DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-176
(b) (4)

WRITTEN REQUEST 2 – AMENDMENT #2

Sankyo Pharma Development
Attention: Sandra Smith, R.Ph., MBA
Director, Regulatory Affairs
399 Thornall Street, 11th Floor
Edison, NJ 08837

Dear Ms. Smith:

Please refer to your correspondence to IND (b) (4) dated February 14, 2006, requesting a change to FDA's August 31, 2004, Written Request for pediatric studies for colesevelam hydrochloride.

We have reviewed your proposed change and are amending the below-listed section of the Written Request. All other terms stated in our Written Request issued on August 31, 2004, and as amended on January 19, 2006, remain the same. The change to the previous Written Request is highlighted in **Bold** font.

- *Statistical information, including power of study and statistical assessments:*

  Conduct two primary treatment comparisons with respect to the primary efficacy variable percent change in LDL-C from Day 1 of Period 2 (study baseline) to Week 8 (end of Period 2):

  1. Comparison will first be performed between the high-dose colesevelam group (3750 mg) and the placebo group. If the null hypothesis is rejected in favor of the high-dose colesevelam group,

     then:

  2. A comparison between the low-dose colesevelam group (1850 mg) and the placebo group will be performed.

  Otherwise, no comparison will be performed between the low-dose colesevelam HCl group and the placebo group.

  All other treatment comparisons will be considered secondary. The analyses of the secondary efficacy variables are similar to that used for the primary efficacy variable.

Each primary treatment comparison will test the null hypothesis that the mean percent changes from baseline in LDL-C in the two groups are equal. Null hypotheses should be tested using a parametric ANOVA (with treatment and randomization stratification variable [statin use in Period 1] as factors) or ANCOVA (with treatment and randomization stratification variable [statin use in Period 1] as factors and baseline LDL-C value as a covariate). If assumptions for both parametric tests are not valid, nonparametric ANCOVA may be performed. Secondary analyses should be performed to assess the consistency of treatment effects with and without statins.

The primary analysis population for the primary treatment comparisons of Period 2 data will be the intent-to-treat population consisting of all randomized patients with a baseline and at least one post-baseline lipid measurement**.** Data for patients without Week 8 lipid measurements will be imputed using the Last Observation Carried Forward (LOCF).

Descriptive statistics will be presented for LDL-C and secondary efficacy variables when measured at each visit during Period 3. Descriptive statistics should also be presented for height velocity and sexual maturation **at the end of** Period 3.

Reports of the studies that meet the terms of the Written Request dated January 19, 2006, as amended by this letter, must be submitted to the Agency on or before January 1, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Pat Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M. D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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