DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 58,362

Cadence Pharmaceuticals
12481 High Bluff Drive, Suite 200
San Diego, CA 92130

Attention: James Breitmeyer, MD, PhD
Executive Vice President and Chief Medical Officer

Dear Dr. Breitmeyer:

Reference is made to your April 20, 2007, Proposed Pediatric Study Request submitted to IND 58,362 for acetaminophen.

We also refer to your amendments dated July 2, 2007 and July 25, 2007.

To obtain needed pediatric information on acetaminophen, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

GENERAL REQUIREMENTS

This written request requires you to address three areas regarding the use of intravenous (IV) acetaminophen (APAP) in pediatric patients.

1. Characterize the pharmacokinetic (PK) profile of IV APAP following multiple doses in different pediatric age groups by obtaining adequate pediatric PK data for comparison with adult PK data and identifying the dosage to be used for different age groups in the subsequent studies based on plasma APAP exposure similar to adults. The studies may be conducted in an open-label design in patients who require treatment for fever but who are Nil Per Os (NPO). Because the relationship between APAP plasma concentrations and body temperature change is well characterized, the principal objective of this study is to obtain data to bridge plasma concentrations in children to adults.

2. Characterize the APAP plasma concentrations and pain relationship for IV APAP for the indication of the management of pain following multiple doses in different pediatric age groups by evaluating the efficacy of the short-term use of IV acetaminophen in pediatric patients requiring IV analgesics. Because the PK/PD relationship for APAP and analgesia is not well characterized, the studies must be adequate and well-controlled; specifically, the studies must be conducted with a double-blind design with an appropriate comparator in patients who require treatment for pain but who are NPO. To maximize the trial success, you are strongly encouraged to perform clinical trial simulations to substantiate the choice of the trial design.

Prior exposure and pain relief data from adult studies, literature, and any available pediatric studies should be employed for this purpose.

3. Characterize the safety profile of IV APAP in different pediatric age groups. A total of at least 300 pediatric patients must be studied. This requirement may be addressed in an open-label or double-blind design and will be considered met if the fever and pain studies complete sufficient numbers of patients.

I. PHARMACOKINETIC STUDIES

Type of studies:

These studies will be of a randomized, open-label or double-blind design to obtain safety and pharmacokinetic information following multiple dosing with intravenous acetaminophen administration in pediatric patients. Information will be collected to evaluate the pharmacokinetics of IV acetaminophen by age cohort beginning with pediatric patients who are at less risk as defined by the inclusion and exclusion criteria. In order to obtain pediatric dosing that would result in plasma levels comparable to adults a rationale for the dose selection must be provided in the submitted protocol. The choice of doses may be guided by the literature or current medical practice.

Number of Patients and Age Groups in which studies will be performed:

Studies must include an adequate number of patients to characterize the pharmacokinetics parameters of acetaminophen and select a therapeutic dose for the age ranges studied, taking into account inter-subject variability. The number of patients must be approximately evenly distributed between genders and must be approximately evenly distributed across the age ranges, and reasonably distributed within the age ranges. These groups have been determined by assessment of differences in developmental physiology. A minimum of 12 patients are required per dose group for traditional pharmacokinetic analysis in each of the age groups indicated below. This number of patients should be adjusted appropriately when considering population PK analysis by sparse sampling approach:

- Birth (28 weeks to $\leq$ 40 weeks gestational age) to $\leq$ 28 days chronological age
- 29 days to < 6 months
- 6 to < 12 months
- 12 to < 24 months
- 2 to < 12 years
- 12 to $\leq$ 16 years

Inclusion criteria:

- Pediatric inpatients with fever who must be NPO due to their underlying medical condition and who require (with the consent of the parent or guardian) IV therapy for the duration of the study.

Blood sampling:

A sufficient number of blood samples must be drawn in order to capture the acetaminophen PK profile in each patient. The total volume of blood drawn and the PK methods to be employed in the data analysis must be determined *a priori* and stated in the protocol. It is acceptable to use a population pharmacokinetic approach with sparse sampling; however, blood samples must be dispersed throughout the profile to ensure proper parameter estimation. The proposed design must ensure precise estimates of the mean clearance and volume of distribution (central).

Plasma concentrations of glutathione, and plasma and urine concentrations of acetaminophen and the following metabolites must be determined in a pre-specified number of patients:

- acetaminophen glucuronide
- acetaminophen sulfate
- 3'-methoxyacetaminophen
- 3'-(S-cysteinyl)acetaminophen
- acetaminophen mercapturate
- 3'-S-methylacetaminophen

Study endpoints:

1. Pharmacokinetics

   Descriptive statistics must be derived employing traditional or population PK methods for PK parameters of acetaminophen such as clearance, volume of distribution, elimination $T_{1/2}$, Cmax, and AUC.

   The PK of acetaminophen in pediatric subjects should be qualitatively compared to the PK data from ongoing or completed PK trials in adults using IV acetaminophen. This is to qualitatively compare the exposures shown to be effective and safe in adults.

   Plasma and urine levels of acetaminophen and its metabolites must be reported.

2. Safety*:*

   - Incidence of adverse events
   - Vital signs
   - Laboratory testing to include pertinent tests of hepatic function such as transaminase levels

3. Efficacy:

   Serial body temperature measurements using standardized methodology may be performed while pediatric patients are treated with study drug.

II. EFFICACY STUDIES

Type of studies:

The studies will be designed as randomized, double-blind, adequately-controlled, parallel, multiple-dose, superiority trials to obtain both efficacy data and data on the PK/PD relationship with regard to IV APAP treatment in pediatric patients with pain who must be NPO due to their underlying medical condition. A rationale for the choice of doses and the proposed trial design must be provided in the submitted protocol. We encourage you to base these on information obtained from clinical trial simulations. The choice of dose(s) may also be guided by prior PK studies, literature, or current medical practice.

Number of Patients and Age Groups in which studies will be performed:

Studies must include a sufficient number of patients to produce a sample size adequately powered for detecting treatment differences based on estimates of the effect size of the primary efficacy endpoint. The number of patients must be approximately evenly distributed between genders, approximately evenly distributed across the age ranges, and reasonably distributed within the age ranges. These groups have been determined by assessment of differences in developmental physiology. A minimum of 12 patients are required per dose group for traditional pharmacokinetic analysis in each of the age groups indicated below. This number of patients should be adjusted appropriately when considering population PK analysis by sparse sampling approach:

- Birth (28 weeks to $\leq$ 40 weeks gestational age) to $\leq$ 28 days chronological age
- 29 days to < 6 months
- 6 to < 12 months
- 12 to < 24 months
- 2 to < 12 years
- 12 to $\leq$ 16 years

Inclusion criteria:

- Pediatric inpatients with pain who must be NPO due to their underlying medical condition and who require (with the consent of the parent or guardian) IV therapy for the duration of the study.

Blood sampling:

A sufficient number of blood samples must be drawn in order to capture the acetaminophen PK profile in each patient. The total volume of blood drawn and the PK methods to be employed in the data analysis must be determined *a priori* and stated in the protocol. It is acceptable to use a population pharmacokinetic approach with sparse sampling; however, blood samples must be dispersed throughout the profile to ensure proper parameter estimation. The proposed design must ensure precise estimates of the mean clearance and volume of distribution (central).

Plasma concentrations of glutathione, and plasma and urine concentrations of acetaminophen and the following metabolites must be determined in a pre-specified number of patients:

- acetaminophen glucuronide
- acetaminophen sulfate
- 3'-methoxyacetaminophen
- 3'-(S-cysteinyl)acetaminophen
- acetaminophen mercapturate
- 3'-S-methylacetaminophen

Study endpoints:

1. Pharmacokinetics

   Descriptive statistics must be derived employing traditional or population PK methods for PK parameters of acetaminophen, such as clearance, volume of distribution, elimination $T_{1/2}$, Cmax, AUC.

   The PK of acetaminophen in pediatric subjects should be qualitatively compared to the adult PK data from ongoing or completed adult PK trials using IV acetaminophen. This is to qualitatively compare the exposures shown to be effective and safe in adults.

   The relationship of exposure (infusion rate/dose/AUC/Cmax) must be explored with regard to:

   - pharmacodynamic endpoints, such as analgesic effects, time to use of rescue medication, amount of rescue medication, and

   - safety endpoints, such as major adverse events and most frequent adverse events (see below).

   The plasma levels of acetaminophen and its metabolites must be reported.

2. Efficacy

   Analgesic effects (including analgesic duration) must be studied. It is essential to identify a single primary efficacy outcome reflecting adequacy of analgesia. Clinical assessments will be made using validated, age-appropriate instruments. Inter-rater variability will be evaluated. Evaluation will include assessment by blinded caretakers and assessors. Rationale for choice of scale will be provided in the protocol and must be agreed upon by the Division of Anesthesia, Analgesia, and Rheumatology Products. The same scale must be used at all sites. Clinical assessments must be made at appropriate intervals in relation to the PK sampling, to the extent possible, to provide understanding of the concentration-response relationship.

   Secondary efficacy parameters will include duration of analgesic effect and rescue medication which will be pre-specified and should be reflective of standard of care.

3. Safety

   - Incidence of adverse events

   - Vital signs

- Laboratory testing to include pertinent tests of hepatic function such as transaminase levels

III. SAFETY STUDIES:

Type of studies:

Depending on the numbers of pediatric patients enrolled in the pharmacokinetic and efficacy studies, it may be necessary to conduct a separate safety study. This study may be either an open-label or a double-blind design and must obtain multiple-dose safety data for up to 5 days on the use of IV APAP in pediatric patients with fever or pain and for whom ongoing parenteral therapy is warranted.

Age Groups in which studies will be performed:

Pediatric patients should be evenly distributed among the following age groups:

- Birth (28 weeks to $\leq$ 40 weeks gestational age) to $\leq$ 28 days chronological age
- 29 days to < 6 months
- 6 to < 12 months
- 12 to < 24 months
- 2 to < 12 years
- 12 to $\leq$ 16 years

Inclusion Criteria:

- Pediatric inpatients with fever and/or pain who must be NPO due to their underlying medical condition and who require IV therapy for the duration of the study.

Study Endpoints:

Safety:

- Incidence of adverse events
- Vital signs
- Laboratory testing to include pertinent tests of hepatic function such as transaminase levels

IV. FOR ALL STUDIES:

Drug Information:

Dosage form: acetaminophen injection

Route of administration: intravenous

Regimen: Single and/or multiple dose. Dose ranging is encouraged. The dosing regimen will not exceed 15 mg/kg or 1 gm per dose. The total daily dose will not exceed 4 grams per 70 kg (normalized for pediatric patients of lower weight).

If your current formulation contains an ingredient not appropriate for all ages to be investigated, develop an age-appropriate formulation. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Drug-specific safety concerns:

Liver function will be assessed during the studies and in selected patients at short-term follow-up. Those patients manifesting hepatotoxicity will be followed until resolution of the hepatotoxicity (a level below ULN) or until a new stable baseline is established. Elevations in transaminases will trigger further evaluation of hepatic function, specifically coagulation studies.

Statistical information, including power of study and statistical assessments:

The open-label studies are non-powered trials. Results of all assessments will be presented descriptively.

Efficacy studies will be powered (at least 80%). The sample size for the treatment arms will be determined based on the estimates of the effect size for the primary efficacy endpoint to show statistically significant and clinically meaningful treatment differences. A detailed statistical analysis plan is required and must be submitted prior to the start of the study.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before December 31, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be 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. Please also 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);

2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, the proposed changes and the reasons for the proposed changes must be submitted to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Deptuy 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/

Curtis Rosebraugh
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