CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214028Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214028
Assessment # 1

Drug Product Name	Pilocarpine Hydrochloride Ophthalmic Solution
Dosage Form	Ophthalmic solution
Strength	1.25%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	AbbVie Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Feb 22, 2021	All disciplines
Quality Amendment	May 11, 2021	Quality microbiology
Quality Amendment	Jul 22, 2021	Quality microbiology
Quality Amendment	Aug 3, 2021	Manufacturing process
Quality Amendment	Sep 27, 2021	Drug product
Quality Amendment	Oct 5, 2021	Manufacturing process
Quality Amendment	Oct 12, 2021	Manufacturing facilities
Quality Amendment	Oct 13, 2021	Drug product
Quality Amendment	Oct 15, 2021	Drug product
Quality Amendment	Oct 21, 2021	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Zhengfu Wang	Suong Tran
Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Rose Xu	Vidya Pai
Microbiology	Jesse Wells	Jennifer Sykora
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	

Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Milton Sloan	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Drug substance Pilocarpine Hydrochloride USP	Adequate	10/21/2019	Reviewed by Weixiang Dai
	III		(b) (4)	Adequate	8/23/2016	Reviewed by Yushi Feng
	III			NA		

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	122483	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology		Adequate	10/22/2021	Erin Ruhland
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects.

The product is regulated as a drug device combination product per the Genus decision. The drug product is packaged in a multi-dose LDPE eyedropper and OPPQ considered it as a class 2 combination product and no CDRH quality system (QS)/GMP consult is necessary. The 356h form was updated including all the device facilities per the Agency's request on Oct 12, 2021. OPMA has issued an overall acceptable recommendation for all the facilities on Oct 14, 2021. Therefore, NDA 214028 is recommended approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product Pilocarpine Hydrochloride Ophthalmic Solution, 1.25% is a sterile and preserved solution packaged in a 5 mL multi-dose LDPE bottle with a polystyrene dark green cap with 2.5mL fill for commercial products and 1.5 mL fill for physician samples.

Proposed Indication(s) including Intended Patient Population	For the treatment of treatment of presbyopia in adults
Duration of Treatment	Instill one drop into each eye once daily
Maximum Daily Dose	(b) (4) mg/day. As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, Pilocarpine hydrochloride, USP is colorless, translucent, odorless, faintly bitter crystals. Pilocarpine hydrochloride is manufactured by chemical synthesis. The chemistry, manufacturing, and controls information for Pilocarpine hydrochloride, was referenced to DMF (b) (4), which was recently reviewed and found adequate.

Drug Product: Adequate

Pilocarpine hydrochloride ophthalmic solution, 1.25% is sterile, clear, colorless and preserved with 0.0075% benzalkonium chloride (BAK). The product has a USP monograph. All the excipients are compendial.

The revised drug product specifications are acceptable and include the following quality attributes: description, identification, assay, related substances, benzalkonium chloride assay, osmolality, pH, particulate matter, specified leachable, and sterility. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in USP<232> and ICH Q3D guidance. A risk assessment was demonstrated that there is not at risk for the formation or introduction of (b) (4) impurities during the manufacturing process. Average drop size is determined to be (b) (4) µL. Extractable/leachable studies were performed. A leachable ((b) (4)) originated from the (b) (4) was is controlled with NMT (b) (4) ppm in the drug product specifications and the proposed limit was found qualified by Pharm/Tox reviewer Dr. Erin Ruhland on 10/22/2021.

Pilocarpine hydrochloride ophthalmic solution, 1.25% is packaged in a multi-dose LDPE bottle with a high impact polystyrene dark green cap. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted four primary stability batches for commercial products and three batches for physician samples with 18 months stability data when stored at long term storage condition (25°C/40%RH) and 6 months at accelerated condition (40°C/25%RH). All the quality attributes met the specifications. The drug product is not sensitive to light. The in-use stability study indicated that the drug product can be stored at room temperature for 28 days after opening. Therefore, the expiration date of 24 months for commercial products and 12 months for physician samples is granted when stored at 15°C to 25°C (59°F to 77°F).

The storage statement is “Store at 15°C to 25°C (59°F to 77°F)” and will be finalized at the OND’s labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

The manufacturing process includes: (b) (4) . The applicant adequately responded to all identified process deficiencies. All the manufacturing sites are acceptable based on the previous inspection history and manufacturing capability.

Biopharmaceutics: N/A

The drug product is a topical ophthalmic solution. No biopharmaceutics review is necessary.

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The manufacturing process is (b) (4) .

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification.	L	
Impurities	• Formulation • Container closure • Process parameters • Scale/equipment	H	Leachable (b) (4) included in the DP specifications.	M	
pH	• Formulation • Container closure • Process parameters • Scale/equipment	L	(b) (4); No trend on stability observed. Impact on other quality attributes is very minimal.	L	
Particulate matter	• Formulation • Container closure • Process parameters • Scale/equipment	L	Particulate matter test is included in the DP specifications. Comply with USP <789>.	L	

LDPE multi-dose vial	• Formulation • Container closure	L	Class 2 combination product. No CDRH QS/GMP consult necessary.	L	
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment	H	Sterility (USP <71>) included in the DP specification.	M	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Oct 22, 2021

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214028
Assessment Cycle Number	01
Drug Product Name/ Strength	Pilocarpine Hydrochloride, 1.25% ophthalmic solution
Route of Administration	Topical, Ophthalmic
Applicant Name	Abbvie, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OAP/DTOP
Manufacturing Site	Allergan Sales LLC, 8301 Mars Drive, Waco TX 76712 USA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001	**02/22/2021**
Seq 0005	**04/29/2021**
Seq 0006	**05/11/2021**
Seq 0009	**07/22/2021**

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: At the time of NDA filing, this reviewer noted that abbreviated or summarized validation studies and data were provided. This information included, CCIT, AET, manufacturing facilities and equipment, environmental monitoring, (b) (4) drug solution sterility, sterility and depyrogenation validation studies, and media fill studies. IR deficiencies were issued to the firm on 04/13/2021 and the responses (dated 05/11/2021) are incorporated into the review below, along with the submitted information in the table listed above. After the initial review, that included the IR responses (dated 5/11/2021), more IRs were sent (dated Jun 22, 2021). The following is a review of the second-round of IR response dated (Jul 22, 2021).

Concise Description of Outstanding Issues: None

Supporting Documents:

Reference ID: 4877210

- **Microbiology review n022548s001r1.doc (dated Aug 08, 2013, Recommended for Approval) for revalidation frequency on (b) (4) at the Allergan facility in Waco, TX.**

(b) (4)

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

Allergan hereby claims a categorical exclusion from the requirements to prepare an Environmental Assessment for pilocarpine in accordance with 21 CFR 25.31(b).

Pursuant to 21 CFR§25.15(d) and 21 CFR§25.31(b), Allergan affirms that to the best of our knowledge, no extraordinary circumstances exist (as defined by 21 CFR§25.21 and 40 CFR§1508.4) that indicate that the proposed Agency action upon approval of this application may significantly affect the quality of the human environment.

Under 21 CFR 25.31(b), a categorical exclusion exists for:
"Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion."
The Agency's approval of the application increases the use of the active moiety pilocarpine hydrochloride, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). The calculated maximum Expected Introduction Concentrations (EIC) from direct use of pilocarpine hydrochloride (from all of Allergan's pilocarpine containing drug products) entering into the aquatic environment is (b) (4) ppb and is unlikely to have a significant effect on the environment.

The estimated concentration of pilocarpine hydrochloride at the point of entry into the aquatic environment has been calculated in accordance with the FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application dated July 1998. The concentration is estimated using the highest quantity (in kg) of the active moiety expected to be produced for all strengths for direct use in highest forecast year within the next five years.
The calculations of the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment are provided in Table 1.12.14–1.

No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

Reference ID: 4877210

Table 1.12.14–1 Calculation of Expected Introduction Concentration (EIC) for pilocarpine hydrochloride

EIC – Aquatic (ppb) = A x B x C x D	
where	A = kg/year produced for direct use (as active moiety) = (b) (4) kg (maximum annual forecasted production over the next 5 years)
	B = 1 day / 1.214 x 10^{11} liter (1/liters per day entering POTWS – default value)
	C = year/365 days
	D = 10^{9} µg/kg (conversion factor)
EIC	= (b) (4) **ppb**

Assessment: ***Adequate***

The claim of categorical exclusion is acceptable and no additional information is required.

Primary Environmental Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name		Acceptable
Established name(s)	Pilocarpine hydrochloride	Acceptable
Route(s) of administration	Topical; Ophthalmic	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	ophthalmic solution 1.25%	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	USP monograph exception for historical established salt name inclusion
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	Applicant has included a salt equivalency statement.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N/A	

Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

(b) (4)

Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	Acceptable
Dosage strength	Yes	Acceptable
Route of administration	Yes	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes	Acceptable
Net contents (e.g. tablet count)	N/A	
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Yes	Acceptable
Lot number and expiration date	Yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Acceptable
Medication Guide (if applicable)	Yes	Acceptable
No text on Ferrule and Cap overseal		
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

The firm has provided acceptable updated labeling.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

The firm has provided acceptable updated labeling.

Primary Labeling Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

Milton Sloan

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Chunchun Zhang

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/s/

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