CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203510Orig1s000

CHEMISTRY REVIEW(S)

Addendum #1 to Review #1

From: George Lunn, Ph.D.
To: Rapti Madurawe, Ph.D.
Date: March 13, 2013

Subject: NDA 203-510 from Paragon BioTeck, Inc.
Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
Post-Marketing Commitments

In Chemistry Review #1 Post-Marketing Commitments that required chiral HPLC testing of drug product on stability and leachables testing for aged drug product were recommended. The applicant agreed to do this testing in a telecon on 2/13/13 (see Minutes dated 3/8/13). After subsequent internal discussion the chiral HPLC testing PMC was withdrawn and the applicant was so notified in a telecon on 3/13/13. The leachables PMC remains in effect.

The expiration dating period of 18 months was communicated to the applicant in a General Advice Letter dated 2/21/13.

An FDA laboratory will be asked to test various aqueous solutions of phenylephrine for racemization on storage.

The application continues to be recommended for approval from the CMC point of view.

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

/s/

GEORGE LUNN
03/14/2013

RAPTI D MADURAWE
03/14/2013

NDA 203510

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%

Paragon BioTeck, Inc.

George Lunn, Ph.D.
Division of Transplant and Ophthalmology Products

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Chemistry Review Data Sheet

1. NDA 203510

2. REVIEW #: 1

3. REVIEW DATE: 20-Feb-2013

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	19-Oct-2011
Amendment N-004	20-Sep-2012
Amendment	24-Oct-2012
Amendment	19-Dec-2012
Amendment	18-Jan-2013
Amendment	30-Jan-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Paragon BioTeck, Inc.

Reference ID: 3264058

Address:	11501 SW Pacific Highway, Suite 201 Tigard, OR 97223
Representative:	Patrick H. Witham President and CEO
Telephone:	888-424-1192, ext 3

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 7
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Mydriatic

11. DOSAGE FORM: Ophthalmic Solution

12. STRENGTH/POTENCY: 2.5% and 10%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: _X__Rx ___OTC

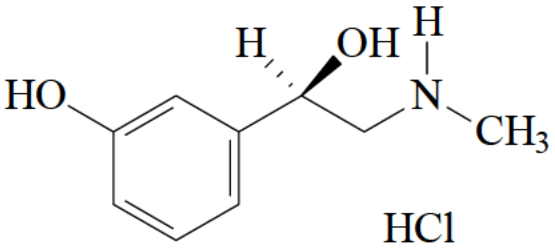
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

Reference ID: 3264058

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Phenylephrine hydrochloride

(R)-3-Hydroxy-alpha-[(methylamino)methyl]-benzenemethanol hydrochoride

$C_9H_{13}NO_2.HCl$

MW 203.67

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	2/20/13	Reviewed by George Lunn
	III			1	Adequate	11/14/12	Reviewed by George Lunn
	III			1	Adequate	11/14/12	Reviewed by George Lunn
	III			3	Adequate	10/24/12	Reviewed by Donald Klein
	III			1	Adequate	11/26/12	Reviewed George Lunn

Reference ID: 3264058

(b) (4)		(b) (4)				
	III		3	Adequate	12/19/2012	Reviewed by George Lunn

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	12/3/12	R. Safaai-Jazi
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	Not required		
OPDRA	NA		
EA	Categorical exclusion requested and accepted	10/12/12	George Lunn
Microbiology	See separate Quality Micro review		

The Chemistry Review for NDA 203510

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an Overall Recommendation of Acceptable has been made by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following post-marketing commitments are recommended. Note that the exact wording has not yet been finalized and that these issues are not thought to pose a safety risk.

1. Develop a chiral HPLC method to measure [redacted] (b) (4) phenylephrine in the drug product and analyze newly manufactured batches, stability batches as they become available, and retained samples of drug substance (if available). When sufficient information has been collected please prepare a report with numerical data to show that chiral inversion does not occur in solution or, if inversion is observed on stability, propose a regulatory control.

2. Drug product that has been stored 6 months at accelerated (25C/60% RH) and 24 months long-term (refrigerated) storage conditions should be analyzed for the presence of leachables using the [redacted] (b) (4) HPLC method (from P.2.6). The control solution used for this analysis should preferably be drug product solution that has been stored in glass ampoules for 6 months accelerated and 24 months long-term storage conditions.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

This is a Type 7 NDA for a drug already marketed without an approved NDA. These solutions have been manufactured by the drug product manufacturer, [redacted] (b) (4). since 2001 except that the previously manufactured solutions had a [redacted] (b) (4). The solutions described in this NDA have no [redacted] (b) (4)

Phenylephrine hydrochloride is a white [redacted] (b) (4) powder that is freely soluble in water and alcohol. It is manufactured under DMF [redacted] (b) (4) by: [redacted] (b) (4)

Reference ID: 3264058

Executive Summary Section

The DMF has reviewed and found to be adequate in a review dated 2/20/12.

The drug substance specification is the USP specification with tests for residual solvents and impurities (performed by the manufacturer) added and is adequate to control the quality of the drug substance. Incoming material is also tested by the drug product manufacturer to the USP specification. The analytical methods are the USP methods and therefore they do not need to be validated. Satisfactory batch analyses are provided for 3 commercial batches. The drug substance has a shelf life of 5 years when stored at 25°C/60% RH.

The drug product is a sterile, (b) (4), preserved, multi-use solution in opaque white LDPE bottles fitted with dropper tips and caps. The 2.5% solution contains 15 mL per bottle and the 10% solution contains 5 mL per bottle. A phosphate (b) (4) solutions contain 0.01% benzalkonium chloride as a preservative. The 2.5% solution also contains boric acid (b) (4). Antimicrobial effectiveness has been established by testing at (b) (4) of the labeled concentration of benzalkonium chloride.

The drug product is manufactured by (b) (4). An Overall Recommendation of Acceptable has been made in EES. The manufacturing process is described in detail. It is a (b) (4) followed by pH adjustment (b) (4).

The drug product specification includes tests for appearance, identity, pH, osmolality, assay, benzalkonium concentration, impurities, particulates, minimum fill, deliverable volume, sterility and endotoxins. The specification is adequate and an acceptable justification is provided. The analytical methods are described in reasonable detail and three satisfactory batch analyses are provided for each strength.

The 2.5% solution is packaged in a (b) (4) opaque white LDPE bottle fitted with an LLDPE dropper tip and a red cap. The 10% solution is packaged in a (b) (4) opaque white LDPE bottle fitted with an LLDPE dropper tip and a red cap. The container closure components are manufactured from materials that are described in DMFs which have been reviewed and found to be adequate. Drawings of the various components and the specifications used by the drug product manufacturer to test the incoming components are supplied. The components of the labels are described and the manufacturers certify that the adhesive and the varnish comply with the relevant 21 CFR regulations.

Twelve months of satisfactory stability data obtained under long-term storage conditions (2-8°C) are supplied for one batch of each strength and 6 months of satisfactory data are supplied for 2 batches of each strength. In addition up to 36 months of limited stability data are provided for historical batches that are the same as the proposed commercial formulation except for a (b) (4) There are no out of specification results and no obvious trends. An expiration dating period of 18 months is recommended.

The applicant requests a categorical exclusion from the requirement to perform an Environmental Assessment.

Reference ID: 3264058

B. Description of How the Drug Product is Intended to be Used

Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% is indicated to dilate the pupil [redacted] (b) (4). One drop should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye. The product is supplied as sterile, [redacted] (b) (4), preserved solutions in opaque white bottles fitted with dropper tips and caps. The 2.5% solution contains 15 mL per bottle and the 10% solution contains 5 mL per bottle. The storage statement is: "Store in a refrigerator at 2°-8°C (36°-46°F)" and the expiration dating period is 18 months.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for the phenylephrine hydrochloride drug substance are described in DMF [redacted] (b) (4), as amended. This DMF has been reviewed and found to be satisfactory. The composition, manufacturing process, and specifications for the phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% are appropriate and the expiration dating period of 18 months is supported by adequate data. The container-closure systems and labeling are appropriate. The manufacturing sites have been found to be acceptable. This NDA is therefore recommended for tentative approval from a CMC perspective. Post-marketing commitments require the applicant to conduct a study using chiral HPLC to determine if chiral inversion of phenylephrine occurs in the drug product and to test expired product for the presence of leachables. These issues do not pose safety risks and they are therefore not approvability issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist:	George Lunn, Ph.D.
Branch Chief:	Rapti Madurawe, Ph.D.
Project Manager:	Althea Cuff

C. CC Block

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/s/

GEORGE LUNN
02/20/2013

RAPTI D MADURAWE
02/20/2013

Initial Quality Assessment Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 203-510
Applicant: Paragon Bio-Teck, Inc.
Stamp Date : 21 Oct, 2011/Resumbitted Sept 21, 2012
Proposed Trademark: None
Established Name: Phenylephrine hydrochloride
Dosage Form: Ophthalmic Solution
Route of Administration: Topical
Strength: 2.5% and 10%
Indication: To dilate the pupil [redacted] (b) (4)
Reviewer : George Lunn
Microbiology Reviewer: Steven Donald
CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter:	☒	☐

Summary and Critical Issues

Summary

Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% was submitted on 21-Oct-2011. The drug substance, Phenylephrine HCl, USP is referenced to DMF [redacted] (b) (4). The drug product is formulated as a [redacted] (b) (4) preserved ophthalmic solution indicated to dilate the pupil [redacted] (b) (4). This is a 505 (b) (2) application submitted in eCTD format and is a Type 7 (Drug Already Marketed without Approved NDA) submission.

The NDA was refused to file for lack of adequate stability data (please see IQA dated December 9, 2011). The NDA provided fragmentary stability data on the historical batches and release data on the two exhibit batches. In a t-con, the company agreed to provide 9-months long-term and 6-months stability data on the exhibit batch manufactured in July 2011 and 6-months long-term and accelerated data for two additional batches manufactured in Dec 2011.

The filing review determined that the application is complete from Quality perspective.

Drug Substance

Drug Substance	DMF #/holder	LOA provided (Yes/No)	Status	Comments
Phenylephrine HCl, USP	(b) (4)	Y	**Deficient** per last review dated 6/26/09 by Sheldon Markofsky.	Response to the deficiency letter, a Quality submission and an Annual Report has been submitted since the last review.

Drug Product

Deficiencies (from Initial IQA):

1. The application does not provide stability data on either of the two exhibit batches. The submission indicates that stability studies are underway.
2. The NDA provides stability data for 10 historical batches. Please note that these batches were manufactured with (b) (4) while the current formulation has no (b) (4). The data provided is inadequate to justify the requested shelf-life and cannot be considered as primary stability batches for the following reasons:
   a) The batches were tested per USP monograph with testing only for a few quality attributes such as description, assay, pH, preservative effectiveness and sterility. These samples were not tested for impurities, osmolality and particulate matter (see representative data in appendix 1 which also includes figure indicating inconsistent trends in assay among different batches).
   b) The accelerated and real-time stability data submitted (5 batches under each storage condition) were not generated from the same batch. One set of 5 batches were tested under accelerated condition and another set of 5 were subject to real-time studies. It is therefore not possible to compare the batches to evaluate any trend.
   c) The release data (initial time point) is not available for the stability batches
   d) Impurity data (see appendix 2) from retained samples of historical batches shows extremely low levels (b) (4) of impurities. This suggests that the method may need to be evaluated by the FDA laboratory to confirm it is indeed stability indicating.

Meetings:

T-con on December 1, 2011 - To discuss the lack of stability data and to determine how much stability data from the exhibit batches will be available during the review cycle. The company, in its response dated December 5, 2011 indicated that it anticipates a 3-month pull on December 16th and that real-time and accelerated stability data will become available end of January 2012. Also, the company mentioned that additional retained samples are available for further evaluation. However, it is unclear if release data

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is available for these batches. A one time point data will not provide much information for us to evaluate the stability of the product. The response from the company clearly indicated that only 3-months accelerated (Acc) and long-term (LT) stability will be available which admittedly will not be sufficient to establish the stability profile of the drug product and justify the request of (b) (4) shelf-life.

Second T-con on Feb 10, 2012:
The company accepted our recommendation to provide in the NDA:

1. 9-months LT stability and 6-months accelerated on exhibit batch manufactured in July 2011
2. 6-mo LT/Acc on the two exhibit batches manf. Dec 2011
3. 12-mo LT data on the first exhibit batch to be submitted within 55-days of submitting the NDA.

What the resubmitted NDA provides:

Two additional exhibit batches: 6-mo LT/Acc
Original exhibit batch: 9-mo LT/6-mo Acc
12-mo will be submitted within 55-days

Summary of Stability Data Submitted:

Phenylephrine 2.5% Batches (b) (4)

Batch Number/Manf. date	Long-term (mo)	Accelerated (mo)	Agreed upon
11302/ July 2011	12	6	9/6
11577/Dec 2011	6	6	6/6
11578/Dec 2011	6	6	6/6

Phenylephrine 10.0% Batches (b) (4)

Batch Number/Manf. date	Long-term (mo)	Accelerated (mo)	Agreed upon
11323/ July 2011	12	6	9/6
11581/Dec 2011	6	6	6/6
11582/Dec 2011	6	6	6/6

Potential review issues for consideration:

- Manufacturing appears to be straightforward with (b) (4) . There is no mention of hold time either for the bulk or sterile solution. This may be verified with the company and if they do indicate having a limit for hold time, details of the tests conducted before the solution is used for further processing should be requested.
- Since (b) (4) of phenylephrine is used, the specification for assay should be revised from (b) (4)

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- The tonicity of both 2.5% and 10.0% formulation is hypertonic in the range of 450-550 and 950-1050 mOsm/kg, respectively. The proposed values are significantly higher compared to other ophthalmic preparations. The ranges may be acceptable from a clinical standpoint since the product is proposed to be used (only once) to dilate but it may be better to confirm that the proposed osmolality range indeed would be acceptable for Clinical and that it does not pose any safety risk.
- Test for description describes the product to be "clear, colorless (b) (4) solution". Batch analyses and stability data shows negligible levels of impurity and it is not clear what may cause the (b) (4) coloration. This may be clarified with the company and the description revised if needed.
- The requested shelf-life is (b) (4). However, 12-month stability data is available only for one batch.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be complete and therefore can be filed from CMC perspective.

Balajee Shanmugam — *See DARRTS*
CMC Lead — Date

Rapti Madurawe Ph.D. — *See DARRTS*
Branch Chief — Date

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PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 203-510	**Supplement Number and Type:**	**Established/Proper Name: Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%**
Applicant: Paragon, BioTek, Inc.	**Letter Date: 20-Sep-2012**	**Stamp Date: 20-Sep-2012**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		The Drug substance is referenced to DMF (b) (4) and a LOA has been provided.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		

Reference ID: 3221595

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

Reference ID: 3221595

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			The drug substance is referenced to DMF (b) (4). LOA has been provided in the NDA.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?			Referenced to DMF
15.	Does the section contain controls for the DS?			Referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

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E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		The DMFs referenced for container closure are: a) DMF (b) (4) b) DMF c) DMF d) DMF
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			NA
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			NA

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I. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
33.	Is there a methods validation package?	✓		

F. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	✓		

G. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Phenylephrine HCl, USP	(b) (4)	
	III		(b) (4)		
	III				
	III				
	III				

H. LABELING				
	Parameter	**Yes**	**No**	**Comment**
31.	Has the draft package insert been provided?	✓		
32.	Have the immediate container and carton labels been provided?	✓		

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J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	✓		
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	✓		

{See appended electronic signature page}

Balajee Shanmugam Ph.D.
CMC Lead
Division of Pre-Marketing Assessment
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Rapti Madurawe Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

Reference ID: 3221595

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/s/

BALAJEE SHANMUGAM
11/27/2012

RAPTI D MADURAWE
11/27/2012

Initial Quality Assessment Branch V
Pre-Marketing Assessment Division II

OND Division: Division of Transplant and Ophthalmology Products
NDA: 203-510
Applicant: Paragon Bio-Teck, Inc.
Stamp Date : 21 Oct, 2011
Proposed Trademark: None
Established Name: Phenylephrine hydrochloride
Dosage Form: Ophthalmic Solution
Route of Administration: Topical
Strength: 2.5% and 10%
Indication: To dilate the pupil [redacted] (b) (4)

Reviewer : Lin Qi
Microbiology Reviewer: Brian Riley
CMC Lead : Bala Shanmugam

	YES	NO
Acceptable for filing:	☐	☒
Comments for 74-Day Letter:	☒	☐

Summary and Critical Issues

Summary

Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% was submitted on 21-Oct-2011. The drug substance, Phenylephrine HCl, USP is referenced to DMF [redacted] (b) (4). The drug product is formulated as a [redacted] (b) (4), preserved ophthalmic solution indicated to dilate the pupil [redacted] (b) (4). This is a 505 (b) (2) application submitted in eCTD format and is a Type 7 (Drug Already Marketed without Approved NDA) submission.

Important timelines:
60-Day Filing Date: December 20, 2011
Primary reviews completion date: March 28, 2012
PDUFA: April 21, 2012 (if this application is granted Priority status).

The filing review determined that the application is incomplete from Quality perspective, specifically in that the application does not provide adequate stability data. Therefore, this IQA will focus only on the filing issue.

Drug Substance

Drug Substance	DMF #/holder	LOA provided (Yes/No)	Status	Comments
Phenylephrine HCl, USP	(b) (4)	Y	**Deficient** per last review dated 6/26/09 by Sheldon Markofsky.	Response to the deficiency letter, a Quality submission and an Annual Report has been submitted since the last review.

Drug Product

Phenylephrine HCl is formulated as a sterile, (b) (4), aqueous solution in concentrations of 2.5% and 10%. Two batches, one for each strength have been manufactured (b) (4) of 2.5 strength and (b) (4) of the 10% strength) and the release data for both batches has been provided. Typically, we expect a NDA to provide batch analyses data for at least 3 batches. It is not clear if the commercial scale will be the same as the exhibit batches.

Deficiencies

Several deficiencies were noted and those related to the cause for "refuse to file" are listed below:

1. The application does not provide stability data on either of the two exhibit batches. The submission indicates that stability studies are underway.
2. The NDA provides stability data for 10 historical batches. Please note that these batches were manufactured with (b) (4) while the current formulation has (b) (4) The data provided is inadequate to justify the requested shelf-life and cannot be considered as primary stability batches for the following reasons:
    a) The batches were tested per USP monograph with testing only for a few quality attributes such as description, assay, pH, preservative effectiveness and sterility. These samples were not tested for impurities, osmolality and particulate matter (see representative data in appendix 1 which also includes figure indicating inconsistent trends in assay among different batches).
    b) The accelerated and real-time stability data submitted (5 batches under each storage condition) were not generated from the same batch. One set of 5 batches were tested under accelerated condition and another set of 5 were subject to real-time studies. It is therefore not possible to compare the batches to evaluate any trend.
    c) The release data (initial time point) is not available for the stability batches
    d) Impurity data (see appendix 2) from retained samples of historical batches shows extremely low levels (b) (4) of impurities. This suggests that the method may need to be evaluated by the FDA laboratory to confirm it is indeed stability indicating.

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The Agency had a T-con with the company on December 1, 2011 to discuss the lack of stability data and to determine how much stability data from the exhibit batches will be available during the review cycle. The company, in its response dated December 5, 2011 indicated that it anticipates a 3-month pull on December 16th and that real-time and accelerated stability data will become available end of January 2012. Also, the company mentioned that additional retained samples are available for further evaluation. However, it is unclear if release data is available for these batches. A one time point data will not provide much information for us to evaluate the stability of the product. The response from the company clearly indicated that only 3-months accelerated and long-term stability will be available which admittedly will not be sufficient to establish the stability profile of the drug product and justify the request of (b) (4) shelf-life.

The lack of stability data for the exhibit batches makes this application incomplete from Chemistry perspective.

In addition to the above noted RTF deficiency, the following information is either missing or needs to be clarified.

1. The submission does no provide the composition of the historical batches.

2. Section 3.2.P.7, Table 1, DMF (b) (4) has been listed and referenced for the (b) (4) bottle but no LOA has been provided.

3. The NDA provides a LOA for DMF (b) (4) but it is not clear what it is being referenced for. This DMF is not listed in Section 3.2.P.7. Need to clarify.

4. It is not clear if the batch sizes provided in Section 3.2.P.3 are the intended commercial scale. Also, how many units are expected to be filled and batch reconciliation data is missing.

5. No data on freeze-thaw study and weight loss study.

Comments and Recommendation:

Based on the perusal of this NDA, it is determined to be incomplete and therefore refuse to file from CMC perspective.

Balajee Shanmugam — *See DARRTS*
CMC Lead — Date

Terrance Ocheltree Ph.D., R.Ph. — *See DARRTS*
Director — Date
Division of New Drug Quality Assessment II

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/s/

BALAJEE SHANMUGAM
12/09/2011

TERRANCE W OCHELTREE
12/09/2011

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 203-510	**Supplement Number and Type:**	**Established/Proper Name: Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%**
Applicant: Paragon, BioTek, Inc.	**Letter Date: 19-Oct-2011**	**Stamp Date: 21-Oct-2011**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			NA

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		The Drug substance is referenced to DMF (b) (4) and a LOA has been provided.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		(b) (4). is listed under "Establishment information" in Section 1.1.2, with no apparent manufacturing related activity listed. This facility need not be submitted to the EES.

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9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		Yes, provided along with establishment information.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

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PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			The drug substance is referenced to DMF (b) (4). LOA has been provided in the NDA.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Referenced to DMF
14.	Does the section contain information regarding the characterization of the DS?			Referenced to DMF
15.	Does the section contain controls for the DS?			Referenced to DMF
16.	Has stability data and analysis been provided for the drug substance?			Referenced to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		✓	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		✓	

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PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		The DMFs referenced for container closure are: a) DMF (b) (4) b) DMF c) DMF d) DMF LOA's have been provided in the NDA. However, a LOA for DMF (b) (4) has not been provided. Additionally, DMF (b) (4) for which a LOA has been provided is not listed for what this DMF is referenced in Section 3.2.P.7.
25.	Does the section contain controls of the final drug product?	✓		

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26.	Has stability data and analysis been provided to support the requested expiration date?		✓	Stability data has not been provided for the two primary batches. "Historical" batches were tested per USP which included testing for quality attributes such as description, assay, pH, preservative effectiveness and sterility but not for impurities, particulate matter, and osmolality. The data presented on impurities for the few older batches suggests that the method may not be stability indicating. The lack of stability data from well defined stability studies fails to establish the stability profile of the drug product and justify the requested expiration date.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			NA
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			NA

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F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	✓		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Phenylephrine HCl, USP	(b) (4)	
	III		(b) (4)		
	III				
	III				
	III				
	III				LOA not provided

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		

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J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**		✓	
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	✓		**Filing Comments** The NDA does not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Per ICH Q1A (R2), 12-months long-term and 6-months accelerated stability data for three batches should be provided for us to be able to evaluate the stability of the drug product over the requested shelf-life. Release data for the two exhibit batches, one each for the two strengths, 2.5% and 10% has been provided in the NDA but the submission does not provide stability data for these batches. Stability data submitted for the historical batches are inadequate since they were only tested for a few quality attributes. Furthermore, the long-term and accelerated data were generated from different batches which limits evaluating stability of any one batch stored under different conditions. Additionally, the NDA lacks data on freeze-thaw and weight loss studies. The NDA does not meet the requirement of 21 CFR 314.50 (d) (1) (ii) (a) and is therefore considered incomplete from CMC perspective.
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			

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{See appended electronic signature page}

Balajee Shanmugam
CMC Lead — Date
Division of Pre-Marketing Assessment
Office of New Drug Quality Assessment

{See appended electronic signature page}

Terrance Ocheltree Ph.D., R.Ph.
Director — Date
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Reference ID: 3056251

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/s/

BALAJEE SHANMUGAM
12/09/2011

TERRANCE W OCHELTREE
12/09/2011