CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

CHEMISTRY REVIEW(S)

CMC Memo To File

Date	18 June 2014
NDA	204300
Sponsor:	Eclat Pharmaceuticals
Drug:	Phenylephrine Hydrochloride Injection
Reviewer	Jean Nashed, Ph.D.
CMC Lead	Julia Pinto, Ph.D.

The CMC NDA reviews 1 and 2 by Jean Nashed, Ph.D. finds that sufficient CMC information is provided, to assure the identity, strength, purity, and quality of the drug product. However, on pg 6 of Dr.Nashed's review 2 (June 17, 2014), the EES recommendation is listed as pending from the Office of Compliance. However, the OC report attached at the end of her review, recommends all facilities as acceptable. The table, on page 6 is therefore in error.

The table is reproduced below and the error is corrected. The report from OC has also been reproduced and follows the table. Therefore, from the CMC perspective, this NDA is recommended for approval.

Consults	Recommendation	Date	Reviewer
Microbiology	Acceptable		Stephen Langille
EES	Acceptable	June 6, 2014	Office of Compliance
Pharm/Tox	Acceptable	June 2014	Marcus Delatte
Biopharmaceutics	Acceptable	March 28, 2013	Elsbeth Chikhale
Methods Validation	N/A		
DMEPA	Acceptable	June 2013/Feb 2014	Alex Winiarski
EA	Acceptable		Jean Nashed

Julia Pinto, Ph.D.
CMC Lead

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204300/000	**Sponsor:**	ECLAT PHARMS
Org. Code:	170		1129 20TH ST NORTHWEST STE 600
Priority:	5		WASHINGTON, DC 20036
Stamp Date:	08-FEB-2013	**Brand Name:**	PHENYLEPHRINE HYDROCHLORIDE INJECTION, U
PDUFA Date:	06-AUG-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	
District Goal:	27-FEB-2014	**Product Number; Dosage Form; Ingredient; Strengths**	001; INJECTION; PHENYLEPHRINE HYDROCHLORIDE; 10MG

FDA Contacts:			
E. NASHED	Prod Qual Reviewer	(HFD-820)	3017961723
S. LANGILLE	Micro Reviewer	(HFD-805)	3017961557
L. RIVERA	Product Quality PM		3017964013
K. COMPTON	Regulatory Project Mgr		3017961191
J. PINTO	Team Leader		3017961733

Overall Recommendation:	ACCEPTABLE	on 06-JUN-2014	by J. WILLIAMS	()	3017964196
	WITHHOLD	on 05-MAY-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 28-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-JUN-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-JUL-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-JUL-2013

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

JULIA C PINTO
06/18/2014

NDA 204-300

Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL

Éclat Pharmaceuticals, LLC
(US Representative: The Weinberg Group, Inc.)

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III

for

Division of Anesthesia, Analgesia, and Addiction Products

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 204-300

2. REVIEW #: 2

3. REVIEW DATE: June 13, 2014

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Submission(s) Reviewed (CMC Rev #1)	Document Date
Original	February 8, 2013 (RTF)
Original (Resubmission after RTF)	June 28, 2013 (Resubmission)
Amendement	February 26, 2013
Amendement	July 1, 2013
Amendement	July 8, 2013
Amendement	September 18, 2013
Amendement	November 1, 2013
Amendement	January 6, 2014
Amendement	February 13, 2014
Amendement	March 7, 2014
Amendement	March 11, 2014
Amendement	March 18, 2014
Amendement	March 19, 2014

6. SUBMISSIONS BEING REVIEWED (Chem. Rev #2):

Resubmission Class1	June 6, 2014

7. NAME AND ADDRESS OF APPLICANT:

Name: Eclat Pharmaceuticals, LLC
Address: 702 Spirit 40 Park Drive, Suite 108
Chesterfield, MO 63005
Phone 636-449-1830

8. Product Drug Code and Name:
   a) Proprietary Name: Vazculep
   b) Non-Proprietary Name (USAN): Phenylephrine Hydrochloride Injection
   c) Code name/#(ONDQA only): (b) (4)
   d) Chem. Type/Submission Priority (ONDQA only): 5 S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: α1- adrenergic receptor agonist (vasoconstrictor)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg/mL; Has to be diluted before administration.
Supplied as 1 mL vial, 5 mL vial and 10 mL vial

13. ROUTE OF ADMINSITRATION: Intravenous

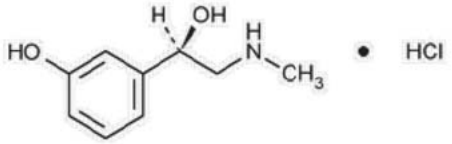
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM:
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

INN Name: Phenylephrine (Hydrochloride)
USAN name: Phenylephrine Hydrochloride
IUPAC name: (R)-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol hydrochloride
Molecular formula: $C_9H_{13}NO_2$. HCl
Relative molecular weight 203.67



17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	Jun 13, 2011 Kamal Tiwari	LOA dated Aug 21, 2012, on file (DMF and NDA) Electronic amendment

							dated Jul 18, 2013, includes older data in a new format; (b) (4) (b) (4)
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Mar 28, 2013 Art Shaw	LOA dated Aug 27, 2012 on file (b) (4)
(b) (4)	III	(b) (4)	(b) (4))	3	Adequate	Jan 28, 2011	LOA dated Oct 3 27, 2012, on file (b) (4)
(b) (4)	III	(b) (4)	(b) (4) (b) (4)	3	Adequate	Jan 12, 1998	LOA dated Sep 10, 2012 (b) (4)

[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:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	113,044	Phenylephrine Hydrochloride Injection, USP, 1%; EOP2: Sep 27, 2012; Mtg Min. Jan 30, 2013
NDA	204-078	Neostigmine Methylsulfate Injection, USP

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	Acceptable; Response to IR comments was reviewed and found acceptable on Mar 12, 2014	New Drug Microbiology	Stephen Langille
EES	Pending; All sites have Acceptable status as of June 6, 2014	June 6, 2014	Office of Compliance
Pharm/Tox	Acceptable;	June, 2014	Marcus Delatte Review of qualification data on specific impurities
Biopharmaceutics	Acceptable	Mar 28, 2013	Elsbeth Chikhale Literature data are reviewed by Div. Clinical Pharmacology
Methods Validation	Not needed		Standard USP and HPLC methods are used in this application
DMEPA	Acceptable	June 2013 & Feb 2014	Alex Winiarski Name acceptable; labeling acceptable
EA	Acceptable		Categorical exclusion request is satisfactorily supported

The Chemistry Review for NDA 204-300

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval from the CMC perspective. An acceptable recommendation is provided by the Office of Compliance (OC) regarding the status of the manufacturing and testing facilities for this product, as of June 6, 2014.

Two Post-Marketing Commitments (PMC) pertaining to controls for the content of sodium metabisulfite (b) (4), and an agreement pertaining to submission of a special stability assessment report, are recommended by the CMC team, as described below.

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

Post-Marketing Commitments

(PMC #1)
Éclat commits to establish final, data-based (b) (4) acceptance criteria for the content of sodium metabisulfite in the drug product, (b) (4)
(b) (4)

(PMC #2)
Éclat commits to tighten the currently proposed tentative release acceptance criteria (b) (4)
for the content of sodium metabisulfite in the drug product, (b) (4)
(b) (4)

Agreement

Éclat agrees to provide annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches, as described in NDA amendment dated March 11, 2014. The analysis will be focused on different instability trends for smaller fill volumes with a large head space (i.e., 1 mL and 5 mL) in comparison to the 10 mL fill volume with a small head space. Also, Éclat agrees to submit an evaluation of trends in sodium metabisulfite content in the context of changes in pH and impurity levels as well as analyze the

impact of storage orientation on instability trends. The first report is scheduled to be submitted by April 2015, and it will contain analysis of 6 months stability data collected at the accelerated (40 ± 2 °C/75% ± 5% RH) and at long-term (25 ± 2°C/60% ± 5% RH) storage conditions for commercial manufacturing.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

The drug product is a sterile, nonpyrogenic solution of phenylephrine hydrochloride in a (b) (4) (pH 3.5-5.5) with addition of sodium metabisulfite (b) (4). The product is formulated in one strength, 10 mg/mL, and it is intended for dilution and administration *via* intravenous route.

The drug substance, phenylephrine hydrochloride, is a (b) (4) soluble in the aqueous media. For the purpose of this NDA it is purchased from (b) (4), who manufactures it under DMF (b) (4) (Adequate status) in (b) (4). (b) (4) The manufacturing site has a history of GMP issues and had a Withold Approval status during previous review cycle. The status is ACCEPTABLE for this site as of June 6, 2014.

The drug product is manufactured by (b) (4)

The Microbiology evaluation of (b) (4) and process controls and validation was performed by the OPS Microbiology Team and adequate-for-approval status is recommended in the review dated March 12, 2014, by Dr. S. Langille.

(b) (4) Three fill volumes are proposed for marketing: 1 mL, 5 mL, and 10 mL, with 5 mL and 10 mL vials designated for pharmacy distribution only. The drug product should be stored at controlled room temperature of 25ºC (77ºF) with excursions permitted to 15°-30°C (59° to 86°F) and protected from light. The submitted stability data (18 months for 9 pilot scale batches) in combination with the provided PMCs and Agreements are sufficient to support the requested expiry period of 24 months.

The overall EER recommendation for all manufacturing and testing facilities is ACCEPTABLE as of June 6, 2014.

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

The drug product, VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL is a sterile, nonpyrogenic solution for intravenous use. It must be diluted before administration as an intravenous bolus or continuous intravenous infusion. 1 mL fill vials are intended for single use whereas the 5 mL fill and 10 mL fill products are designated for pharmacy distribution only.

C. Basis for Approvability Recommendation

The approval recommendation by the CMC team is based on adequate submission of supporting data, two PMCs regarding content and controls for sodium matabisulfite and ACCEPTABLE EER recommendation from the Office of Compliance. The following is a summary of the outstanding issues to be addressed post-approval.

- Establishing specifications for the content of sodium metabisulfite during shelf-life of the product as described in PMC #1.

- Tightening of the tentative release specifications for the content of sodium metabisulfite as described in PMC #2.

  The proposed PMCs are considered sufficient to address the potential safety and quality aspects associated with the level of sodium metabisulfite (b) (4) in the drug product formulation. Although most likely there is a minimum level of the (b) (4) required to assure the strength of the drug product, the stability of the formulation is indirectly controlled by the acceptance criteria for pH, individual impurities and total impurities. (b) (4) In addition, a report will be provided to the Agency documenting the changes occurring in the level of sodium metabisulfite throughout the life-time of the drug product, along with a study documenting a minimum level of sodium metabisulfite required to sustain the (b) (4) function.

- Special stability report to be submitted in each Annual Report. It will include analysis of instability trends, including results for all stability-indicating attributes, including the requested data (b) (4) level, storage orientation), as described in Agreement #1.

  The stability data submitted to this NDA include results for 9 registration batches (b) (4) for samples stored in one orientation (b) (4) for 18 months. Data do not include content of (b) (4) (see PMCs) and indicate different instability trends (pH, impurities) for small fill vials (1 mL and 5 mL) with large head volume in comparison to the 10 mL fill with small head volume, most likely due to the (b) (4) As a result, the impurity levels and pH are (b) (4) for different

product fills after storage, however the results are within specification limits. Also, no report or data documenting the preferred-for-storage orientation for the product is currently available.

The provided Agreement, to include additional storage orientation for stability samples and to provide analysis of the instability trends for the commercial products in each annual report, is adequate to monitor the quality of the proposed-for-marketing product and sufficiently addresses the CMC concerns.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Eugenia Nashed, Ph.D.
CMC Lead: Julia Pinto, Ph.D.
Division Director: Eric Duffy, Ph.D.

Office of New Drug Quality Assessment, Division III

12 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

EUGENIA M NASHED
06/15/2014

JULIA C PINTO
06/17/2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 204300/000

S Date: 08-FEB-2013

Regulatory: 06-AUG-2014

Action Goal:

District Goal: 27-FEB-2014

Applicant: ECLAT PHARMS
1129 20TH ST NORTHWEST STE 600
WASHINGTON, DC 20036

Brand Name: PHENYLEPHRINE HYDROCHLORIDE INJECTION, U

Estab. Name:

Generic Name:

Priority: 5

Org. Code: 170

Product Number; Dosage Form; Ingredient; Strengths
001; INJECTION; PHENYLEPHRINE HYDROCHLORIDE; 10MG

Application Comment:

FDA Contacts:				
	E. NASHED	Prod Qual Reviewer	(HFD-820)	3017961723
	S. LANGILLE	Micro Reviewer	(HFD-805)	3017961557
	L. RIVERA	Product Quality PM		3017964013
	K. COMPTON	Regulatory Project Mgr		3017961191
	J. PINTO	Team Leader		3017961733

Overall Recommendation:					
	ACCEPTABLE	on 06-JUN-2014	by J. WILLIAMS	()	3017964196
	WITHHOLD	on 05-MAY-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 28-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		
	PENDING	on 13-FEB-2013	by EES_PROD		

NDA 204-300

Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL

Éclat Pharmaceuticals, LLC
(US Representative: The Weinberg Group, Inc.)

Eugenia M. Nashed, Ph.D.
Office of New Drug Quality Assessment, Division III

for

Division of Anesthesia, Analgesia, and Addiction Products

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Sheet

1. NDA 204-300

2. REVIEW #: 1

3. REVIEW DATE: March 17, 2014

4. REVIEWER: Eugenia M. Nashed, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSIONS BEING REVIEWED (Chem. Rev #1):

Submission(s) Reviewed	Document Date
Original	February 8, 2013 (RTF)
Original (Resubmission after RTF)	June 28, 2013 (Resubmission)
Amendement	February 26, 2013
Amendement	July 1, 2013
Amendement	July 8, 2013
Amendement	September 18, 2013
Amendement	November 1, 2013
Amendement	January 6, 2014
Amendement	February 13, 2014
Amendement	March 7, 2014
Amendement	March 11, 2014
Amendement	March 18, 2014
Amendement	March 19, 2014

7. NAME AND ADDRESS OF APPLICANT:

Name: Eclat Pharmaceuticals, LLC
Address: 702 Spirit 40 Park Drive, Suite 108
Chesterfield, MO 63005
Phone 636-449-1830

8. Product Drug Code and Name:
   a) Proprietary Name: Vazculep
   b) Non-Proprietary Name (USAN): Phenylephrine Hydrochloride Injection
   c) Code name/#(ONDQA only): (b) (4)
   d) Chem. Type/Submission Priority (ONDQA only): 5 S

9. LEGAL BASIS FOR SUBMISSION: FD&C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY: α1- adrenergic receptor agonist (vasoconstrictor)

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 10 mg/mL; Has to be diluted before administration.
Supplied as 1 mL vial, 5 mL vial and 10 mL vial

13. ROUTE OF ADMINSITRATION: Intravenous

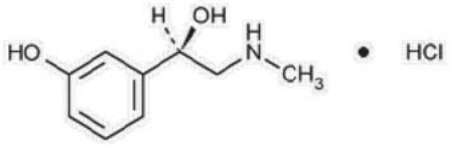
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

INN Name: Phenylephrine (Hydrochloride)
USAN name: Phenylephrine Hydrochloride
IUPAC name: (R)-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol hydrochloride
Molecular formula: $C_9H_{13}NO_2$. HCl
Relative molecular weight 203.67



17. RELATED/SUPPORTED DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	Status	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	Jun 13, 2011 Kamal Tiwari	LOA dated Aug 21, 2012, on file (DMF and NDA) Electronic amendment dated Jul 18, 2013,

							includes older data in a new format; stable (b) (4)
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Mar 28, 2013 Art Shaw	LOA dated Aug 27, 2012 on file (b) (4)
(b) (4)	III	(b) (4) (b) (4) o	(b) (4)	3	Adequate	Jan 28, 2011	LOA dated Oct 3 27, 2012, on file (b) (4)
(b) (4)	III	(b) (4)	(b) (4) (b) (4)	3	Adequate	Jan 12, 1998	LOA dated Sep 10, 2012 (b) (4)

[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	DESCRIPTION

Chemistry Review Data Sheet

	NUMBER	
IND	113,044	Phenylephrine Hydrochloride Injection, USP, 1%; EOP2: Sep 27, 2012; Mtg Min. Jan 30, 2013
NDA	204-078	Neostigmine Methylsulfate Injection, USP

18. Status

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Microbiology	Acceptable; Response to IR comments was reviewed and found acceptable on Mar 12, 2014	New Drug Microbiology	Stephen Langille
EES	Pending; 3 sites have AC status and 1 site (drug substance manufacturing in (b) (4)) is under review with interim "withhold" status	Feb 13, 2013	Office of Compliance
Pharm/Tox	Pending; Response to IR comments under review	Feb 8, 2013	Marcus Delatte Review of qualification data on specific impurities
Biopharmaceutics	Acceptable	Mar 28, 2013	Elsbeth Chikhale Literature data will be reviewed by Div. Clinical Pharmacology
Methods Validation	Not needed		Standard USP and HPLC methods are used in this application
DMEPA	Acceptable	June 2013 & Feb 2014	Alex Winiarski Name acceptable; labeling pending
EA	Not needed		Categorical exclusion request is satisfactorily supported

The Chemistry Review for NDA 204-300

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from the CMC perspective providing that the Applicant addresses satisfactorily the remaining CMC agreement (submission data for leachables by April 2, 2014) and an acceptable recommendation is provided by the Office of Compliance (OC) regarding the status of the manufacturing and testing facilities for this product.

Also, two Post-Marketing Commitments (PMC) pertaining to specifications for the content of sodium metabisulfite (b) (4), and an agreement pertaining to submission of a special stability assessment report, are recommended by the CMC team, as described below.

The Evaluation Establishment Request (EER) was submitted and the final recommendation from the Office of Compliance is pending. An acceptable recommendation is available for the drug product manufacturing facility (b) (4) and two testing sites. However, the results of inspection at the drug substance manufacturing site owned by (b) (4) (current status: Withold) are under evaluation by the Office of Compliance.

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

Post-Marketing Commitments

(PMC #1)
Éclat commits to establish final, data-based (b) (4) acceptance criteria for the content of sodium metabisulfite in the drug product, and (b) (4)
(b) (4)

(PMC #2)
Éclat commits to tighten the currently proposed tentative release acceptance criteria ((b) (4)
for the content of sodium metabisulfite in the drug product, and (b) (4)
(b) (4)

Agreement

Éclat agrees to provide annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches, as described in NDA amendment dated March 11, 2014. The analysis will be focused on different instability trends for smaller fill volumes with a large head space (i.e., 1 mL and 5 mL) in comparison to the 10 mL fill volume with a small head space. Also, Éclat agrees to submit an evaluation of trends in sodium metabisulfite content in the context of changes in pH and impurity levels as well as analyze the impact of storage orientation on instability trends. The first report is scheduled to be submitted by April 2015, and it will contain analysis of 6 months stability data collected at the accelerated (40 ± 2 °C/75% ± 5% RH) and at long-term (25 ± 2°C/60% ± 5% RH) storage conditions for commercial manufacturing.

II. Summary of Chemistry Assessment

A. Description of Drug Substance and Drug Product:

The drug product is a sterile, nonpyrogenic solution of phenylephrine hydrochloride in a (b) (4) (pH 3.5-5.5) with addition of sodium metabisulfite (b) (4). The product is formulated in one strength, 10 mg/mL, and it is intended for dilution and administration *via* intravenous route.

The drug substance, phenylephrine hydrochloride, is a (b) (4) soluble in the aqueous media. For the purpose of this NDA it is purchased from (b) (4), who manufactures it under DMF (b) (4) (Adequate status) in (b) (4). (b) (4) he manufacturing site has a history of GMP issues and currently is under evaluation after the inspection (Withold status) which took place on (b) (4).

The drug product is manufactured by (b) (4). (b) (4)

The Microbiology evaluation of (b) (4) and process controls and validation was performed by the OPS Microbiology Team and adequate-for-approval status is recommended in the review dated March 12, 2014, by Dr. S. Langille.

The EER for the manufacturing and testing facilities is pending with the Office of Compliance. The drug product manufacturing facility (b) (4) and two testing contractor sites have

acceptable (AC) status, whereas the overall EER recommendation is pending due to the GMP issues at the drug substance manufacturing facility in (b) (4)

The drug product is (b) (4) Three fill volumes are proposed for marketing: 1 mL, 5 mL, and 10 mL, with 5 mL and 10 mL vials designated for pharmacy distribution only. The drug product should be stored at controlled room temperature of 25ºC (77ºF) with excursions permitted to 15°-30°C (59° to 86°F) and protected from light. The submitted stability data (18 months for 9 pilot scale batches) in combination with the provided PMCs and Agreements are sufficient to support the requested expiry period of 24 months.

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

The drug product, VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL is a sterile, nonpyrogenic solution for intravenous use. It must be diluted before administration as an intravenous bolus or continuous intravenous infusion. 1 mL fill vials are intended for single use whereas the 5 mL fill and 10 mL fill products are designated for pharmacy distribution only.

C. Basis for Approvability Recommendation

The approval recommendation by the CMC team is contingent upon the satisfactory resolution of the remaining CMC issues. The complete list of CMC post-marketing commitments and agreements for forwarding to the Applicant is listed at the end of this review. The major issues include the following:

- Data documenting the absence of potential leachable, (b) (4) to be submitted by April 2, 2014, per agreement provided on March 19, 2014.

  The Applicant discussed preliminary results for the content of potential (b) (4) leachable in communication dated March 19, 2014, indicating that stability samples stored for 22 months at 30°C have (b) (4). Applicant agreed to provide final test results and brief method validation in NDA amendment by April 2, 2014. The preliminary negative results for the potential (b) (4) leachable and the provided agreement alleviate the CMC safety concerns regarding this leachable. At this point we do not consider it necessary to include the testing for leachables in the drug product stability protocol.

- Specifications for the content of sodium metabisulfite during shelf-life of the product as described in PMC #1.

- Tightening of the tentative release specifications for the content of sodium metabisulfite as described in PMC #2.

  The proposed PMCs are considered sufficient to address the potential safety and quality aspects associated with the level of sodium metabisulfite (b) (4) in the drug product

formulation. Although most likely there is a minimum level of the [redacted] (b) (4) required to assure the strength of the drug product, the stability of the formulation is indirectly controlled by the acceptance criteria for pH, individual impurities and total impurities. [redacted] (b) (4). In addition, a report will be provided to the Agency documenting the changes occurring in the level of sodium metabisulfite throughout the life-time of the drug product, along with a study documenting a minimum level of sodium metabisulfite required to sustain the [redacted] (b) (4) function.

- Special stability report to be submitted in each Annual Report. It will include analysis of instability trends, including results for all stability-indicating attributes, including the requested data [redacted] (b) (4) level, storage orientation), as described in Agreement #1.

The stability data submitted to this NDA include results for 9 registration batches [redacted] (b) (4) for samples stored in one orientation [redacted] (b) (4) for 18 months. Data do not include content of [redacted] (b) (4) (see PMCs) and indicate different instability trends (pH, impurities) for small fill vials (1 mL and 5 mL) with large head volume in comparison to the 10 mL fill with small head volume, most likely due to the [redacted] (b) (4) As a result, the impurity levels and pH are [redacted] (b) (4) for different product fills after storage, however the results are within specification limits. Also, no report or data documenting the preferred-for-storage orientation for the product is currently available.

The provided Agreement, to include additional storage orientation for stability samples and to provide analysis of the instability trends for the commercial products in each annual report, is adequate to monitor the quality of the proposed-for-marketing product and sufficiently addresses the CMC concerns.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemistry Reviewer: Eugenia Nashed, Ph.D.
CMC Lead: Julia Pinto, Ph.D.
Project Manager: Kimberly Compton, R.Ph.
Branch Chief: Prasad Peri, Ph.D.

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/s/

EUGENIA M NASHED
03/20/2014

PRASAD PERI
03/20/2014

CMC NDA Filing Memorandum

1. NEW DRUG APPLICATION NUMBER: **204-300**
2. SUBMISSION TYPE : Original NDA, Resubmission in response to RTF Letter
3. SUBMISSION NUMBER: 005 (06/28/2013)

Trade or Proprietary Name:	Vazculep (currently proposed)
Established or Non-Proprietary Name	Phenylephrine Hydrochloride Injection, USP, 1%
Dosage Form:	Injection

4. NAME & ADDRESS OF APPLICANT:

Name:	Éclat Pharmaceuticals
Address:	699 Trade Center Blvd. Suite A Chesterfield, MO 63005
Representative:	Marla E. Scarola, MS, Senior

5. SUBMISSION PROPERTIES:

Review Priority :	Standard
Property (Legal Basis):	505(b)(2)
Responsible Organization:	CDER

6. FILING ASSESSMENT

The CMC team recommends the NDA application for filing, as specified in the Filing Review dated February 28, 2013, by Dr. Stephens (see copy attached to this review). The original NDA was recommended for filing from the CMC perspective and this recommendation is maintained after the resubmission dated June 28, 2013. The initial application contained only 6 months of the stability results, however the resubmission was updated for total of 12 months stability data. The acceptability of the stability data will be assessed during review.

CMC Reviewer: Eugenia Nashed, Ph.D.

CMC Team Lead: Olen Stephens, Ph.D.

ONDQA Branch Chief: Prasad Peri, Ph.D.

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/s/

EUGENIA M NASHED
08/26/2013

PRASAD PERI
08/26/2013
I concur

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer: Juandria Williams

2. NDA/BLA Number: **NDA 204300**
   Submission Date: **June 28, 2013**
   21st C. Review Goal Date: TBD
   PDUFA Goal Date: **April 28, 2014**

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Vazculep (currently proposed)
Established or Non-Proprietary Name (USAN) and strength:	Phenylephrine Hydrochloride Injection, USP, 1%
Dosage Form:	Injection

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Eclat Pharmaceuticals, Inc.
Responsible Organization (OND Division):	DAAAP

II. Application Detail

1. INDICATION: For the treatment (b) (4) of hypotension during anesthesia
2. ROUTE OF ADMINISTRATION: Intravenous
3. STRENGTH/POTENCY: 10 mg/mL
4. Rx/OTC DISPENSED: xRx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug	x			Per IQA dated 2/28/2013
5.	Medically Necessary Determination	x			Per IQA dated 2/28/2013
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission		x		
8.	Drug/device combination product with consult		x		
9.	Complex manufacturing		x		Refer to Section IV
10.	Other (e.g., expedited for an unlisted reason)		x		

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
12.	Do all sites indicate they are ready to be inspected (on 356h)?	x		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	x		DS: Section 3.2.S.2.1 in eCTD DP: Section 3.2.P.2.1 in eCTD
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	x		
	2. Do comments in EES indicate a request to participate on inspection(s)?		x	
	3. Is this first application by the applicant?		x	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		x	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?		x	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	x		
	Have all EERs been updated with final PAI recommendation?		x	Two sites are pending an inspection: • (b) (4) •
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		

V. Overall Conclusions and Recommendations

Is the application fileable? Yes
Based on Section IV, is a KTM warranted for any PAI? No If yes, please identify the sites in the above chart. While no formal KTM will be written, a briefing with the investigators will be planned for: • (b) (4)
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

J. Williams – 8/26/2013
M. Ramanadham – 8/26/2013
D. Henry – 8/26/2013

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/s/

JUANDRIA WILLIAMS
08/26/2013

DON L HENRY
08/26/2013

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER:204-300

2. SUBMISSION TYPE :Original

3. SUBMISSION NUMBER:0000

Trade or Proprietary Name:	Vazculep (currently proposed)
Established or Non-Proprietary Name (USAN):	Phenylephrine Hydrochloride Injection, USP, 1%
Dosage Form:	Injection

4. NAME & ADDRESS OF APPLICANT:

Name:	Éclat Pharmaceuticals
Address:	699 Trade Center Blvd. Suite A Chesterfield, MO 63005
Representative:	Marla E. Scarola, MS, Senior Consultant

5. SUBMISSION PROPERTIES:

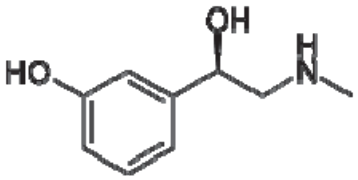
Review Priority :	Standard
Property (Legal Basis):	505(b)(2)

Responsible Organization:	CDER

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #:

Review Information

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



•HCl

Molecular Formula: $C_9H_{13}NO_2$•HCl
Molecular Weight: 203.67 g/mol

2. INDICATION: For the treatment (b) (4) of hypotension during anesthesia

3. PHARMACOLOGICAL CATEGORY: α_1-adrenergic receptor agonist (vasoconstrictor)

4. ROUTE OF ADMINISTRATION: Intravenous

5. STRENGTH/POTENCY: 10 mg/mL

6. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

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

Is this a SPOTS product? ☐ Yes ☒ No ☐ Not evaluated at time of IQA.

8. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	21-Aug-2012	Last

		(b) (4)			reviewed 13-Jun-2011; (adequate)
(b) (4)	III	(b) (4)	(b) (4)	27-Aug-2012	
(b) (4)	III	(b) (4) .	(b) (4)	3-Oct-2012	
(b) (4)	III	(b) (4)		10-Sep-2012	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☒	
EES	☒	☐	EER sent to Compliance by ONDQA PM on 13-FEB-2013
Pharm/Tox	☒	☐	Review of qualification information on specific impurities
Methods Validation	☐	☒	
EA	☐	☒	
New Drug Micro	☒	☐	Review of sterility assurance
CDRH	☐	☒	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	01-Dec-2011	113,044	Phenylephrine Hydrochloride Injection, USP, 1% IND under same name
NDA	31-Jul-2012	204-078	Neostigmine Methylsulfate Injection, USP; (b) (4)

d. Previous Communications with the Applicant to note (if any):

NDA #:

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
pIND	17-Nov-2011	113,044	
EOP2	27-Sep-2012	113,044	
T-con minutes	30-Jan-2013	113,044	

Vazculep™ (Phenylephrine Hydrochloride, USP) 1% injectable solution is a [redacted] (b) (4) parenteral product indicated for the treatment [redacted] (b) (4) of hypotension during anesthesia. This product has been marketed without approval and is deemed medically necessary. As such, the applicant was approached and asked to submit an NDA for review. The drug substance is covered under DMF [redacted] (b) (4), which was last reviewed 13-Jun-2011 when it was found adequate to support referenced ANDA products. The drug product is manufactured [redacted] (b) (4) No QbD elements were found in a triage of the application. CMC recommends the NDA be filed.

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
☒	☐	1. At the End-of-Phase 2 (EOP2) meeting on September 27, 2012, the Sponsor stated that they would like to file their application as soon as possible and so would like to submit with the stability data they have on hand (only 6 months). The firm stated that they are prepared to accept a shorter expiry and could amend their application with updated data once it is available. The Agency reiterated our expectations regarding stability data and stated that, if Éclat chooses to submit the application with less than the recommended stability data, the Agency would discuss the acceptability of the submission at that time. Due to the fact that this is a marketed unapproved product, I recommend that we allow this application to be filed and potentially approved with a shorted shelf-life.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
☒	☐	1. As stability updates become available, submit these to the NDA so that they might be reviewed. We do not commit to reviewing these amendments, but will make efforts to do so as resources allow.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA #:

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?		
Yes	No	Biopharmaceutics Filing Issues
☐	☐	1. Refer to the biopharmaceutics filing review.

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
☐	☐	1. Refer to the biopharmaceutics filing review.

CMC Summary:
Critical Issues and Complexities

CMC Critical Issues or Complexities			
There are no unusually or complex issues readily apparent at the time of filing.			
Does the submission contain any of the following elements? No.			
Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?		
Yes	No	Suggested expertise for team
☐	☒	A reviewer familiar with review of small molecules is recommended.

Summary or Highlights of the Application ***(not already mentioned in other sections)***
None.
Description of Facility Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.
No unusual or complex issues are noted at this time.

Biopharmaceutics Summary:
Critical Issues, Complexities, and Consults

Critical Issues or Complexities
No unusual or complex issues are noted at this time.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #:

FILING REVIEW CHECKLIST

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?	☒	☐	

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

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)	☒	☐	
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)	☒	☐	

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)	☐	☐	NA
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.

Table 1: Phenylephrine Hydrochloride Injection, USP, 1%, NDA 204300, Establishment Information for Form 356h

Facility Name	DMF # (if available)	CFN # (if applicable)	Ready for Inspection? Yes/No	Facility Responsibility
(b) (4)				

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA #:

Facility Name	DMF # (if available)	CFN # (if applicable)	Ready for Inspection? Yes/No	Facility Responsibility
(b) (4)				

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	☐	☒	The applicant is claiming a categorical exclusion from requirement to prepare an environmental assessment as under 21 CFR 25.31(b)

D. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☒	☐	*See table on cover page.*

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
13.	Does the section contain a description of the DS manufacturing process?	☐	☒	This information is contained in DMF (b) (4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	☐	☒	This information is contained in DMF (b) (4)
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☐	☒	This information is contained in DMF (b) (4)
17.	Does the section contain controls for the DS?	☐	☒	This information is contained in DMF (b) (4)
18.	Has stability data and analysis been provided for the drug substance?	☐	☒	This information is contained in DMF (b) (4)
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	This information may be contained in DMF (b) (4)
21.	Does the section contain container and closure information?	☒	☐	

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ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

NDA #:

F. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Does the section contain quality controls of excipients?	☒	☐	All excipients are compendial
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	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?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	
28.	Have any biowaivers been requested?	☒	☐	Yes. Clin Pharm and Biopharm reviewers (Elsbeth Chikhale) will evaluate the request.
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	Only 6 months of long-term data has been provided. The applicant will be asked to promptly provide stability updates as they are available.
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	No elements were seen in this IQA.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	

Table 1: Composition of Phenylephrine Hydrochloride Injection, USP, 1%

Component	Purpose	Quantity (per mL)	Quality Standard
Phenylephrine Hydrochloride	API	10 mg	USP, Ph. Eur., JP
Sodium Chloride	(b) (4)	3.5 mg	USP-NF, Ph. Eur., JP
Sodium Citrate Dihydrate		4 mg	USP-NF, Ph. Eur.
Citric Acid Monohydrate		1 mg	USP-NF, Ph. Eur., JP
Sodium Metabisulfite		2 mg	USP-NF, Ph. Eur.
Sodium Hydroxide		As needed	USP-NF, Ph. Eur., JP
Hydrochloric Acid		As needed	USP-NF, Ph. Eur., JP
Water For Injection		q.s. to 1 mL	USP, Ph. Eur., JP

The formulation includes a (b) (4) overfill.

Table 1: Specifications for Phenylephrine Hydrochloride Injection, USP, 1%

Test	1.0 mL fill in 2 mL vial	5.0 mL fill in 10R[1] vial	10.0 mL fill in 10R vial
Appearance of container (ATP007)	Clear, glass 2 mL vial with gray rubber stopper, aluminum seal and white flip-off lid	Clear, glass 10R vial with gray rubber stopper, aluminum seal and white flip-off lid	Clear, glass 10 R vial with gray rubber stopper, aluminum seal and white flip-off lid
Appearance of the drug product (ATP007)	Clear, colorless solution essentially free of visible particulate matter	Clear, colorless solution essentially free of visible particulate matter	Clear, colorless solution essentially free of visible particulate matter
Particulate Matter per container (USP <788>)	(b) (4)		
pH of the solution (USP <791>, ATP164)			
Container Content (USP <1>)			
Identity of (b) (4) by UV – HPLC (ATP1167)			
Identity of (b) (4) by PDA – HPLC (ATP1167)			
Content of (b) (4) (ATP1167)			
Osmolality (ATP841)	Report	Report	Report

Test	1.0 mL fill in 2 mL vial	5.0 mL fill in 10R[1] vial	10.0 mL fill in 10R vial
Degradation Products (ATP1167) Report each individual degradation product (b) (4) (b) (4) Individual Unknowns Total Related Substances	(b) (4)		
Endotoxin USP <85>			
Sterility USP <71>	Complies	Complies	Complies

[1] The 10R vial is the manufacturer's designation for a 10 mL vial. See Section 3.2.P.7.
[2] NMT = Not More Than
[3] NLT = Not Less Than
[4] RRT = Relative Retention Time

The drug product specifications are based on, but more extensive than the USP monograph for Phenylephrine HCl, injection.

G. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is there a methods validation package?	☐	☒	Because this is a product with a compendial monograph, a methods validation package is not likely to be necessary.

H. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☒	☐	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	

38.	Does section contain tradename and established name?	☒	☐	Vazculep (proposed)

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
39.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	☒	☐	The application contains only 6 months of stability data. The current practice of our Office is to expect 12 months of stability data at a minimum. Discussion at EOP2 left the option open to file the NDA with limited stability data. Due to the fact that this is a marketed unapproved drug, I recommend this NDA be filed.
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	NA
41.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	☒	☐	Additional stability data is requested to accommodate a longer shelf life.

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Olen Stephens, CMC Lead
Prasad Peri, Branch Chief

{See appended electronic signature page}

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/s/

OLEN M STEPHENS

02/28/2013

Pending the biopharmaceutics recommendation, the CMC recommendation is that this NDA may be filed. There is one comment to be added to the 74-day letter to the applicant.

PRASAD PERI

02/28/2013

I concur