CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207926Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 207926/000	**Sponsor:**	AKORN INC
(ode:	590		1925 WEST FIELD CT STE 300
Priority:	7		LAKE FOREST, IL 60045
Stamp Date:	11-JUL-2014	**Brand Name:**	PHENYLEPHRINE HYDROCHLORIDE OPHTHALMIC
PDUFA Date:	11-MAY-2015	**Estab. Name:**	
Action Goal:		**Generic Name:**	PHENYLEPHRINE HYDROCHLORIDE OPHTHALMIC
District Goal:	12-NOV-2014	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 25MG 002; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 100MG	

FDA Contacts:	M. CHELLIAH	Prod Qual Reviewer		3017961724
	N. SWEENEY	Micro Reviewer	(HFD-805)	2404023793
	N. BHANDARI	Product Quality PM		2404023815
	E. LWIN	Regulatory Project Mgr		3017960728

Overall Recommendation:	ACCEPTABLE	on 14-AUG-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 12-AUG-2014	by EES_PROD		

Establishment: **CFN:** 1450114 **FEI:** 1450114

AKORN, INC.

DECATUR, , UNITED STATES 625221412

DMF No: **AADA:**

F nsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-AUG-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE OTHER TESTER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-AUG-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.

2. NDA Number: NDA 207926
   Submission Date: July 11, 2014
   21st C. Review Goal Date:
   PDUFA Goal Date: January 11, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established or Non-Proprietary Name (USAN) and strength:	Phenylephrine HCl
Dosage Form:	Ophthalmic Solution

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Akorn Inc
Responsible Organization (OND Division):	DTOP

II. Application Detail

1. INDICATION: Indicated to dilate pupil
2. ROUTE OF ADMINISTRATION: Topical ocular
3. STRENGTH/POTENCY: 2.5% and 10%
4. Rx/OTC DISPENSED: X ☐Rx ☐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		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]	X			Other suppliers discontinued manufacturing
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
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		
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		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?		X	Just "testing" listed, implying all testing: release and stability
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? Have all EERs been updated with final PAI recommendation?	X		
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		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	DMF (b) (4) for phenylephrine Hydrochloride USP

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

(b) (4)

[redacted]

3. **Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.** None

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product. None. EES overall recommendation provided August 14, 2014.

Additional information not covered above
None

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

NDA:	**207926 Phenylephrine Hydrochloride Ophthalmic**									
Sponsor:	**AKORN INC**									
Indication:	**Indicated to dilate pupil**									
PDUFA:	**5/11/2015 under STANDARD Review**									
Responsible Organization:	**CDER/OAP/DTOP**									
EERS Submitted By:										
Chart Generated On:	**9/15/2014**									
			Overall OC Recomendation:			**ACCEPTABLE entered into EES on 8/14/2014 3:38:24 PM**				
			Reevaluation date:				**4/12/2015**			
Establishment Name	**EER Creation Date**	**FEI Num**	**District Short**	**Country Code**	**Responsibilities**	**Profile Code**	**Firm Profiles - Current Status**	**Inspection History, Dates, Classifications**	**Most Recent Milestone**	**Most Recent EER Compliance**
										(b) (4)
AKORN, INC.	7/28/2014	1450114	CHI	USA	Manufacturing - Quality Control Laboratory - Microbiology Laboratory	(b) (4)	http://intranetapps.fda.gov/scripts/mpga/profile.cfm?FEI=1450114	Acceptable SLQ from 6/6/2014 inspection	OC RECOMMENDATION	AC

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No. Facilities have recently been inspected with acceptable recommendation.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL

(DARRTS)

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

/s/

LINDA L NG
09/26/2014

MAHESH R RAMANADHAM
10/02/2014

NDA 207926

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5%, and 10%

Akorn

Mariappan Chelliah, PhD
Division of Transplant and Ophthalmology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 207926

2. REVIEW #: 1

3. REVIEW DATE: 19-Dec-2014

4. REVIEWER: Mariappan Chelliah, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	11-July-2014
Amendment	24-July-2014
Amendment	04-Sep-2014
Amendment	25-Nov-2014
Amendment	11-Dec-2014
Amendment	16-Dec-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Akorn

Address: 1925 West Field Court, Lake Forest, IL 60045

Representative: Sam Boddapati, PhD

Telephone: (847) 353-4909

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
   c) Code Name/# (ONDC only): N/A
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 7
      - Submission Priority: S (However, due to drug shortage, the application was reviewd on a Priority timeline)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Mydriatic

11. DOSAGE FORM: Ophthalmic Solution

12. STRENGTH/POTENCY: 2.5% and 10%

13. ROUTE OF ADMINISTRATION: Topical

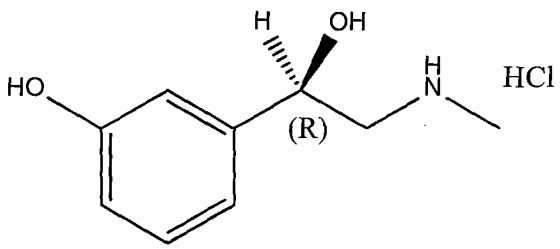
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

    __X___Not a SPOTS product

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

USAN: Phenylephrine Hydrochloride
Chemical Name: (*R*)-(-)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride



Molecular Formula: $C_9H_{13}NO_2.HCl$
Molar Mass: 203.67 g/mol
Chemical Abstract #: 61-76-7

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	11-Dec-2014	Reviewed by Mariappan Chelliah
	III			4	N/A	--	--
	III			4	N/A	--	--
	III			3	Adequate	08-Sep-2014	Reviewed by Libaniel Rodriguez
	III			3	Adequate	13-Nov-2012	Reviewed by George Lunn
	III			4	N/A	--	--
				4	N/A	--	--
	III			4	N/A	--	--
	III			4	N/A	--	--
	III			4	N/A	--	--

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA	--	--
EES	Acceptable	02-Oct-2014	Linda Ng
Pharm/Tox	Approval	08-Dec-2014	Maria Rivera
Biopharm	Approval	09-Dec-2014	Banu Zolnik
LNC	NA	--	--
Methods Validation	Not required	--	--
OPDRA	NA	--	--
EA	Categorical exclusion requested and accepted	26-Nov-2014	Mariappan Chelliah
Microbiology	Approval	12-Dec-2014	Neal Sweeny

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 207926

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA provides adequate information to assure the identity, strength, purity, and quality of the drug product. All CMC issues have been resolved satisfactorily and there are no outstanding issues. The office of compliance has given an acceptable recommendation for both the drug substance manufacturing facility (b) (4), and the drug product manufacturing facility (Akorn). Therefore, this NDA is recommended Approval from the CMC perspective. Both Micro and Biopharm reviews also recommend Approval of the NDA. The labeling will be finalized by the review team.

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

There are no post-marketing commitments that are recommended by the CMC review team. However, the sponsor has voluntarily committed to conduct post-marketing stability studies on the commercial batches of the drug products. Akorn had revised the drug product specification after the exhibit batches were manufactured for the purposes of this NDA. As a result, only a partial list of the specification tests were captured by the completed stability studies. Therefore, as a post approval commitment, Akorn has promised to carry out future stability studies according to the revised stability protocol on three commercial batches for each fill-volume of the drug product. However, the available data is sufficient to grant the 2 year shelf-life requested by the sponsor. This is further discussed under section 3.2.P.8.2 of the review.

The stability data submitted in the NDA is adequate to assure the identity, strength, purity and quality of the drug product.

II. Summary of Chemistry Assessments

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

The drug substance is manufactured under DMF (b) (4). Phenylephrine hydrochloride is a white (b) (4) solid that melts at 140.0-145.0°C. The compound is freely soluble in water and ethanol. It has one chiral center with an absolute chirality of *(R)* and a specific (b) (4) The drug substance specification, excluding impurities, is identical to the USP specification for phenylephrine hydrochloride. USP monograph does not specify

impurities for phenylephrine hydrochloride ophthalmic solution. The specification for related compounds is in-line with the ICH guideline. Akorn has provided the batch analysis data for 3 commercial batches of the drug substance. The drug substance has a shelf-life of (b) (4) under the long-term storage condition of 25°C/60%RH.

The phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, have been marketed in the USA by Akorn since 1993 under the "Grandfathered" status. However, in this application, the sponsor is seeking FDA approval for the same product for the two strengths. Akorn claims that there are no changes between the legacy marketed products and the products for which they are seeking approval. The drug product is formulated as a sterile ophthalmic solution buffered with sodium phosphates. Sodium hydroxide and phosphoric acids are listed as pH adjusting reagents. Benzalkonium chloride, 0.01%, is used as an antimicrobial preservative. The bulk formulated solution is (b) (4) filled-into LDPE containers.

The drug product is manufactured at different fill-volume configurations depending on the strength. The 10% solution has a 5 mL fill-size in a 10 mL container. The 2.5% solution is filled in 15 mL and 2 mL fill-sizes in 15 mL and 6 mL containers respectively. The container closure system for all the three drug product configurations have satisfactory leachable profile and deliver the drug product in consistent drop sizes. The freeze-thaw study indicates that the quality of the drug product remains uncompromised.

The drug product specification and the justification are adequate. Akorn has manufactured three exhibit batches for each configuration of the drug products. However, since Akorn has revised the specification after the exhibit batches of the drug products were manufactured, the batch analysis data as well as the stability data does not capture the data for all the tests that are part of the specification. Therefore, Akorn has committed to test future batches using the revised specification. This proposal is acceptable since the existing data permits evaluation for the requested shelf-life. Akorn has submitted the 24 month long-term stability data for the exhibit batches of the drug product. The drug product is stable under the long-term storage condition of 25°C/40% RH and supports a 2 year shelf-life.

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

Phenylephrine hydrochloride ophthalmic solution is indicated for use as a mydriatic agent. The drug product is formulated as 2.5% and 10% phenylephrine hydrochloride, sterile, buffered and preserved solution. The drug product is filled in multi-dose containers. The 10% solution is filled at a 5 mL fill-size in a 10 mL container. The 2.5% solution is filled at a 15 mL fill-size in a 15 mL container and 2 mL fill-size in a 2 mL containers. The LDPE containers are fit with a dropper tip and a cap. One drop of the solution should be instilled at 3-5 minutes interval for a maximum of 3 drops per eye. The container should be stored at 20-25°C.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance is manufactured under DMF (b) (4), which is found to be adequate. The manufacturing of the drug product has been described adequately. Furthermore, the batch analysis data, stability data and information on the container closure systems are adequate. Office of compliance has given an acceptable recommendation for the drug substance and drug product manufacturing facilities. Therefore, the NDA is recommended for approval from CMC perspective.

The risk assessment table is give below

Executive Summary Section

From Initial Risk Identification				Review Assessment		
DP attribute/ CQA	**Factors that can impact the CQA[1]**	**FMECA RPN Number**	**From Initial Quality Assessment**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay for Phenylephrine HCl	Quality of the incoming API; analytical method;	4	Evaluate the in-coming material specification and COA provided. Additionally, evaluate the assay method.	(b) (4)	Acceptable Low risk	DP Assay upper range is (b) (4)% compared to USP 115%.
Osmolality	Incorrect weighing; loss of water on storage	6	Check MBR for accuracy of the salts added.		Acceptable Low Risk	Osmolality is not monitored over stability.
Assay for (b) (4)	Assay method	36	Analytical method for assay of (b) (4) should be validated. (b) (4)		Acceptable Low Risk	None

Executive Summary Section

From Initial Risk Identification				Review Assessment		
DP attribute/ CQA	**Factors that can impact the CQA[1]**	**FMECA RPN Number**	**From Initial Quality Assessment**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
				(b) (4)		
Impurities including extractables and leachables (E & L)	Quality of the raw material; container closure; carton label	6	Analytical method should be validated to capture the impurities. Calculate levels and if it exceeds Q3B qualification threshold, consult Pharm/Tox reviewer. Evaluate the need to control E & L in the drug product specification.		Acceptable Medium risk	The carton contains a statement "Do not use if solution is brown or contains a precipitate." No evidence of this was observed in the data provided. However, the DP batch analysis and stability data capture only a partial list of tests that are listed in the specification as Akorn revised the DP specification after the exhibit batches were manufactured. Therefore, evaluate the full-set of data (per approved specification) that is expected to be submitted for commercial batches and evaluate if "brown/precipitates" or different impurity profiles are observed over lifecycle.
Weight loss	Container closure properties	32	Evaluate data and if (b) (4) consider options available (such as shorter expiration date; alternate storage conditions if there is sufficient data for this route)		Acceptable Medium Risk	The water loss trend could not be evaluated due to missing data for the earlier time points (as discussed above).
Sterility	(b) (4)	75	Satisfactory validation of the		Acceptable Low Risk	Initial risk high, but control strategy appears sufficient to mitigate risk,

Executive Summary Section

From Initial Risk Identification				Review Assessment		
DP attribute/ CQA	**Factors that can impact the CQA[1]**	**FMECA RPN Number**	**From Initial Quality Assessment**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
	filling process; sterilization of container closures	[redacted]	sterilization process will mitigate this issue. Consult Product Quality Micro reviewer.	(b) (4)	[redacted]	and is supported by the data provided.

III. Administrative

A. Reviewer's Signature

Mariappan Chelliah, CMC Reviewer, Branch V, ONDQA

B. Endorsement Block

Balajee Shanmugam, CMC Lead, Branch V, ONDQA
Rapti Madurawe, Branch Chief, Branch V, ONDQA

C. CC Block

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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/

BALAJEE SHANMUGAM
08/29/2014

BANU S ZOLNIK
08/29/2014

ANGELICA DORANTES
08/29/2014

RAPTI D MADURAWE
09/03/2014