DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203389

WRITTEN REQUEST – AMENDMENT 1

Raptor Pharmaceuticals, Inc.
Attention: Christine Murray
Vice President, Global Regulatory Affairs
7 Hamilton Landing, Suite 100
Novato, CA 94949

Dear Ms. Murray:

Please refer to your correspondence dated June 15, 2015, requesting changes to FDA's August 19, 2013 Written Request for pediatric studies for cysteamine bitartrate.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on August 19, 2013, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Timeframe for submitting reports of the study (ies):* Reports of the above studies must be submitted to the Agency on or before June 30, ~~2016~~2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated August 19, 2013, as amended by this letter, must be submitted to the Agency on or before June 30, 2017, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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.

If you have any questions, call Jessica Benjamin, Senior Regulatory Project Manager, at 301-796-3924.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 203389

Raptor Therapeutics, Inc.
9 Commercial Boulevard, Suite 200
Novato, CA 94949

Dear Ms. Kim:

Reference is made to your March 30, 2012 Proposed Pediatric Study Request for Procysbi™ (cysteamine bitartrate) delayed-release capsules.

BACKGROUND:

This study will investigate the potential use of cysteamine bitartrate in the treatment of patients with nephropathic cystinosis aged birth to <6 years old.

Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder characterized by accumulation of the amino acid, cystine in almost all cells. It has been found in all ethnic groups and has an estimated prevalence of 1:100,000-200,000. An estimated 500 patients are affected by the disorder in the United States. Classic nephropathic cystinosis (early-onset or infantile) is the most common of three variants of the disease, with onset of disease within the first year of life. Intermediate nephropathic cystinosis (juvenile/late-onset) shares all of the clinical features of classic nephropathic cystinosis, with onset typically after 10 years of age. The third variant, non-nephropathic (adult) cystinosis is characterized by ocular involvement only. Clinical features of the disease include impaired renal function, renal Fanconi syndrome, growth failure, hypophosphatemic rickets, hypothyroidism, and primary hypogonadism in males. Nephropathic cystinosis is the major cause of inherited Fanconi syndrome.

The current standard of care for nephropathic cystinosis is treatment with a cystine depleting agent (cysteamine bitartrate) to decrease cellular deposits of cystine. Cystine depletion therapy slows progression of both renal and non-renal disease. The adequacy of cystine depletion is assessed by measuring white blood cell cystine (WBC) concentration. Published data demonstrate that clinically significant reductions in WBC levels correlate with improved renal and non-renal clinical outcomes in patients with nephropathic cystinosis. Therefore, WBC cystine level is considered a relevant clinical endpoint for this disease.

The reference product Cystagon®, an immediate-release formulation of cysteamine bitartrate, was approved in 1994 and is indicated for management of nephropathic cystinosis in children and adults. Approval of Cystagon® was based on 3 clinical trials evaluating the efficacy and safety of the drug in nephropathic cystinosis patients. The principal efficacy endpoints in these trials were serum creatinine

and calculated creatinine clearance and growth (height). The studies also evaluated WBC cystine levels. The majority of patients in the trials were young children (mean age at study entry was just under 4 years). Procysbi™ is a cysteamine bitartrate delayed-release formulation that was approved as a 505(b)(2) product on April 30, 2013. Approval was based on a single clinical trial evaluating the pharmacokinetics, efficacy and safety of the drug in nephropathic cystinosis patients ages 6 years and older. The trial demonstrated that Procysbi™ was non-inferior compared to Cystagon® in reducing WBC cystine levels. An ongoing extension trial evaluating long-term safety and efficacy includes patients ages 2 years and older.

Data on the pharmacokinetic (PK) and pharmacodynamic (PD) profile of Procysbi™ in pediatric patients are limited and no PK data are available for children under 6 years old. Therefore, a clinical trial to evaluate the PK and PD profile of Procysbi™ should be conducted in infants and children, aged birth to <6 years.

To obtain needed pediatric information on cysteamine bitartrate, the U.S. 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  Study 1: PK/PD, Safety and Efficacy Study
  A one-year open-label, PK/PD, Safety and Efficacy study in pediatric patients with nephropathic cystinosis aged birth to <6 years.

  Objectives of the Study
  The objectives of the study are to evaluate the PK/PD profile, safety and efficacy of Procysbi™ in patients with nephropathic cystinosis aged birth to <6 years. Efficacy will be assessed in patients measuring white blood cell cystine levels. In addition, growth (length/height and weight for all ages and head circumference for patients, aged birth to 2 years) will be assessed as secondary efficacy endpoints, since growth failure is a hallmark of clinical disease in this pediatric age cohort. Safety will be assessed by physical examination, safety laboratory testing, and adverse events as described in the current protocol for the ongoing extension trial.

  Number of patients to be studied:
  A minimum of 12 patients with nephropathic cystinosis will be enrolled in Study 1 for duration of one year of treatment with Procysbi™.

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If

you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

Pharmacokinetic and pharmacodynamic endpoints
The PD endpoint is the WBC cystine level. The pharmacokinetic and pharmacodynamic endpoints for Study 1 must be combined to explore the exposure-response for safety endpoints. The goals of this analysis are: a) to provide supportive evidence of Procysbi™ activity; and b) to support the dosing recommendations. Safety assessments should include all endpoints listed below, in addition to assessments of the relationship between Procysbi™ exposures (e.g., $C_{0h,}$ $AUC_{0\text{-}24h}$, C_{max}, etc.) and reduction in WBC cystine levels. PK/PD measurements for patients less than 1 year old must be agreed upon with the Agency before proceeding.

For treatment-naïve patients, the starting dose of Procysbi™ will be 1/6 to 1/4 of a maintenance dose of 1.3 g/m^2/day. For patients who were previously treated with Cystagon®, the starting dose of Procysbi™ will be 80% of the prior Cystagon® dose. The dose may be increased to 100% of the prior Cystagon® dose, if tolerated. Dosing adjustments will be made to achieve a WBC cystine level <1 nmol ½ cystine/mg protein, as tolerated.

Efficacy endpoints:
The primary efficacy endpoint of the study will be the WBC cystine level. The secondary efficacy endpoint will be growth as measured using standardized norms for growth based on age (i.e., length/height and weight for age for all age groups and head circumference for ages birth to 2 years).

Safety endpoints:
Safety outcomes must include: reporting of clinical adverse events, tolerability, vital signs, physical examination (including neurological, eye, and skin assessments), electrocardiography (ECG), estimated glomerular filtration rate (eGFR) as measured using an appropriate methodology for pediatric patients, and clinical laboratory measurements (chemistry, hematology, and urinalysis).

- ☐ The following adverse events must be actively monitored: gastrointestinal bleeding or ulceration, seizures, renal adverse events, encephalopathy, severe skin rashes, skin or bone lesions, and elevation in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT).

- ☐ All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- ☐ The following adverse events must be captured when spontaneously reported: gastrointestinal bleeding or ulceration, seizures, renal adverse events, encephalopathy, severe skin rashes, and skin or bone lesions, and elevation in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT). All other adverse events must also be captured when spontaneously reported.

- *Known Drug Safety concerns and monitoring:*

Your safety monitoring plan will include a baseline medical history, vital signs, physical examination (including neurological, eye and skin assessments), growth measurements (i.e., length/height and weight), ECG, estimated glomerular filtration rate (eGFR) as measured using an appropriate methodology for pediatric patients, and clinical laboratory tests (chemistry, hematology, and urinalysis).

Blood chemistry analysis must include the following liver enzyme tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and gamma-glutamyl transferase (GGT). Hematology testing must include, at minimum, a complete blood count (CBC), including hemoglobin, hematocrit, platelet count, and white blood cell count (WBC) with differential.

Safety will be assessed by evaluating the number and type of adverse events occurring during the study, and by changes from baseline in vital signs, physical examinations, ECG, eGFR, and clinical laboratory parameters.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form*
    Procysbi™ capsules (cysteamine bitartrate delayed-release capsules) are a (b) (4) , delayed-release formulation of the bitartrate salt of cysteamine

    route of administration
    Oral or via gastrostomy tube

    regimen
    Procysbi™ will be administered at a starting total daily dose that is equal to 80% of the patient's total daily stable Cystagon® dose, divided into two equal doses administered every 12 hours.

    Use an age-appropriate formulation in the study(ies) described above. These studies will use the age-appropriate formulation that is currently available; if this formulation is not proven useful, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- *Statistical information, including power of study(ies) and statistical assessments:* Descriptive analyses of multiple-dose pharmacokinetic, pharmacodynamic, safety, and efficacy data in cystinosis pediatric subjects are required.

- *Labeling that may result from the study (ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study (ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Procysbi™ is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

- Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data

Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study (ies):* Reports of the above studies must be submitted to the Agency on or before June 30, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study (ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study (ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A (n) of the Act.

Submit protocols for the above study (ies) 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.

Reports of the study (ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please 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 to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric

studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes 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.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Jessica Benjamin, Senior Regulatory Project Manager, at 301-796-3924.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
10/06/2015