to 2 years) was 15.4%.
Diaper rash/Fungal Skin Rash 2.3%
The incidence of diaper rash in infants and toddlers was 12.1%.
Other skin rashes 1.8%
Vomiting 2.1%"

14. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, "exfoliative dermatitis" has been added to the *Dermatologic* category under **Incidence less than 1%**.

15. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsectionof the **ADVERSE REACTIONS** section, "decreased salivation, pseudomembranous colitis" have been added to the end of the *Gastrointestinal* category under **Incidence less than 1%**.

16. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, "*Psychiatric*: Hyperactivity/nervousness" has been added as a new category under **Incidence less than 1%**.

17. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, "*Respiratory*: Epistaxis, rhinitis" has been added as a new category under **Incidence less than 1%**.

18. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, two new dosing regimens [100 mg every 12 hours (5 mg/kg/dose every 12 hours) for 5 to 10 days or 200 mg every 24 hours (10 mg/kg/dose every 24 hours) for 10 days] for the treatment of pharyngitis and/or tonsillitis were added. The every 24 hours for 10 days regimens were subsequently dropped from the labeling.

50-687/S-011 and 50-688/S-012:

19. The **Pediatric Use** subsection of the **PRECAUTIONS** section, was revised to read "Safety and efficacy in infants less than 5 months of age have not been established."

20. Under **Granules for Oral Suspension (Multiple dose)** in the **Clinical Trials** subsection of the **ADVERSE REACTIONS** section, "irritability" has been added to the *Central Nervous System* category under **Incidence less than 1%**.

21. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, the first sentence of this subsection was revised to read "BANAN for Oral Suspension may be given without regard to food."

22. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, the age range for children in the dosing tables was expanded to "age 5 months through 12 years."

23. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, the dose frequency for Acute otitis media was revised to read "10 mg/kg Q 24 h (Max 400 mg/dose) or 5 mg/kg Q 12 h (Max 200 mg/dose)".

24. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE ANDADMINISTRATION** section, the dose frequency for Pharyngitis and/or tonsillitis was revised to read "5 mg/kg Q 12 hrs (Max 100 mg/dose)".

25. The **Acute Otitis Media Studies** subsection was added to the **CLINICAL TRIALS** section.

50-687/S-012 and 50-688/S-013:

26. In the **DESCRIPTION** section, "microcrystalline cellulose" was added and "lactose hydrose", "microcrystalline cellulose", and the word "hydrous" in "sodium citrate hydrous" were deleted from the list of inactive ingredients listed for BANAN for Oral Suspension.

27. Under **GRANULES FOR ORAL SUSPENSION** in the **DOSAGE AND ADMINISTRATION** section, the **Preparation of Suspension** table was updated to include constitution directions for the new 50 mL and 75 mL fill sizes (see #28 below).

28. In the **HOW SUPPLIED** section, new 50 mL and 75 mL fill sizes in 50 mg/5 mL and 100 mg/5 mL concentrations of BANAN for Oral Suspension were added.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

29. In the third paragraph of the **DESCRIPTION** section, the word "magnesium" is misspelled.

30. Under **Gram-negative aerobes** in the **Microbiology** subsection of the **CLINICAL PHARMACOLOGY** section, the word "*Moraxella*" is misspelled.

31. In the **SUSCEPTIBILITY TESTING** subsection of the **CLINICAL PHARMACOLOGY** section, the subheader "Dilution Technique" should read "*Dilution Techniques*".

32. Under **SEXUALLY TRANSMITTED DISEASES** in the **INDICATIONS AND USAGE** section, the word "gonorrhea" in the subheader **Acute, uncomplicated urethral and cervical gonorrhea** should be fully bolded.

33. Under **SEXUALLY TRANSMITTED DISEASES** in the **INDICATIONS AND USAGE** section, "gonorrhoeae" in *Neisseria gonorrhoeae* is misspelled throughout the subsection **Acute, uncomplicated ano-rectal infections in women**.

34. Under **Drug Interactions** in the **PRECAUTIONS** section, the second sentence under *Antacids* should read "The rate of absorption ...".

35. In the first sentence under **Acute Otitis Media Studies** in the **CLINICAL TRIALS** section, "B-lactamase-producing" should read "ß-lactamase-producing".

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted January 19, 2000). These revisions are terms of the NDA approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 50-687/S-004, S-007, S-008, S-009, S-010, S-011, S-012, 50-688/S-006, S-008, S-009, S-010, S-011, S-012, S-013." Approval of these submissions by FDA is not required before the labeling is used.

Your submissions state that you do not currently market the Banan® products, however, please submit a comprehensive chemistry, manufacturing, and controls package before marketing Banan® again.

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 fulfilled the pediatric study requirement at this time.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

Gary K. Chikami, M.D.

Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research