CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203389Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA #	NDA 203-389
Applicant Name	Raptor Therapeutics
Date of Submission	3/30/2012
PDUFA Goal Date	4/30/2013
Proprietary Name / Established (USAN) Name	PROCYSBI®/cysteamine bitartrate
Dosage Forms / Strength	Delayed-release capsules, 25 mg and 75 mg
Proposed Indication(s)	Nephropathic Cystinosis, Children $\geq$ 6 years and adults with nephropathic cystinosis
Action/Recommended Action for NME:	*Approval* *Dosing and Administration:* Starting dose: 1/4 to 1/6 of maintenance dose Maintenance dose: Age $\geq$ 6 years: 1.3 gram/m^2/day (2 divided doses, Q12 hrs)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Statistical Review	Behrand Vali, Ph.D. Michael Welch, PhD
Medical Officer Review	Carla Epps, MD
Biopharmaceutics	Kareen Riviere
CMC	Jane Chang, Ph.D. Marie Kowblansky, Ph.D.
Pharmacometrics	Justin Earp, PhD
Clinical Pharmacology	Sue Chih Lee, PhD Justin Earp, PhD Kristin Estes, Ph.D.
Pharmacology Toxicology Review	Fang Cai, PhD David Joseph, Ph.D.
CDTL Review	Lara Dimick, MD

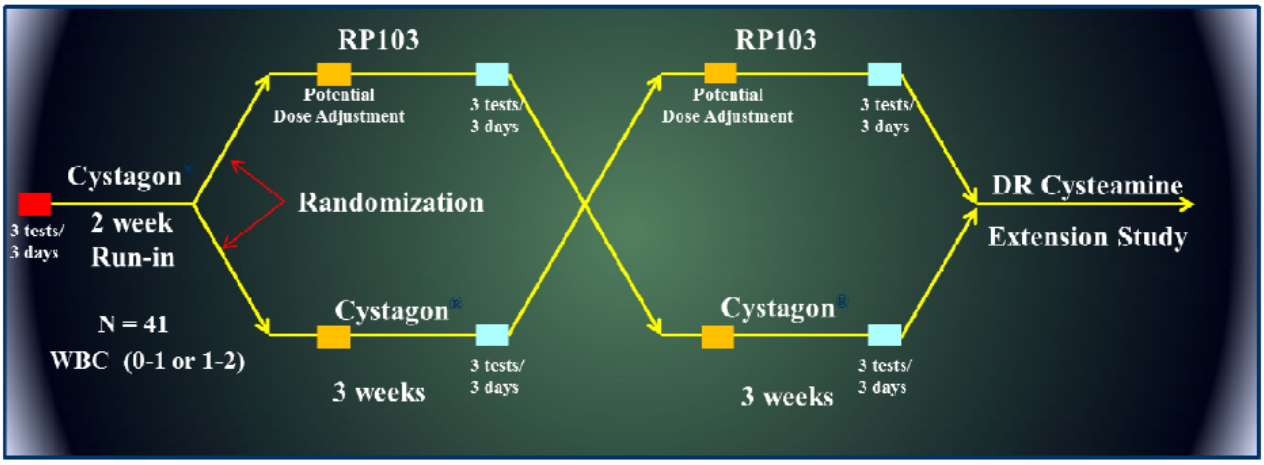
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

In this NDA Raptor Therapeutics is submitting a 505(b)(2) New Drug Application (NDA) for cysteamine bitartrate delayed-release capsules (PROCYSBI®) for the management of nephropathic cystinosis in children and adults. The reference drug and the basis for the application is CYSTAGON®, NDA 20-392. CYSTAGON® was approved for use as a four times daily administration on August 15, 1994. Raptor Therapeutics is seeking approval for a twice-daily administration of cysteamine bitartrate as a modified formulation. The current submission presents new data from clinical trials involving pharmacokinetics, pharmacodynamics, efficacy and safety of cysteamine bitartrate (PROCYSBI®) in children >6 years of age and adults with nephropathic cystinosis. This NDA includes a single pivotal trial (RP103-03) which was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority trial designed to evaluate the safety and efficacy of PROCYSBI® (cysteamine bitartrate delayed release capsules) compared to CYSTAGON®. Forty-three patients were randomized to one of the two treatment sequences, 41 patients completed the trial. In this trial, PROCYSBI® was determined to be non-inferior to CYSTAGON® with regard to steady-state trough WBC cystine levels, the primary endpoint. There were no statistical issues that affected the overall conclusions of trial, RP103-03. The study's design was adjudicated as being adequate, and the applicant's corresponding analysis plan was deemed appropriate.

In the current submission, the efficacy results of the pivotal phase III trial (RP103-03) indicate non-inferiority of PROCYSBI® to CYSTAGON® with regards to reduction in white-blood-cell cystine levels after 3 weeks of therapy in an open-label, randomized, crossover trial. The flowchart of the clinical trial is reproduced below from the review of Dr. Earp, Pharmacometrics.



Reproduced from Justin Earp, PhD Review.

The primary endpoint was to demonstrate that comparable depletion of steady-state cysteamine-trough white-blood-cell cystine levels is achieved following treatment with either CYSTAGON® or PROCYSBI®. The pre-specified analysis was a one-sided, non-inferiority test, conducted at the nominal level of 0.02104 with a non-inferiority margin of 0.3 (overall

significance level of 0.025). PROCYSBI® was determined to be non-inferior to CYSTAGON® within the margin of 0.3. An ongoing long-term, open-label, safety and efficacy study of cysteamine bitartrate delayed-release capsules (RP103) in patients with cystinosis is being executed as Trial RP103 – 04. Subjects in RP103-03 who completed the last visit were offered the opportunity to enroll in this extension study. Subjects who did not participate in RP103-03 are also enrolled in RP103-04. The study is planned to enroll approximately 60 individuals (40 subjects continued from RP103-03). The primary objective of this study is to evaluate the long-term safety and efficacy of RP103. Efficacy is assessed by white-blood-cell cystine concentrations.

In summary, the data in this application establish that PROCYSBI® is effective and is safe for the treatment of patients with nephropathic cystinosis ages 6 years and older. The current application decision is approval in light of the data submitted. For further details of this decision, please see below.

2. Background

Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder characterized by accumulation of the amino acid cystine in almost all cells, affecting an estimated 500 individuals in the US. It is caused by mutations of the *CTNS* gene, which encodes the lysosomal cystine carrier cystinosin. There are various forms of this disease, including a classic nephropathic cystinosis early-onset or infantile), Intermediate nephropathic cystinosis (juvenile/late-onset) shares all of the clinical features of classic nephropathic cystinosis, with onset typically after 10 years of age and non-nephropathic (adult) cystinosis, 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. Presenting features in infants include signs of Fanconi syndrome before age 6 months and growth failure from age six months onward. Onset of corneal involvement may also start within the first year of life and clinical evidence of corneal disease (cystine crystals present on slip lamp examination) is always present by age 16 months. Patients with intermediate cystinosis may have absent or mild Fanconi syndrome and corneal events during childhood. However, progression to end-stage renal disease universally occurs, typically between age 15 and 25 years. The reader is referred to additional clinical background in the review of Dr. Epps, Medical reviewer.

The current standard of care for nephropathic cystinosis is treatment with a cystine-depleting agent (cysteamine bitartrate) to decrease cellular deposits of cystine, with initiation of treatment as soon as possible after diagnosis. Cystine depletion therapy slows progression of both renal and non-renal disease. Therefore, cysteamine is recommended for all nephropathic cystinosis patients, regardless of age or renal transplantation status. Measurement of white blood cell (WBC) cystine levels is used for disease diagnosis and to monitor treatment response. Historically, cystine depletion therapy targeted achievement of WBC cystine levels below 1 nmol ½ cystine/mg protein. However, therapeutic goals for the disease are evolving. In 2005, a group of clinical experts and researchers issued a consensus statement recommending that

consideration be given to dosing patients with cysteamine at levels that will achieve near-normal WBC cystine levels (normal= <0.2 nmol ½ cystine/mg protein).[1]

The current application concerns a delayed-release formulation of cysteamine bitartrate, PROCYSBI® that is an enteric-coated microbead delayed-release capsule. In this submission, the Applicant has proposed dosing for initial treatment and for maintenance treatment of children of ages 6 and older and adults with nephropathic cystinosis. For each of these two dosing regimens, the Applicant proposes two dosing levels (b) (4) for initial treatment and for maintenance treatment, (b) (4)

3. CMC

PROCYSBI® capsules (cysteamine bitartrate delayed-release capsules) are a beaded, enteric-coated, delayed-release formulation of the bitartrate salt of cysteamine, encapsulated in hard gelatin, and intended for oral administration (whole capsules; sprinkles on food or in liquid). PROCYSBI® will be available as 25 mg and 75 mg capsules (expressed as cysteamine free-base). Both 25 mg and 75 mg strength capsules were administered in the pivotal Phase 3 trial (RP103-03) for PROCYSBI®. There have been a number of issues affecting approvability that have now been resolved through the review process. Particularly, there has been much discussion on the ability of this formulation to be administered successfully through nasogastric, gastrostomy and gastrojejunostomy type tubes. Specific instructions for food compatible substrates with PROCYSBI® are labeled after receipt of information supporting passability of the formulation through administration of the product through a gastrostomy tube or (b) (4) The sponsor did not perform an *in vitro* study but provided information from Study RP103-04 on administration of the study drug mixed with applesauce through a gastrostomy tube (b) (4) size 12 French and larger. Dr. Chang determined that the information was acceptable to support labeling for administration via a gastrostomy tube (b) (4) The Clinical team also shared this perspective and I agree that the labeling should reflect administration through a gastostomy type feeding tube.

There also were errors in analyses of the dosage forms of CYSTAGON® and PROCYSBI® used in Study RP103-03. A corrected analysis of the dosage forms revealed that the CYSTAGON® dosage forms contained 85% of the stated dose and the PROCYSBI® contained ~91% of the stated dose in the phase III clinical trial. This issue is also related, to the interpretation of efficacy from a pharmacometrics perspective, and discussed below from Dr. Earp's review. One outstanding PMC concerned the detection of elemental impurities for arsenic, cadmium, lead, and mercury per USP <232> were not included in the drug product specification. This is now a current PMC outlined below. The issue of Eudragit L 30 D-55 exceeded the maximum for oral

[1] Kleta R, Kaskel F et al, First NIH Office of Rare Diseases Conference on Cystinosis: past, present, and future, Pediatr Nephrol 2005; 20:452-454.

tablet/capsule listed in the FDA Inactive Ingredient Search for Approved Drug Products-see Dr. Bai's review. There is an adequate safety margin based on safety margins derived from toxicity studies conducted by the manufacturer of Eudragit.

Dr. Chang concluded that the applicant had provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, she recommended that the NDA not be approved until labeling issues regarding information on dosage forms and strengths, dosage and administration, and storage and handling of the drug product were resolved satisfactorily. These issues have been resolved

Dr. Jane Bai is the CMC reviewer for this NDA and concluded in her review that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

Dr. Riviere from ONDQA did comment that the potential for alcohol dose dumping would be addressed in product labeling

4. Nonclinical Pharmacology/Toxicology

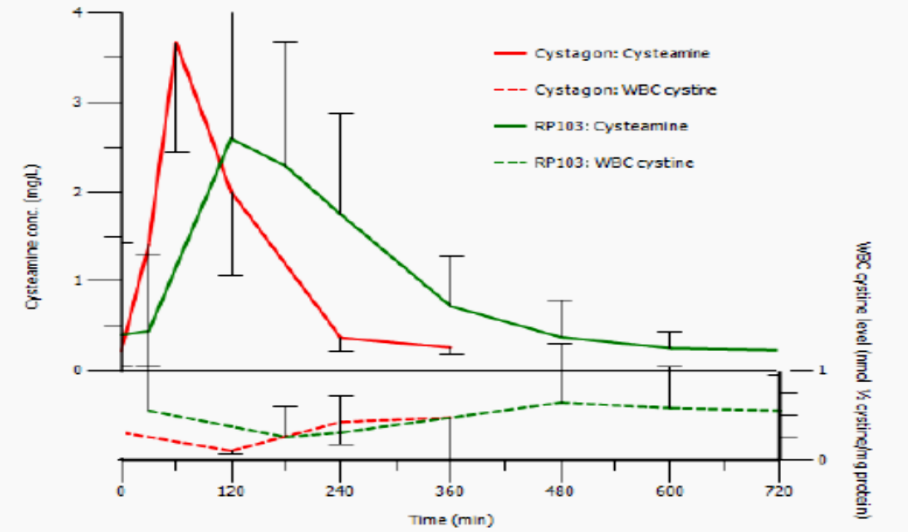
The preclinical Pharmacology/Toxicity reviewer for this application was Fang Cai, Ph.D. No new nonclinical studies were conducted by the applicant. The applicant relied upon published data and the Agency's findings from its review of the reference product CYSTAGON®. Dr. Cai recommended an action of approval for the drug product. Further details of the nonclinical review are referred to Dr. Cai's review.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the reviews of Drs. Earp and Estes for discussion of the pharmacometric and clinical pharmacology of PROCYSBI®. Briefly, the pharmacodynamic endpoint studied in these trials concerned cystine accumulation in reference tissue, i.e. white blood cells. Normal individuals and individuals that are heterozygous for cystinosis have WBC cystine levels of < 0.2 nmol ½ cystine/mg protein and usually <1 nmol ½ cystine/mg protein, respectively. WBC cystine level was the primary efficacy endpoint in the pivotal trial (RP103-03) and its extension study (RP103-04).

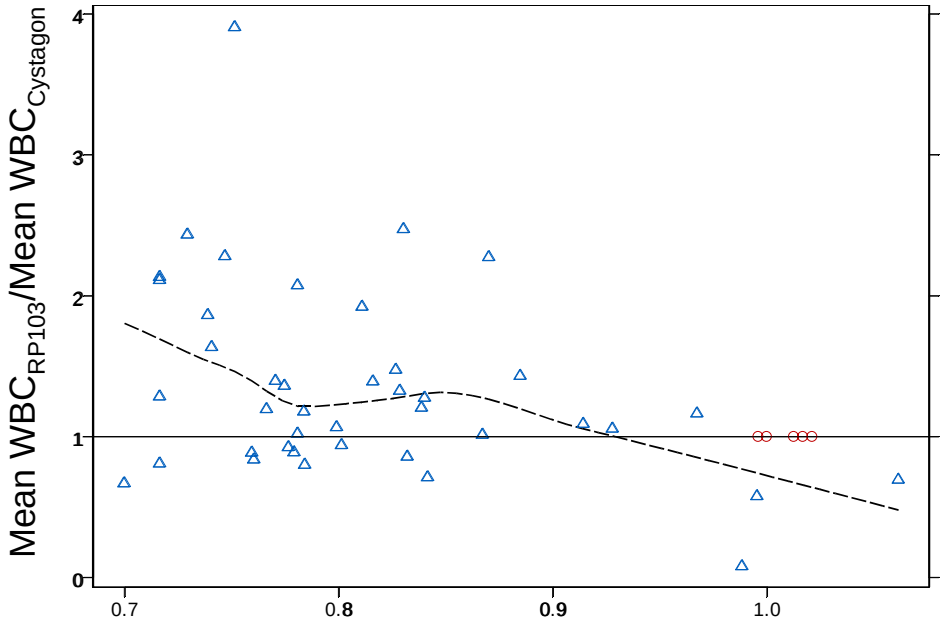
The PK and PD relationship of CYSTAGON® and PROCYSBI® is reproduced below from Dr. Epps' review and nicely delineates some mild differences in the pharmacokinetic aspects between the two molecules but no difference in pharmacodynamic effect:

Figure 1: RP103-03: PK/PD Model of WBC Cystine Level (nmol ½ cystine/mg protein) vs. Cysteamine Plasma Concentrations



A major issue during this review and labeling negotiations with the Sponsor concerned the equivalence or lack of equivalence of the doses of both products and the pharmacodynamic effects. Dr. Earp nicely demonstrated that despite the Sponsor claim of 70-80% dose of PROCYSBI® required for maintenance of WBC cystine level of normal values, the true required amount is equivalent to CYSTAGON®. The original proposed label doses and dose amounts administered during the trial were incorrectly determined. After correct analysis of the dosage forms, it is apparent that the CYSTAGON® dosage forms contained 85% of the stated dose and the RP103 contained ~91% of the stated dose in the phase III clinical trial. This would suggest that the amount of cysteamine administered with PROCYSBI® is closer to that with CYSTAGON® than initially anticipated. As evidenced in the Figure 2 below, the relative WBC cystine after PROCYSBI® to WBC cystine after CYSTAGON® demonstrated relative lack of efficacy in the lower dose of PROCYSBI®. Therefore, the final labeling of the maintenance dose will reflect this dosing paradigm.

Figure 2: Relative WBC Cystine after RP103 to WBC Cystine after CYSTAGON® is higher in patients with reduced total cysteamine bitartrate in the dosage form. Each point represents data for one individual. Blue triangles indicate results from patients receiving PROCYSBI®**. Red circles indicate results from patients receiving CYSTAGON®.**



6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because PROCYSBI® is not intended as an antimicrobial product.

7. Clinical/Statistical-Efficacy

The reader is referred to the Clinical review of Dr. Epps for further information on clinical trial specific information. Table 1 reproduced below describes the datasets used for the determination of efficacy and safety for PROCYSBI® in children >6 years of age and adults. The pivotal trial was a 9-week, open-label, multicenter, randomized, cross-over, pharmacokinetic (PK) and pharmacodynamics (PD), non-inferiority trial designed to evaluate the safety and efficacy of RP103 (cysteamine bitartrate delayed release capsules) compared to CYSTAGON® in patients with nephropathic cystinosis. These data demonstrate the noninferiority margins between Cystagon® and PROCYSBI® were reached successfully (Table 2). The most critical issue reflects the absence of efficacy and safety data in children less than 6 years of age. Further discussion of this issue is in Section 10. This information will be collected through a sub-study on an ongoing study of safety and be performed in a written request-see below.

Table 1: Table of RP103 Studies & Clinical Trials

Study ID Phase	Study Design	Planned/Actual/ Completed	Drug Dose Route of Administration	Study Objective	Study population	Treatment Duration	Status
Pilot Study							
RP103-01 1/2	Single center, single dose, open label, nonrandomized	10/9/9	RP103 450 mg normalized single dose vs. CYSTAGON® 450 mg normalized single dose; Oral (capsules)	PK, Tolerability	Patients with nephropathic cystinosis	Single dose	Completed
Bioequivalence Studies							
RP103-02 1	Single site, randomized, crossover, fed	38/18/17	RP103 600 mg single dose Intact vs. opened capsules mixed with food	BE (intact vs. opened capsules	Healthy volunteers	3 weeks	Completed
RP103-05 1	Single site, randomized, crossover, fasted	40/20/17	RP103 600 mg single dose Intact vs. opened capsules mixed with food; 30 min & 2 hour meal delay	BE (intact vs. opened capsules; meal delay	Healthy volunteers	2 weeks	Completed
RP103-06 1	Single site, randomized, crossover, fasted	20/20/19	RP103 600 mg single dose Intact capsules administered with orange juice vs. capsule contents mixed with food	BE (intact vs. opened capsules)	Healthy volunteers	2 weeks	Completed
Clinical Trials							
RP103-03 2/3	Multi-center, randomized, crossover	36/43/41	RP103 Q12H vs. CYSTAGON® Q6H; Oral (capsules)	Efficacy & Safety	Patients with nephropathic cystinosis	9 weeks	Completed
RP103-04 3	Multi-center, long-term, open label	60/60/0	RP103 Q12H; Oral (capsules)	Long-term Safety	Patients with nephropathic cystinosis	Up to 24 months	Ongoing

Table 2: Statistical Analysis of Pharmacodynamic Parameters of WBC Cystine (nmol ½ cystine/mg protein) (Per Protocol and ITT Populations)

Treatment	N	LS Means (SE)	Difference of LS Means* (SE)	SE of LS Mean Difference	T-Value for CI (DF=37)	95.8% CI of LS Means Difference	P-Value
Per Protocol Population							
CYSTAGON®	39	0.4367 (0.05555)	**0.0785**	0.0323	2.1037	0.0107 to 0.1464	**<0.0001**
RP103	39	0.5152 (0.05555)					
ITT Population							
CYSTAGON®	41	0.7355 (0.13838)	**-0.2089**	0.1285	2.1000	-0.4788 to 0.0609	
RP103	43	0.5266 (0.13740					

S=least squares; SE=standard error; DF= degrees of freedom; CI= confidence interval
*Difference= RP103 LS means minus CYSTAGON® LS means

8. Safety

Overall, the safety profile of RP103 appears to be similar to the reference product CYSTAGON®, although a higher incidence of gastrointestinal adverse events was observed in the pivotal trial with PROCYSBI® compared to CYSTAGON®. The unresolved issue of amelioration of gastrointestinal adverse reactions with concomitant PPIs has been addressed in Dr Dimick's review. The sponsor postulated that the delayed release formulation would result in decreased requirement for acid reducing medications but this was not demonstrated in the controlled trial and therefore labeling will not reflect this issue. Due to the similarity in safety, in this reviewer's opinion, the data appear adequate to support an indication in treatment-naïve patients as well as patients previously treated with CYSTAGON®. However, safety data were not available for pediatric patients under 6 years old. The applicant has submitted a Proposed Pediatric Study Request (PPSR) for the evaluation of PROCYSBI® in pediatric patients (b) (4)

For further review of the safety issues, the reader is referred to Dr. Epps Clinical review.

I agree with the approval recommendation based on review of the Safety of PROCYSBI® in this population labeled from 6 years and above.

9. Advisory Committee Meeting

There was no Advisory Committee for this application.

10. Pediatrics

The issue of (b) (4) PROCYSBI® for children (b) (4) will be pursued later (b) (4) with data collected as part a written request to the Sponsor and data collected as part of the ongoing clinical program. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, the Sponsor is exempt from this requirement. Therefore, the mechanism of the written request will be used to gather this information (b) (4) The applicant has submitted a Proposed Pediatric Study Request (PPSR) for the evaluation of PROCYSBI® in pediatric patients (b) (4) Upon discussion with the Sponsor, the written request will be modified (b) (4)

(b) (4)

11. Other Relevant Regulatory Issues

A. Financial Disclosures

All of the data from studies reviewed with this supplement were originally submitted for review with the original NDA. Therefore, there was new financial disclosure information submitted with this supplement.

B. DSI audits

The Division of Scientific Investigations (DSI) was consulted to determine the reliability of date by evaluating US and foreign clinical sites with most enrolled patients for trials RP103-03 and RP103-04. A total of two clinical sites were inspected. These sites were selected for inspection because of their high enrollment and geographic location (one domestic and one foreign site). The DSI inspector reported that no significant regulatory violations were noted and concluded that data from the two sites could be used in support of the NDA.

In addition, due to concerns about the calculation errors for WBC cystine concentration for Study RP103-03, DSI conducted a "for cause" data validation inspection at the bioanalytical site that performed the analyses: (b) (4) (b) (4) also performed analyses at a second site in the (b) (4) however, this site is now closed. DSI reported that no significant regulatory violations were noted. However, the inspectors observed that several testing methodologies are used to measure protein when determining WBC cystine levels and that the absolute (but not relative) values obtained vary

depending upon the methodology used. Per the review in the CDTL memorandum of Dr. Dimick, inspectors observed that several testing methodologies are used to measure protein when determining WBC cystine levels and that the absolute (but not relative) values obtained vary depending upon the methodology used to assess the protein content of the WBC's. This can result in variations the absolute value of the WBC cystine level as much as one-half to twice the absolute value. There iwill be appropriate language in the label to address the performance of the WBC cystine level to be done reproducibly in the same laboratory to assure local methodology and calibration of protein assays to assure targeting the WBC cystine level to <1 nmol ½ cysteine/mg protein.

12. Labeling

I concur with the recommendations made by all reviewers specifically related to use of gastrostomy or other types of feeding tubes with PROCYSBI®. In addition dosing and administration shall address the equivalence of recommended doses of PROCYSBI® compared to CYSTAGON® and risk of alcohol dose dumping as noted by the CMC reviewer. Furthermore, labeling of the safety section will not appear differently than CYSTAGON®, as the adverse reactions are similar and equivalent.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:
All of the review disciplines recommended the product for approval pending approved labeling. This Signatory concurs with the approval recommendation.

13.2 Risk Benefit Assessment:
All of the review disciplines recommended the product for approval. This Signatory concurs with the approval recommendation.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
There are no requirements for postmarketing evaluation.

Recommendation for other Postmarketing Requirements and Commitments
We remind you of your postmarketing commitments:

2043-1 Revise the drug product specification to add testing of elemental impurities for arsenic, cadmium, lead, and mercury per USP <232>.

The timetable you submitted on March 4, 2013, states that you will provide this information according to the following schedule:

Final Report Submission: 06/2013

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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

/s/

ANDREW E MULBERG
04/30/2013