CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200740Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 200740 SUPPL # HFD #

Trade Name Cystaran

Generic Name cysteamine ophthalmic solution 0.44%

Applicant Name Sigma-Tau Pharmaceuticals, Inc.

Approval Date, If Known October 2, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Seven years orphan exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020392 Cystagon

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	STP869294 (CAPTOC)	YES ☐	NO ☒
Investigation #2	98 EI0109E	YES ☐	NO ☒
Investigation #3	98 EI019S	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	STP869294 (CAPTOC)	YES ☐	NO ☒
Investigation #2	98 EI-1090E	YES ☐	NO ☒

Investigation #3 98 EI-0109S YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 STP869294 (CAPTOC)

Investigation #2 98 EI-1090E

Investigation #3 98 EI-0109S

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 40,593 YES ☐ NO ☒

Explain:
Transfer of sponsorship to Sigma-Tau in Feb. 2010

Investigation #2

IND # 40,593 YES ☐ NO ☒

Explain:
Transfer of sponsorship to Sigma-Tau in Feb. 2010

Investigation #2 NO ☒

IND # 40,593 YES ☐

Explain: Transfer of sponsorship to Sigma-Tau in

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: June Germain
Title: Senior Regulatory Project Manager DTOP
Date: 10-4-12

Name of Office/Division Director signing form: Wiley A chambers
Title: Deputy Director-DTOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

JUNE GERMAIN
10/11/2012

WILEY A CHAMBERS
10/16/2012

1.3.5.3 Exclusivity Request

Pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act, Cystoran™ (cysteamine hydrochloride) Ophthalmic Solution was granted orphan drug designation for Owner of Orphan Drug Designation (ODD 97-1059) for the treatment of corneal cystine crystal accumulation in cystinosis patients. See FDA letter dated *August 19, 1997*.

We have notified the Office of Orphan Products Development of our intention to exercise the statutory period of 7 years of orphan drug exclusivity if we are the first sponsor to obtain market approval for Cystoran Ophthalmic Solution for the treatment of the above orphan drug designation indication.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 19, 1997

Sigma-Tau Pharmaceuticals, Inc.
800 South Frederick Avenue
Gaithersburg, MD 20877

Attention: A.C. Hanzas
Director, Regulatory Sciences/Marketed Drugs

Dear Mr. Hanzas:

Reference is made to your orphan drug application of June 12, 1997 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of cysteamine hydrochloride as an orphan drug (application 97-1059).

We have completed the review of this application and have determined that cysteamine hydrochloride qualifies for orphan designation for the treatment of corneal cystine crystal accumulation in cystinosis patients. Please note that it is cysteamine hydrochloride and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity.

Also please be advised that if cysteamine hydrochloride were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of cysteamine hydrochloride as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing

application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 827-0991.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner

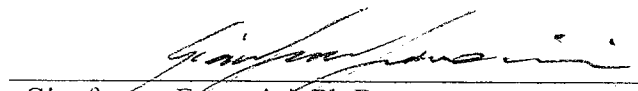
Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

1.3.3 Debarment Certification

Sigma-Tau Pharmaceuticals, Inc. (STP), hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

STP certifies that, during the previous 5 years, it has not sustained a conviction that is described in Sections 306(a) or (b) of the Act. In addition, no person affiliated with STP, nor affiliated persons responsible for the development or submission of this application, have been convicted of an offense described in Sections 306(a) or (b) of the Act.

Furthermore, STP agrees to notify FDA of any changes in status of any employee with respect to Sections 306(a) or (b) of the Act.



02-16-2010

Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
Sigma-Tau Pharmaceuticals, Inc.
Gaithersburg, MD 20878

Date

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time:	September 18, 2012
Meeting Location:	**Teleconference**
Application Number:	NDA 200740
Product Name:	Cystaran (cysteamine ophthalmic solution)
Indication:	treatment of corneal cystine crystal accumulation in patients with cystinosis
Sponsor/Applicant Name:	Sigma-Tau Pharmaceuticals, Inc.
Meeting Chair:	Wiley A. Chamber, MD
Meeting Recorder:	June Germain, MS

FDA ATTENDEES

Renata Albrecht, MD	Division Director, DTOP
Wiley Chambers, MD	Deputy Director, DTOP
William Boyd, MD	Medical Team Leader, DTOP
Derek Smith, PhD	Compliance Officer, OMPQ
Maotang Zhou, PhD	Product Quality Reviewer, ONDQA
Rapti Madurawe, PhD	Supervisor Chemist, ONDQA, Branch V
June Germain, MS	Senior Project Manager, DTOP

APPLICANT ATTENDEES

GianFranco Fornasini	Sr. VP. Scientific Affairs
Nadia Soukhareva	Sr. Manager Regulatory Affairs
Raven Jaeger	Sr. Manger Regulatory Affairs
Christopher Lauderback	Sr. Manager Scientific Affairs
[redacted] (b) (4)	
James Carmelitano	VP Quality Operations
Jan Spitael	VP Manufacturing
Larry Beiter	Technical Project Manager
Lee Althoff	Director Maintenance and Materials
[redacted] (b) (4)	
Mandy Redmond	Manager Site Compliance
Pauline Ginsberg	Project Manager

1. BACKGROUND

The Division requested a Tcon with the applicant to discuss the NDA application the its drug product manufacturing site Sigma-Tau recent inspection and 483 citations.

2. DISCUSSION

The Division noted that during the last inspection of Sigma-Tau manufacturing site the facility received several 483s for serious cGRMP problems that are still unresolved today. The applicant stated they submitted a reply to the FDA on June 13, 2012 of their intention to correct the deficiencies cited in the 483s. They also noted on July 31, 2012 began implementing changes to address the deficiencies and plan to submit an update to the FDA in October. The Division acknowledge the applicants plans to address the deficiencies and also stated that there appears that the applicant have more facilities in which to manufacture the drug product. The applicant acknowledged that there are two sites one Sigma-Tau and High Tech Pharmacal Co, Inc. The applicant stated that High Tech can produce the drug product and had been inspected and was in compliance. The Division confirmed that High Tech was acceptable and in compliance. The Division stated that the application could not be approved if the drug product manufacturing site was not in compliance with cGRMP standards and pending 483s deficiencies. The Division noted that Sigma-Tau facility could be added as a drug product manufacturing site at a later time through a supplemental application when the 483s were addressed and in compliance. The applicant stated that they could remove Sigma-Tau facility from the NDA as the DP manufacturer until they completed the implementation process to address the 483 deficiencies. The Division agreed that could be one pathway forward. However, the Division noted that if the endotoxin testing for drug product manufacturing is only performed at Sigma-Tau then there would be a compliance issue. The applicant stated that Sigma-Tau would only be used for the endotoxin testing and not DR manufacturing. The applicant noted that in order to address the 483 Sigma-Tau would also have to be re-inspected and inquired if they would also have to request a new inspection. The Division stated that at the point where the 483s were addressed and the facility ready for inspection a supplemental application submission to the NDA would trigger an inspection from the Office of Compliance. The Division stated that the applicant will have to submit an amendment, to the NDA, to withdraw Sigma-Tau as the drug product manufacturing site but also include keep Sigma-Tau as the manufacturing site for the endotoxin testing for the drug product. The applicant agreed to provide this amendment by email to project manager on Sept. 19, 2012 and then follow-up with the same submission to the NDA by Sept. 21, 2012.

3. ACTION ITEMS

- The applicant will email the project manager an official letter withdrawing Sigma-Tau as the drug product manufacturing site but note plans to keep Sigma-Tau as endotoxin testing for drug product.
- The applicant will submit with an official amendment to the NDA to withdraw Sigma-Tau as drug product manufacturing site and also include updated labeling to remove Sigma-Tau as the DP manufacturer.

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/s/

JUNE GERMAIN
09/21/2012
Tcon memo held 9-18-12

Sigma-Tau Attendees

Christopher Lauderback, PhD	CMC Senior Manager
[redacted] (b) (4)	
Judy Inge	Senior Director Regulatory Affairs
Gianfranco Fornasini, PhD	Senior Vice President Scientific Affairs

Division of Anti-Infective and Ophthalmology Attendees

Wiley A. Chambers, MD	Acting Director
William Boyd, MD	Medical Team Leader
Fariba Izadi, Pharm.D	Regulatory Health Project Manager

In a teleconference held on August 31, 2010 With Sigma Tau, the Sponsor stated that they are aware that they have manufacturing facilities not in compliance with current good manufacturing practice. The Division explained the concept of Complete Response letters as opposed to previous Approvable or Non-Approval letters if there are unsolved deficiencies remaining in a pending new drug application. At Sigma-Tau's request, the Division also discussed the different ramifications of withdrawing a new drug application versus receiving a Complete Response letter.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
08/31/2010

Germain, June

From: Duvall, Beth A
Sent: Friday, August 31, 2012 12:53 PM
To: Germain, June
Cc: Raggio, Miranda; Bertha, Amy; Roeder, David L
Subject: NDA 200740/Cystaran - cleared for action

Attachments: NDA 200740 - cleared for action; N200740_Assessment_original.doc

June,

Thanks for the clarifications. Your application is now cleared for action from a 505(b)(2) perspective.

Rather than trying to reconcile two different version of the assessment, please make sure the previously communicated changes were made to the ORIGINAL assessment (see attached clearance email) and then also apply these additional changes to the ORIGINAL assessment before archiving in DARRTS (assuming you are now heading towards approval; otherwise, make these changes but defer archiving until an approval). In other words, scrap your more recent version and apply changes based on the original version attached here.

- Application Information: please update receipt and PDUFA due dates to reflect the current review cycle
- Q2: Include the NDA number, NDA20392, for the Cystagon entry
- Q3: The original clearance email on 8/16/10 asked you to "provide an explanation for how the applicant bridged their proposed product to Cystagon. (info described in your 8/3/10 email)" The 8/3/10 email included an email from Bill Boyd that described the bridge as follows: "The information that they are using as the b2 information is toxicology info using an overexposure to the drug substance. This cannot be achieved with the drug product for either a b1 or a b2, but is instead done with a different dosing regimen and formulation of the active ingredient. The bridge is therefore that the drug substance is chemically the same, determined chemically." Please revert back to this description of bridging.
- Q4b: Should be 'no' (b) (4) Leave 4c blank.
- Q8a: Previous assessment answered "No", but current assessment has "Yes" checked. Please clarify if the relied-upon LD, NDA 20392 was a 505(b)(2).
- Q10c: Uncheck "No", as your response to 10a is "No"


NDA 200740 - cleared for actio...


N200740_Assessment_original.do...

Beth Duvall
Associate Director for Regulatory Affairs
CDER/Office of New Drugs
Direct Phone Number: (301) 796-0513
OND IO Phone Number: (301) 796-0700
Fax: (301) 796-9855

From: Germain, June

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 9, 2012

To: Gianfranco Fornasini, PhD Senior Vice President, Scientific Affairs	**From:** June Germain, MS Senior Regulatory Project Manager
Company: Sigma-Tau Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
FAX number: 301-948-1862	**Fax number:** (301)796-9881
Phone number: 301-670-2192	**Phone number:** (301) 796-0424
Subject: NDA 200740 product quality Information Request	
Total no. of pages including cover: 3	

Comments:

Document to be mailed: ☐YES ■NO

NDA 200740 **INFORMATION REQUEST**
cysteamine ophthalmic solution
Sigma-Tau Pharmaceuticals, Inc.
CMC Information Request

Dear Dr. Fornasini,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for cysteamine ophthalmic solution.

We are reviewing the product quality section of your submission and have the following information request. We request a response by August 13, 2012 in order to continue our evaluation of your NDA.

1. Please update the drug substance stability specification, i.e., Table 3.2.S.7.1-5, to reflect the revised acceptance criteria per FDA's 02 July 2012 information request.

2. Please update the drug substance stability data from (b) (4) and the drug product stability data from STPS.

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/s/

JUNE GERMAIN
08/09/2012
CMC information request 8-9-12

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2012

To: GianFranco Fornasini, Ph.D. Senior Vice President, Scientific Affairs	**From:** June Germain, MS Senior Regulatory Project Manager
Company: Sigma-Tau Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Fax number: 301-948-8627	**Fax number:** (301)796-9881
Phone number: 301-670-2192	**Phone number:** (301) 796-0424

Subject: NDA 200740 Request for product quality microbiology information

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** ☑ **NO**

NDA 200740 **INFORMATION REQUEST**
cysteamine hydrochloride ophthalmic solution, 0.44%.
Sigma-Tau Pharmaceuticals, Inc.
CMC Information Request

Dear Dr. Fornasini,

Please refer to your New Drug Application (NDA) submitted under section 505(b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for cysteamine hydrochloride ophthalmic solution, 0.44%.

We are reviewing the product quality section of your submission and have the following information request. We request a response by August 3, 2012, in order to continue our evaluation of your NDA.

1. Provide the results of minimum and maximum equipment load validation studies conducted in the (b) (4)

(b) (4)

3. Provide the (b) (4) bioburden limit for Cystaran.

4. Provide the type(s) of microbiological media and the post-sampling incubation conditions used for (b) (4) bioburden testing.

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/s/

JUNE GERMAIN
07/23/2012
product quality request

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 200740

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Sigma-Tau Pharmaceuticals, Incorporated
9841 Washingtonian Boulevard, Suite 500
Gaithersburg, MD 20878

ATTENTION: GianFranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs

Dear Dr. Fornasini:

Please refer to your New Drug Application resubmission (NDA) dated March 30, 2012, received April 2, 2012, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cysteamine Ophthalmic Solution, 0.44 %.

We also refer to your correspondence, dated and received April 13, 2012, requesting review of your proposed proprietary name, Cystaran. We have completed our review of the proposed proprietary name, Cystaran and have concluded that it is acceptable.

The proposed proprietary name, Cystaran, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 13, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, June Germain, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200-740

INFORMATION REQUEST

Sigma-Tau Pharmaceuticals, Inc.
Attention: GianFranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
9841 Washingtonian Blvd, Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cysteamine hydrochloride ophthalmic solution, 0.44%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by July 17, 2012, in order to continue our evaluation of your NDA.

1. Provide rationales including supporting data to justify your designation of the critical steps and intermediates in Section 3.2.S.2.4.

2. ICH Q6A recommends setting and justifying specifications based on the test results from stability and scaleup/validation batches with emphasis on the primary stability batches. Based on the available batch analysis data and stability data (with emphasis on data from (b) (4)), please make the following modifications on the drug substance specification:

    a. The revised limit for (b) (4) in the drug substance based on the lab batch data is not justified. Based on the primary stability batch data, we recommend that the acceptance criteria for (b) (4) and total residual solvents be tightened to NMT (b) (4) and NMT (b) (4) respectively.
    b. Since the batch data and stability data from all (b) (4) batches and most (b) (4) batches have shown that the level of the (b) (4) impurity is within the range of (b) (4) the proposed limit of NMT (b) (4) for the specified impurity (b) (4) is not justified. We recommend that it be tightened from NMT (b) (4) to NMT (b) (4) This recommendation also takes into consideration of the fact that this impurity level is also an indicator for the container closure integrity as shown by some (b) (4) stability batches.
    c. In accordance with 2.b above, tighten the acceptance criterion for Total Impurities (Specified and Unspecified) from (b) (4) to NMT (b) (4)

3. Provide data (i.e., extractable data) to demonstrate the drug product compatibility of the [redacted (b) (4)] Please confirm that the [redacted (b) (4)] Otherwise, additional data should be provided to demonstrate their suitability for the intended use for the drug product.

4. In Section 2.3.P.8, you state that data from freeze-thaw and simulated usage studies are provided; however, we were not able to locate these data in Section 3.2.P.8.3. Please provide the data.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
07/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200,740

ACKNOWLEDGE – CLASS 2 RESPONSE

Sigma-Tau Pharmaceuticals, Inc.
Attention: GianFranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
9841 Washingtonian Blvd, Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

We acknowledge receipt on April 2, 2012, of your March 30, 2012, resubmission of your new drug application submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for cysteamine hydrochloride ophthalmic solution, 0.44%.

We consider this a complete, class 2 response to our September 3, 2010, complete response action letter. Therefore, the goal date is October 2, 2012.

If you have any questions, call me at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

June Germain, MS
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JUNE GERMAIN
04/16/2012
Acknowledge resubmission

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, August 25, 2010 1:50 PM
To: 'GianFranco Fornasini'
Subject: NDA 200,740 cysteamine hydrochloride ophthalmic solution 0.44 % labeling correspondence of August 16, 2010

Dear Dr. Fornasini,

Please refer to your pending NDA 200740 for Cystaran (cysteamine hydrochloride ophthalmic solution0 0.44%). We are suggesting the following modifications to your revised draft Cystaran label. Please do not hesitate to call me if you have any questions.

1) The following sentence in Section 16 of the package insert:

Store in freezer −25° to −15°C (−13° to 5°F).

Should be replaced with:

Store in freezer −25 to −15°C (−13 to 5°F).

2) The following two sentences on both the carton and container labels:

Store in freezer −25° to −15°C (−13° to 5°F).

Store thawed bottle a [redacted] (b) (4) for up to 1 week.

Should be replaced with:

Store in freezer −25 to −15°C (−13 to 5°F).

Store thawed bottle at 2 - 25°C (36 - 77°F) for up to 1 week.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: STPRegSci [mailto:STPRegSci@sigmatau.com]
Sent: Friday, August 20, 2010 10:41 AM
To: Izadi, Fariba
Cc: GianFranco Fornasini
Subject: NDA 200,740 cysteamine hydrochloride ophthalmic solution 0.44 % labeling correspondence of August 16, 2010

Dear Dr. Izadi,

Please refer to our pending NDA 200740 for Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.44%.

In addition, please refer to your email of August 16, 2010, wherein you provided a revised draft Cystaran label and proposed carton and container mock-ups and to our email of August 17, 2010 wherein we notified you that we have accepted all of your changes and committed to submit revised labeling as soon as possible.

On further review of your changes, we are requesting to modify your suggested labeling to add clarification to the name as follows:

From:
Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.44%.

To:
Cystaran™ (cysteamine hydrochloride ophthalmic solution) 0.44% (b) (4)).

Further please refer to our telephone conversation of August 18, 2010 wherein we discussed that we can expect clarification on the date of initial U.S. Approval in the HIGHLIGHTS Section by next Tuesday (August 24, 2010). It is listed as follows: "Initial U.S. Approval: 1994".

Attached please find the revised labeling with all of your changes incorporated with the exception of our suggested modification to the name as noted above.

To facilitate your review we are attaching final mock-ups of the labeling as well as mark-ups indicating our suggested modification to the name.

We kept the Initial U.S. Approval as 1994, pending your response.

Please note that as mentioned in our email of August 17, 2010, regarding the package insert we have changed the contact information for reporting suspected adverse reactions to a dedicated number used Sigma-tau Pharmacovigilance. Please see the original and revised information below (change is highlighted yellow). In addition, we have added our corporate logo at the end of the insert. These changes are reflected in the attached labeling.

ORIGINAL:
HIGHLIGHTS OF PRESCRIBING INFORMATION
ADVERSE REACTIONS
To report SUSPECTED ADVERSE REACTIONS, contact Sigma-Tau Pharmaceuticals, Inc. at tel: 1- (b) (4) **or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.**

REVISED:
HIGHLIGHTS OF PRESCRIBING INFORMATION
ADVERSE REACTIONS
To report SUSPECTED ADVERSE REACTIONS, contact Sigma-Tau Pharmaceuticals, Inc. at tel: 1-888-393-4584 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

We will follow this request with an official electronic submission to the NDA as soon as possible.

If you have any questions, please do not hesitate to contact me at 301-670-2192.

With kind regards,

Gianfranco Fornasini, **Ph.D.** w. 301-670-1537 | f. 301-948--8627
Sigma-Tau Pharmaceuticals, Inc. | Sr. Vice President Scientific Affairs
R a r e D e d i c a t i o n
9841 Washingtonian Blvd. #500 | Gaithersburg, MD 20878

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
08/27/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Monday, August 16, 2010 11:49 AM
To: 'STPRegSci'
Cc: 'GianFranco Fornasini'
Subject: NDA 200740 (Cystaran) label

Attachments: Cystaran proposed carton container.doc; FDA clean label 8_16_10.doc

Dear Dr. Fornasini,

Attached, please find a copy of draft Cystaran label and proposed carton and container mock-ups. We are available for questions and discussions after you review the label. Please respond by August 23, 2010. Please note that all facilities need to be in compliance with cGMP.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Cystaran proposed carton conta...

FDA clean label 8_16_10.doc (1...

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
08/17/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 200740

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Sigma-Tau Pharmaceuticals, Incorporated
9841 Washingtonian Boulevard, Suite 500
Gaithersburg, Maryland 20878

ATTENTION: Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs

Dear Dr. Fornasini:

Please refer to your New Drug Application (NDA) dated March 3, 2010, received March 4, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cysteamine Hydrochloride Ophthalmic Solution, 0.65%.

We also refer to your May 14, 2010, correspondence, received May 14, 2010, requesting review of your proposed proprietary name, Cystaran. We have completed our review of the proposed proprietary name, Cystaran and have concluded that it is acceptable.

The proposed proprietary name, Cystaran, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 14, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Fariba Izadi, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

CAROL A HOLQUIST
08/12/2010

Teleconference August 4, 2010

Division of Anti-Infective and Ophthalmology Attendees:

William Boyd, MD Clinical Team Leader
Fariba Izadi, Pharm.D. Regulatory Health Project Manager

Sponsor Attendees:

SIGMA-TAU PHARMACEUTICALS, INC. (STP)(NDA Sponsor)
Judith A. Inge, Sr. Director Regulatory Affairs, Sigma-Tau Pharmaceuticals
Wave Sewlall, Regulatory Specialist, Regulatory Affairs
(b) (4)

Diana Bernstein, Project Manager
(b) (4)

(b) (4)

Discussion:

In a teleconference held on August 4, 2010 with Sigma-Tau, Dr. William Boyd explained to the Sponsor that redaction of information in the case report forms is not acceptable. The Division asked the Sponsor to provide non-redacted copies of the CRF pages for the patient 8983818 and 315632.

The Sponsor has committed to submit the non-redacted forms via email and follow up with an electronic submission.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
08/05/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Monday, August 02, 2010 10:06 AM
To: 'STPRegSci'
Cc: 'GianFranco Fornasini'
Subject: NDA 200740 information request

Dear Dr. Fornasini,

We are reviewing your submission for NDA 200740 (Cysteamine HCl) and have the following information request.

Regarding CAPTOC (STP869294), the Case Report forms for three of the five patients (Patients 315632, 727697, and 883818) who died with no cause provided have been redacted. Please Clarify in detail why these CRFs are redacted.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this e-mail.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
08/02/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Friday, July 23, 2010 12:47 PM
To: 'STPRegSci'
Cc: 'GianFranco Fornasini'
Subject: NDA 200740 (Cysteamine Hcl) Response to Information request.

Dear Dr. Fornasini,

Please refer to your submission dated July 20, 2010 and the question on page 2 concerning the endotoxin limit of no more than (b) (4) The Agency is suggesting this limit to all the Sponsors. We encourage you to try to reach this limit. If you are not able to reach the proposed limit, Please submit your proposed limit with a justification.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm the receipt of this e-mail.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
07/23/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Monday, July 12, 2010 3:18 PM
To: 'STPRegSci'
Cc: 'GianFranco Fornasini'
Subject: NDA 200740 (Cysteamine hydrochloride) Information request

Dear Dr. Fornasini,

We are reviewing your application for NDA 200740 (Cysteamine hydrochloride) and have the following information requests from our Quality microbiology team.

1. Please provide the results of bacteriostasis/fungistasis testing in support of the USP <71> sterility test.

2. The medical review division expects that ophthalmic products, including those used for topical applications, have a target endotoxin content level of no more than (b) (4) unless there is a justification for another level. Provide the test validation results (i.e. inhibition/enhancement data) for the endotoxin test and, if necessary, rationale for exceeding the targeted endotoxin concentration.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this e-mail.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
07/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200,740 **GENERAL ADVICE**

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice president, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Gianfranco:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65 % Sterile.

We have reviewed the referenced material and based on evaluation of the stability data, we recommend the following:

1. An expiry dating period of 12 months for Cystaran™ (Cysteamine hydrochloride ophthalmic solution) 0.65% when stored frozen at (b) (4)

2. Please revise the stability specification acceptance criterion for assay to (b) (4)

If you have any questions regarding this letter, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

STEPHEN P MILLER
07/08/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Tuesday, July 06, 2010 12:39 PM
To: 'GianFranco Fornasini'
Subject: RE: NDA 200740 Endotoxin Testing Plan (response to June 14-16, 2010 Information requests)

Dear Dr. Fornasini,

Please provide the results of the inhibition/enhancement studies to support your endotoxin test method.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this email.

From: STPRegSci [mailto:STPRegSci@sigmatau.com]
Sent: Friday, June 18, 2010 1:25 PM
To: Izadi, Fariba
Subject: NDA 200740 Endotoxin Testing Plan (response to June 14-16, 2010 Information requests)

Dear Ms. Izadi,
Please refer to our pending NDA 200740 for cysteamine hydrochloride ophthalmic solution, 0.65%.

In addition, please refer to your e-mail of June 14, 2010 wherein you requested that we provide the endotoxin limit for Cysteamine hydrochloride, the endotoxin test method, and a summary of the test verification data as soon as possible. Also, please refer to our June 14, 2001 response wherein we replied that we had not conducted endotoxin testing and to your reply e-mail of June 15, 2010 wherein you requested that we propose a time table for implementing this testing as soon as possible. Further please refer to your e-mail of June 16, 2010 wherein you indicated in response to our question of June 14, 2010 that testing should be conducted on Drug Product.

Attached please find, as requested in your e-mail of June 15, 2010, our plan for implementing drug product testing for endotoxin.

We will follow this request with an official electronic submission to the NDA as soon as possible.

If you have any questions, please do not hesitate to contact me at 301-670-2192.

With kind regards

Gianfranco Fornasini, **Ph.D.** w. 301-670-1537 | f. 301-948--8627
Sigma-Tau Pharmaceuticals, Inc. | Sr. Vice President Scientific Affairs
R a r e D e d i c a t i o n
9841 Washingtonian Blvd. #500 | Gaithersburg, MD 20878

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
07/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200,740 **INFORMATION REQUEST**

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice president, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Gianfranco:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65 % Sterile.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product

1. Table 3.2.P.2.2-3 indicates that batches 69819, 69818 and 71356 were used in efficacy studies. Please provide COA and stability data if available, for these batches.

2. Please provide osmolality data for the clinical lots and the primary stability batches.

3. In response to our IR regarding revising the acceptance criteria for individual unspecified degradation you have provided justification to set the limit at NMT (b) (4). Please note that for ophthalmic products, (b) (4) is what we consider acceptable and to keep it consistent, please revise the acceptance criteria appropriately.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Althea Cuff, Regulatory Project Manager in the Office of New Drug Quality Assessment (althea.cuff@fda.hhs.gov), and Fariba Izadi, Regulatory Project Manager the Office of New Drugs (Fariba.Izadi@fda.hhs.gov). Please provide comments within 7-10 days from receipt of this letter.

If you have any questions regarding this letter, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

STEPHEN P MILLER
06/29/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 200740

PROPRIETARY NAME REQUEST
WITHDRAWN

Sigma-Tau Pharmaceuticals, Inc.
9841 Washingtonian Blvd., Suite 500
Gaithersburg, Maryland 20878

ATTENTION: Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs

Dear Dr. Fornasini:

Please refer to your New Drug Application (NDA) dated March 4, 2010, received March 4, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cysteamine Hydrochloride Ophthalmic Solution, 0.65%.

We acknowledge receipt of your May 13, 2010, correspondence, received May 13, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name Cystoran. This proposed proprietary name request is considered withdrawn as of May 13, 2010.

We acknowledge that you have proposed an alternate proprietary name, Cystaran, in your submission dated May 14, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Fariba Izadi at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

CAROL A HOLQUIST
06/25/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, June 23, 2010 2:40 PM
To: 'GianFranco Fornasini'
Subject: NDA 200740 (Cysteamine HCL) Information Amendment submitted to the IND 40593

Dear Dr. Fornasini,

Please refer to the your Information Amendment (Chemistry, Manufacturing, and Control Change of Drug Substance Manufacturer) submitted to the IND 40593 on June 15, 2010. Please submit this information formally to the NDA 200740 as well.

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Please confirm receipt of this email.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
07/01/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, June 16, 2010 3:01 PM
To: 'GianFranco Fornasini'
Subject: RE: NDA 200740 (Cysteamine HCL) Information Request

Dear Dr. Fornasini,

Please note that the endotoxin testing should be conducted on the final drug product.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: GianFranco Fornasini [mailto:GianFranco.Fornasini@sigmatau.com]
Sent: Tuesday, June 15, 2010 10:21 AM
To: Izadi, Fariba
Subject: RE: NDA 200740 (Cysteamine HCL) Information Request

Dear Ms Izadi,
Sigma-tau will prepare and submit a plan for the endotoxin test.
Please confirm that the test should be carried on cysteamine hydrochloride active pharmaceutical ingredient only.
Thank you
Regards
GFF

Gianfranco Fornasini, Ph.D. w. 301-670-1537 | f. 301-948--8627
Sigma-Tau Pharmaceuticals, Inc. | Sr. Vice President Scientific Affairs
R a r e D e d i c a t i o n
9841 Washingtonian Blvd. #500 | Gaithersburg, MD 20878

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Monday, June 14, 2010 4:15 PM
To: GianFranco Fornasini
Subject: RE: NDA 200740 (Cysteamine HCL) Information Request

Dear Dr. Fornasini,

Please propose a time table for implementing this process as soon as possible. Please do not hesitate to contact me if you have any further questions.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

From: GianFranco Fornasini [mailto:GianFranco.Fornasini@sigmatau.com]
Sent: Monday, June 14, 2010 1:33 PM
To: Izadi, Fariba
Cc: STPRegSci
Subject: RE: NDA 200740 (Cysteamine HCL) Information Request

Dear Ms Izadi,

Indeed, I receive your email.

We do not have any data regarding endotoxin for drug substance or drug product for cysteamine hydrochloride.

Actually, we are not aware that the endotoxin test is required for an ophthalmic formulation.

With kind regards

GFF

Gianfranco Fornasini, Ph.D. w. 301-670-1537 | f. 301-948--8627
Sigma-Tau Pharmaceuticals, Inc. | Sr. Vice President Scientific Affairs
R a r e D e d i c a t i o n
9841 Washingtonian Blvd. #500 | Gaithersburg, MD 20878

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Monday, June 14, 2010 12:58 PM
To: GianFranco Fornasini
Subject: NDA 200740 (Cysteamine HCL) Information Request

Dear Dr. Fornasini,

We are reviewing your application for NDA 200740 (Cysteamine Hcl) and have the following information request.

Please provide the endotoxin limit for Cysteamine hydrochloride, the endotoxin test method, and a summary of the test verification data as soon as possible.

Please confirm the receipt of this email.

Best regards.

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
06/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200,740 **INFORMATION REQUEST**

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice president, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Gianfranco:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65 % Sterile.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Please remove the following statement from the footnote of the specification table: (b) (4) . Please be advised that the drug substance lot is out of the current specification if an unspecified impurity is tested to be greater than (b) (4)

2. For the HPLC method for drug substance, the Limit of Quantitation (LOQ) for the (b) (4) impurity was determined to be (b) (4) during validation at the drug product manufacturing site (Hi Tech) while it was validated at (b) (4) at the drug substance manufacturing site (b) (4) We recommend that Hi-Tech incorporate the (b) (4) sensitivity test method during system suitability test.

3. Please provide a brief explanation regarding how the acceptance limit for the assay (b) (4) (b) (4) was determined based on the batch analysis data from (b) (4) Farchemia (b) (4)

4. Significant increases in the (b) (4) impurity (b) (4) with a corresponding drop in assay were seen for some time points under accelerated storage condition (40 °C/75% RH) and the trend were not consistent among batches. Please explain the cause of the changes. Please explain whether or not these impurity changes/variability observed were caused by the variability within batch, or the variability of the container closure system? Were similar changes observed in the Farchemia batches when stored at 40 °C/75% RH?

5. Please submit 9 month stability data as soon as possible, and the 12 month stability data once available.

Drug Product

1. Given the sensitivity of the drug substance to [redacted] please comment on what protocols will be enforced in the event of a [redacted] Please provide specifics of the plan including storage conditions, and maximum hold time that the solution will be stored before processing.

[redacted]
APPEARS THIS WAY ON ORIGINAL

3. Please revise the release acceptance criteria for individual unspecified degradation product to NMT [redacted]

4. A one-time [redacted] study through the requested shelf-life should be conducted and data submitted.

5. Please provide updated stability data for the supporting batches 603240, 603244, and 603316.

6. Table 3.2.P.5.6-1, "Justification of Specifications for Cystoran", mentions, "NIH products with low assay levels used in clinical trials demonstrated efficacy and safety". Please identify these NIH lots (with manufacturing date) and details of the clinical study (study number/date etc) in which these lots were used. Also, please provide CoA for these and other clinical lots, if any.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Althea Cuff, Regulatory Project Manager in the Office of New Drug Quality Assessment (althea.cuff@fda.hhs.gov), and Fariba Izadi, Regulatory Project Manager the Office of New Drugs (Fariba.Izadi@fda.hhs.gov). Please provide comments within 2 weeks from receipt of this letter.

If you have any questions regarding this letter, call Althea Cuff, Regulatory Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

STEPHEN P MILLER
06/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200740

FILING COMMUNICATION

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

Please refer to your new drug application (NDA) dated March 3, 2010, received March 4, 2010, pursuant to under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for cysteamine hydrochloride ophthalmic solution 0.65%.

We also refer to your submission(s) dated March 26, April 9, and April 26, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 4, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to initiate discussion of the proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 14, 2010.

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 drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

WILEY A CHAMBERS
05/07/2010

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**FDA-Initiated TeleconferenceMeeting Date and**
Time:	May 6, 2010; 11:45 AM – 12:00 PM EST
Meeting Location:	WO Bldg 22, RM 4266
Application Type and Number:	**NDA** 200740
Product Name:	Cystoran
Indication:	Treatment of corneal cystine accumulation in cystinosis patients
Sponsor/Applicant Name:	Sigma-Tau Pharmaceuticals, Inc.

Meeting Chair:	Denise Toyer
Meeting Recorder:	Brantley Dorch

FDA ATTENDEES

Office of Surveillance and Epidemiology (OSE)

Denise Toyer, Deputy Director, DMEPA
Deveonne Hamilton-Stokes, Safety Evaluator, DMEPA
Doris Bates, Team Leader, Project Management Staff

Office of New Drugs (OND)

Wiley Chambers, Acting Director, DAIOP
William Boyd, Medical Officer, DAIOP
Fariba Izadi, Project Manager, DAIOP

SPONSOR PARTICIPANTS

Sigma-Tau Pharmaceuticals, Inc.

Gianfranco Fornasini, Vice President of Regulatory Affairs
Judy Inge, Senior Director of Regulatory Affairs
Marc Tewey, Vice President of Commercial Operations
(b) (4)
Wave Sewlall, Regulatory Specialist

BACKGROUND:

NDA 200740 is a new NDA with Priority review status in OND. The OND PDUFA date is September 4, 2010. The applicant amended the NDA with a request for proprietary name review on March 26, 2010, proposing the name Cystoran.

The Division of Medication Error Prevention and Analysis (DMEPA) has evaluated the proposed proprietary name Cystoran, and found the name unacceptable (b) (4) Because of the NDA's Priority review status and the limited time available for additional proprietary name reviews, DMEPA requested a teleconference with the applicant to explain our concerns with the proposed name.

MEETING OBJECTIVES:

- Discuss DMEPA's objection to the proposed proprietary name
- Discuss the sponsor's options regarding proposed proprietary name
- Obtain clarification regarding the distribution of product and how supplied

DISCUSSION POINTS:

- FDA indicated that the proposed proprietary name, Cystoran, was unacceptable for the following reasons:
  (b) (4)

- The sponsor inquired if using 'cys' as a prefix, in an alternate name, would be problematic. FDA responded that would not be an issue.

- The sponsor had not submitted any alternate names. They asked if they should submit two or three more proposed names. FDA advised Sigma Tau to submit two names at this point, and explained that only one name will be reviewed at a time.

- FDA informed the applicant that there is an Approved USAN Stems website that can be referenced prior to submitting their new name proposals.

- The sponsor asked if they could withdraw their name via email. FDA informed the applicant that they could submit a withdrawal via electronic mail but they would need to follow up with a formal amendment to the NDA. FDA also advised the applicant that they could include a new proprietary name request in the same submission. If they use a single submission to withdraw one name and submit new proposed names, the applicant should clearly indicate both actions in the cover letter. FDA also recommended that the submission be electronic if possible, to expedite delivery to the reviewers.

- FDA asked the sponsor for clarification regarding the distribution of the product and how it is supplied. The applicant stated that the medication will be dispensed

by way of a single specialty pharmacy only, for a population of 250-300 patients. Sigma Tau also stated the medication will be shipped frozen, has a short expiration date, and will be dispensed as a one month supply which is equivalent to 4 to 5 bottles.

- FDA thanked Sigma Tau for this information and the teleconference concluded cordially.

ACTION ITEMS:

- Sponsor will withdraw the name Cystoran and submit a new name for review. Revised container labeling showing the new name will also be submitted.

POST MEETING NOTES:

- Sigma Tau submitted three separate amendments to the NDA on May 13, May 14, and May 24, 2010. All were electronic submissions.
  - May 13: withdrawal of Cystoran
  - May 14: submission of Cystaran as preferred proprietary name, with (b) (4) as alternate
  - May 24, 2010: revised container labeling showing Cystaran.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

BRANTLEY H DORCH
06/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200740

FILING COMMUNICATION

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice President, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Fornasini:

Please refer to your new drug application (NDA) dated March 3, 2010, received March 4, 2010, pursuant to under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for cysteamine hydrochloride ophthalmic solution 0.65%.

We also refer to your submission(s) dated March 26, April 9, and April 26, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 4, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to initiate discussion of the proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 14, 2010.

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 drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

WILEY A CHAMBERS
05/07/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, April 28, 2010 12:49 PM
To: Gamalo, Mark; Boyd, William M; Zhang, Yongheng; Nostrandt, Amy C; Shanmugam, Balajee; Langille, Stephen; Ayalew, Kassa; Dorch, Brantley
Cc: Chambers, Wiley A; David, Jeannie C; Schmidt, Wendelyn J; Miller, Stephen; Bonapace, Charles; Wang, Yan; Hamilton-Stokes, Deveonne
Subject: NDA 200740 (Cysteamine Hcl)- Teleconfernce held 4-28-10

Hello All,

In a teleconference held on April 28, 2010 with Sigma Tau, Dr. Chambers asked whether or not the proposed NDA formulation was utilized in any of the submitted clinical trials in NDA 200740.

Sigma Tau said "no." The proposed commercial NDA formulation is identical to Formulation 3 (b) (4)

Dr. Chambers explained the formulation used during the IND Development should match the proposed NDA formulation.

Sigma Tau has committed to send an amendment to the NDA to revise the commercial NDA formulation so that it matches Formulation 3 (see April 26, 2010 submission, Table 3.2.P.2.2-2.) used in clinical development. They will be manufacturing new batches of this commercial formulation.

Please proceed with your reviews as scheduled.

Thank you,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
04/29/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200,740 **INFORMATION REQUEST**

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice president, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Gianfranco:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65 % Sterile.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

> *Please identify the active pharmaceutical ingredient (API) lot that was used in the manufacture of the drug product used for clinical trial. Also, please provide the Certification of Analysis (COA) for the clinical batch material.*

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Fariba Izadi, Regulatory Project Manager the Office of New Drugs (Fariba.Izadi@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch IV
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

STEPHEN P MILLER
04/23/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Tuesday, April 20, 2010 12:34 PM
To: 'GianFranco Fornasini'
Subject: NDA 200740 (Cysteamine hydrochloride ophthalmic solution) Information request

Dear Dr. Fornasini,

We are reviewing your submission for NDA 200740 (Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile and request response to the following as soon possible.

Statistics:

1) In your data sets folder located under M5, only tabulations can be found. If analysis data sets were created to generate the study results, please submit them.

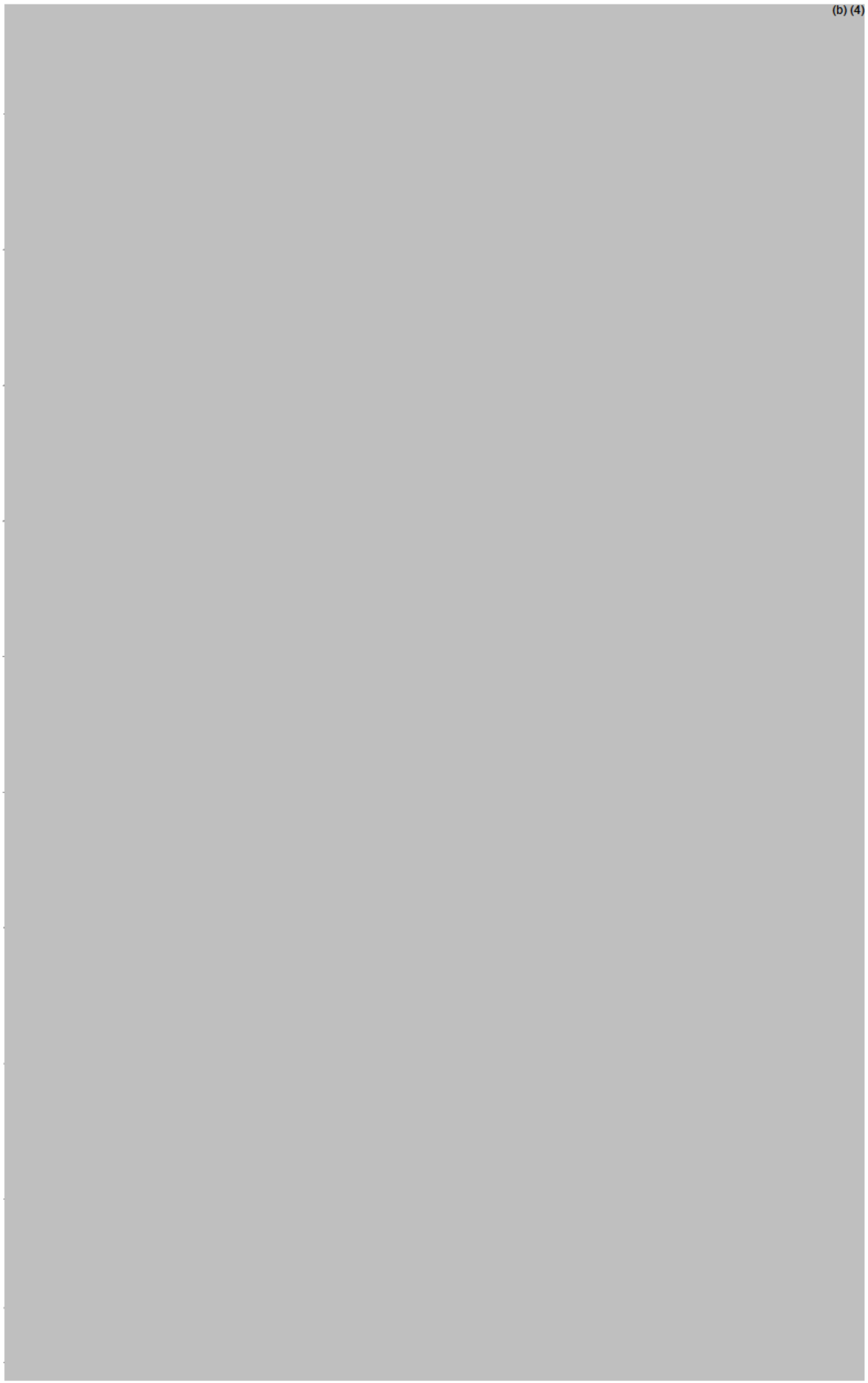
2) Please provide the SAS codes used to generate the study results. We have experienced difficulty replicating some of the primary efficacy results for Study STP869294. The following tables display the key discrepancy. Please verify and provide clarification for the discrepant findings.

Table 1: Proportion of Eyes with Corneal Cystine Crystal Score (CCCS) Response (mITT Population)

Time Point	Total Eyes (N=322)	
	Sigma-Tau[a] n (%)	FDA[b] n (%)
Response at any time during the study[a]	154/321 (48.0%)	98/321 (30.5%)
Eyes with CCCS ³ 1.00 at Baseline	150/291 (51.5%)	94/291 (32.3%)
Eyes with CCCS < 1.00 at Baseline	4/30 (13.3%)	4/30 (13.3%)

[a] Based on Table 12 in applicant's study report on p.83.
[b] Calculated using the dataset d-effres.xpt and based on the definition in the footnote of Table 12. The sample code for defining the responder is given in the following:

(b) (4)



3) It appears that the data set folder for Study 98-EI-109E and Study 98-EI-109S contains the combined data from the two studies. Please confirm this and provide a study indicator for these data sets.

4) In your diagram for Study STP869294 protocols and amendments, please clarify accumulation of patients per amendment/protocol. We could not reconcile the number of patients given in the diagram presented on page 40 in your study report with the total 247 patients recruited in the study.

Please confirm receipt of this e-mail and formally submit your responses to the NDA.

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: fariba.izadi@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
04/22/2010

Izadi, Fariba

From: Izadi, Fariba
Sent: Wednesday, April 14, 2010 1:55 PM
To: 'Gianfranco.fornasini@sigmatau.com'
Subject: NDA 200740 (Cysteamine HCL) Information Request.

Dear Dr. Fornasini,

We are reviewing your submission for NDA 200740 (Cysteamine HCL Ophthalmic Solution) and request response to the following as soon as possible.

Based on the information provided in Section 3.2.P.2.2 of the submitted NDA, the IND Development Formulation (Formulation 3) and the proposed NDA Formulation differ (b) (4) *It does not appear that the proposed NDA formulation was utilized in any of the submitted clinical trials in NDA 200740.*

Please submit, as soon as possible, a revised Table 3.2.P.2.2-3. which also includes all the other components of Formulation 3 for comparison.

Please follow-up your e-mail response also by formally submitting your responses to the NDA..

Best regards,

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

Please confirm receipt of this e-mail.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	(Cysteamine hydrochloride ophthalmic solution) 0.65% Sterile

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/s/

FARIBA IZADI
04/15/2010

Izadi, Fariba

From: GianFranco Fornasini [GianFranco.Fornasini@sigmatau.com]
Sent: Thursday, March 18, 2010 4:06 PM
To: Izadi, Fariba
Subject: RE: The Proprietary Name Submission NDA 200740 (Cystoran)

Dear Ms Fariba,
Indeed, I received this and your previous e-mail.
Thanks also for the guidance.
We already activated the process to summit the request for the review of the proprietary name "Cystoran™".
We are committed to file the submission electronically through our Agent (b)(4) which helped us for the eCTD submission.
Tentatively, we would like to submit the request by the end of the following week.
I will inform you by e-mail when the submission is ready.
With kind regards
GFF

Gianfranco Fornasini, Ph.D. w. 301-670-1537 | f. 301-948--8627
Sigma-Tau Pharmaceuticals, Inc. | Sr. Vice President Scientific Affairs
R a r e D e d i c a t i o n
9841 Washingtonian Blvd. #500 | Gaithersburg, MD 20878

From: Izadi, Fariba [mailto:Fariba.Izadi@fda.hhs.gov]
Sent: Thursday, March 18, 2010 2:52 PM
To: GianFranco Fornasini
Subject: FW: The Proprietary Name Submission NDA 200740 (Cystoran)

Dear Dr. Fornasini,

Please note that you may submit the request for review electronically to the NDA.

Best regards,

Please confirm receipt of this e-mail.

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

3/18/2010

From: Izadi, Fariba
Sent: Tuesday, March 16, 2010 12:34 PM
To: 'Gianfranco.fornasini@sigmatau.com'
Subject: The Proprietary Name Submission NDA 200740 (Cystoran)

Dear Dr.Fornasini,

Please refer to your new Drug application submitted for Cystoran (cysteamine hydrochloride solution) 0.65% Sterile on March 4, 2010. Please submit a request for review of the proposed proprietary name for approval. Attached is the Proprietary name Guidance for industry, I hope you can find helpful.

Best regards

<<Proprietary Name Submission Guidance.pdf>>

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@FDA.HHS.GOV

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	CYSTEAMINE HYDROCHLORIDE (CYSTORAN)

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/s/

FARIBA IZADI
03/22/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 200740

NDA ACKNOWLEDGMENT

Sigma-Tau Pharmaceuticals, Inc.
Attention: Gianfranco Fornasini, Ph.D.
Senior Vice president, Scientific Affairs
9841 Washingtonian Blvd. Suite 500
Gaithersburg, MD 20878

Dear Dr. Gianfranco:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cystoran (cysteamine hydrochloride ophthalmic solution) 0.65 % Sterile

Date of Application: March 4, 2010

Date of Receipt: March 4, 2010

Our Reference Number: NDA 200740

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 3, 2010 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for

review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200740	ORIG-1	SIGMA TAU PHARMACEUTICALS INC	CYSTEAMINE HYDROCHLORIDE (CYSTORAN)

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/s/

MAUREEN P DILLON PARKER
03/15/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 200740 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cystaran Established/Proper Name: cysteamine ophthalmic solution, 0.44% Dosage Form: sterile ophthalmic solution		Applicant: Sigma-Tau Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: June Germain		Division: Transplant and Ophthalmology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Cystagon (cysteamine bitartrate) Capsules

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: October 2, 2012

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is _____	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 9-3-10

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	9-2-12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 9-2-12, CR 9-3-10
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	9-24-12
• Original applicant-proposed labeling	8-30-10
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	9-24-12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Acceptable 8-10-12, 8-12-10
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM ☒ DMEPA 8-27-12, 8-13-10 ☒ DMPP/PLT (DRISK) 8-13-10 ☒ ODPD (DDMAC) 8-11-10 ☐ SEALD ☐ CSS ☐ Other reviews

Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	5-27-10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 8-31-12
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 10-2-12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	8-9-12, 7-23-12, 7-2-12, 4-16-12, 8-25-10-8-16-10, 8-2-10, 7-23-10, 7-12-10, 7-8-10, 7-6-10, 6-23-10, 6-29-10, 6-25-10, 6-16-10, 6-10-10, 5-7-10, 4-23-10, 4-20-10, 4-16-10, 3-18-10, , 3-15-10,
❖ Internal memoranda, telecons, etc.	9-21-12, 4-29-10, 8-5-10
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10-19-2001
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 10-2-12, 9-3-10
Division Director Summary Review *(indicate date for each review)*	☐ None 10-2-12, 9-3-10
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 9-26-12, 9-3-10
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	9-2-10
• Clinical review(s) *(indicate date for each review)*	9-18-12, 9-2-10
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical review pg
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 8-23-10
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 8-9-10
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6-21-12, 8-4-10
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 7-7-10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 9-25-12, 8-24-12, 4-16-12
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 8-20-12, 4-11-12
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review pg 89
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 9-24-12 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.