CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208-653
Review 2

Drug Name/Dosage Form	**KP201/APAP (Benzhydrocodone Hydrochloride /Acetaminophen) Tablet**
Strength	**6.67 mg/ 325 mg**
Route of Administration	**Oral**
Rx/OTC Dispensed	**Rx**
Applicant	**KemPharm, Inc.**
US agent, if applicable	**NA**

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*Dec 9 2015*	*OPQ all – Reviewed in 1st Cycle*
Amendments	*Feb 8 2016* *Feb 24 2016* *Mar 23, 2016* *April 15 2016* *May 6 2016*	*– Reviewed in 1st Cycle*
Amendments	*Jun 7 2016* *Aug 23 2017*	*– Reviewed in this Cycle*

Quality Review Team (in this cycle)

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Xiaobin Shen**	**OPQ/ONDP/DNDPII/BIV**
Drug Product	**Xiaobin Shen**	**OPQ/ONDP/DNDPII/BIV**
Regulatory Business Process Manager	**Steven Kinsley**	**OPQ/OPRO/RBPMI/BI**
Application Technical Lead	**Julia Pinto**	**OPQ/ONDP/DNDPII/BIV**

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	Jun 6 2016	Dr. Benjamin D Stevens
	Type II			Adequate	Oct 14 2016	Dr. Weixiang Dai

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This application is recommended for approval from CMC perspective.

The outstanding CMC issues from the last review cycle have been fully addressed, as outlined below —

a) The benzhydrocodone HCl drug substance specifications have been tightened in both this NDA and the corresponding drug substance DMF, as requested and agreed upon in the prior review cycle.
b) Acceptable product stability data collected from tablets packaged in blisters has been provided to support the addition of blister packaging.
c) An additional in vitro abuse deterrent extraction study report has been provided. The study tested the different extraction efficiency of the benzhydrocodone HCl and APAP from the test product in comparison to the reference product hydrocodone/APAP tablet. The study supports its related in vitro extraction language in Section 9 of the package insert although the study itself is not meaningful. This has no impact to the product quality itself. Hence it does not affect a review recommendation from the CMC perspective.
d) The product prescribing information has been revised to address outstanding deficiencies from the prior review cycle. The edits have been made in conjunction with review teams from other disciplines.

II. Summary of Quality Assessments

A. Product Overview

The drug product, KP201 Tablets 6.67mg/325mg, comprises Benzhydrocodone HCl, a benzyl ester prodrug of hydrocodone and Acetaminophen (APAP). The drug product tablet, is an immediate release product, that has been submitted as an abuse deterrant composition, based on the prodrug form of hydrocodone. Benzhydrocodone will hydrolyze to the active hydrocodone and benzoic acid. The two APIs are referenced to DMFs which have been reviewed as adequate. Benzhydrocodone API has a retest period o (b) (4) years (based on the most recent DMF holder amendment) and APAP has a retest period o (b) (4) years.

The tablets are packaged into both HDPE bottles and (b) (4) blister strips. The HDPE bottles are closed wit (b) (4) caps, (b) (4) It also contains a 1g silica gel desiccant canister. The blister strips are (b) (4) with push-through (b) (4) lidding.

Sufficient data is provided to support the quality and safety of the manufacture and release of the drug substance and drug product.

Sufficient data is provided to support an expiry of 36 months for tablets packaged in the HDPE bottles when stored at 20 – 25°C (68 –77 °F) with excursions permitted between 15 – 30°C (59 – 86°F).

However, the provided data only supports an expiry of 12 months for tablets packaged in the blister strips when stored at 20 – 25°C (68 –77 °F) with excursions permitted between 15 – 30°C (59 – 86°F).

Proposed Indication(s) including Intended Patient Population	***Management of pain***
Duration of Treatment	***Short term, no more than 14 days***
Maximum Daily Dose	***12 tablets***
Alternative Methods of Administration	***None***

Special Product Quality Labeling Recommendations (NDA only): NONE

B. Final Risk Assessment

Product Attribute CQA	Factors that can impact CQA	Prob-ability	Severity of Effect	Detectability	FMECA RPN #	Comment
Assay , stability	Formulation • Raw materials • Process parameters • Scale/equipments • Site	3	4	Release (1) Stability (3)	Release (6) Stability (18) (low)	
Content Uniformity	Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	4	4	64 (high)	
Dissolution	Immediate release • Slow release	1	2	4	15 (low)	IR tablets

Reviewer Signature:

Xiaobin Shen -S

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Date: 2018.01.03 15:40:45 -05'00'

Xiaobin Shen, Ph.D.
Chemist, ONDP/Division II/Branch IV

Approval Signature:

Julia C. Pinto -S

Digitally signed by Julia C. Pinto -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -S, 0.9.2342.19200300.100.1.1=1300366849
Date: 2018.01.03 18:47:36 -05'00'

Julia C. Pinto, Ph.D.
Branch Chief, ONDP/Division II/Branch IV

Primary Quality Review

(Only new and updated quality related information are summarized and evaluated below. All other sections including those that have editorial revisions do not have related information that warrants formal review write up)

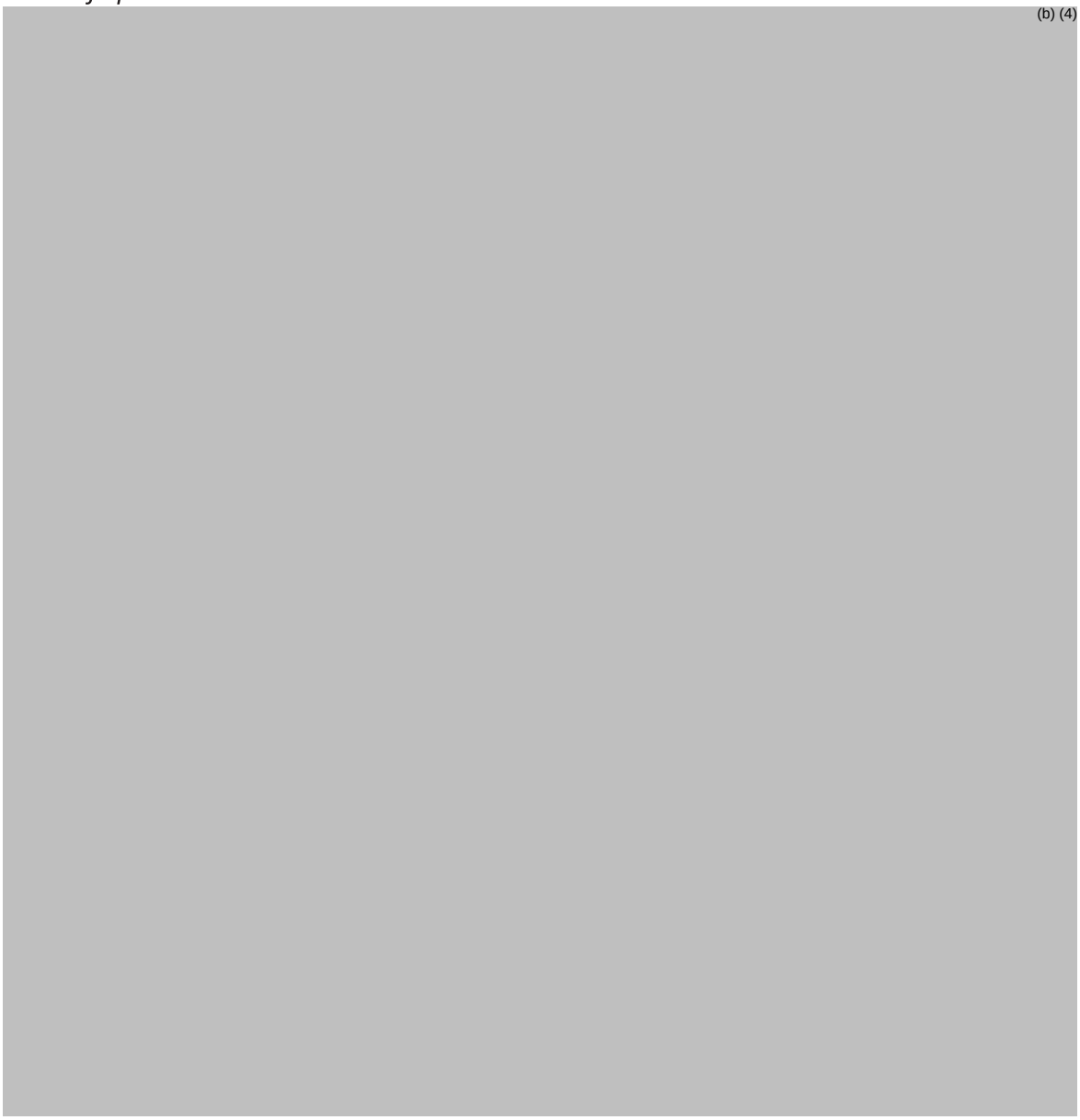
CHAPTER I: DRUG SUBSTANCE

3.2.S.4.1. Drug Substance Specification

The updated drug substance specifications are reproduced below.

Start of Sponsor Material

(b) (4)



End of Sponsor Material

Reviewer's Assessment: ADEQUATE

Th [redacted] acceptance limits have been tightened as requested by the Agency. Th [redacted] acceptance limits have been revised in the corresponding DMF and has been deemed acceptable by Dr. Benjamin D. Stevens. So is the newly added acceptance limi [redacted] All changes are the same as those already deemed acceptable in Dr. Stevens's DMF [redacted] review.

3.2.P.2. Pharmaceutical Development

[redacted]

(b) (4)

3.2.P.7. Container Closure System

In addition to the already reviewed HDPE bottle, the applicant has added a 6-Count Blister Strip as a second container closure system. The relevant information is summarized below.

Start of Sponsor Material

Table 3.2.P.7:4 Component Manufacturer Information – 6-Count Blister Strip

Component	Manufacturer	Address	DMF No.	DMF Letter of Access (LOA)[1]
(b) (4)				Yes
				Yes

[1]LOA's allowing FDA access to these DMFs on behalf of KemPharm, Inc are provided in Module 1.4.1

End of Sponsor Material

Based on information provided in Section 3.2.P.2, the blister (b) (4) and its components comply with the FDA requirements for indirect food additives contained in all applicable sections within 21 CFR 174 through 186. The blister lidding and its components comply with the FDA requirements for indirect food additives contained in all applicable sections within 21 CFR 175.105 (b) (4)

Detailed testing and quality control for the blister packaging materials are provided but not reproduced as it is a commonly used packaging system.

Reviewer's Assessment: ADEQUATE

All components' material of construction conforms to the corresponding CFR sections. There is no safety concern when used to package the drug product tablets. The described quality control procedures are commonly used approaches to control the blister packaging quality.

3.2.P.8. Stability

Up to 24 months of long term registration batch (at pilot scale) stability data were submitted for the tablets packaged in HDPE bottles and evaluated in the prior submission cycle. In this resubmission, additional long term stability data for these batches has been provided for the bottled product, with time points up to 35 – 41 months, depending on the batch.

The provided data exhibited no significant changes in appearance (b) (4) KP201 content, APAP content, dissolution, and APAP drug related impurities. All results complied with the stability specifications proposed over 36 months.

Levels of th (b) (4) impurity, identified during development studies, were observed (b) (4) in the accelerated stability studies. However, all results remained within the acceptance limits of NMT (b) (4)%.

All individual unspecified degradation products that were observed were below the specification of NMT (b) (4)% with the majority of results below the reporting threshold of NMT (b) (4)%.

The applicant used the collective stability information above to support their proposed product expiry of 36 months when stored at 20 - 25°C (68 - 77°F) with excursions permitted between 15 - 30°C (59 - 86°F) [USP Controlled Room Temperature]. Hence it supports the applicant proposed 36 months expiry.

To support the alternate blister packaging configuration, they also provided up to 6 months of 25°C/60% RH and up to 6 months of 40°C/75% RH stability data for commercial scale drug product batches packaged in blister strip. As expected, all data showed no apparent trend and complied to the regulatory specifications, **for up to 6 month of data reported**.

Note the following three aspects —

1. The bottle packaging configuration contain (b) (4) (b) (4)
2. The blister packaging configuration (b) (4) (b) (4)

3. Note the two tables reproduced below that for the bottle package (b) (4)

Start of Sponsor Material

(b) (4)

End of Sponsor Material

Reviewer's Assessment: ADEQUATE for the bottle configurations, but only 12 months of shelf life can be granted to the blister package configuration.

With the support of real time stability data, the bottled product can be granted a 36 months expiry.

(b) (4)

(b) (4) Based on ICH Q1E, not more than 6 months can be extended beyond the 6 months long term stability data, hence only 12 month expiry can be granted to the blister packaged product.

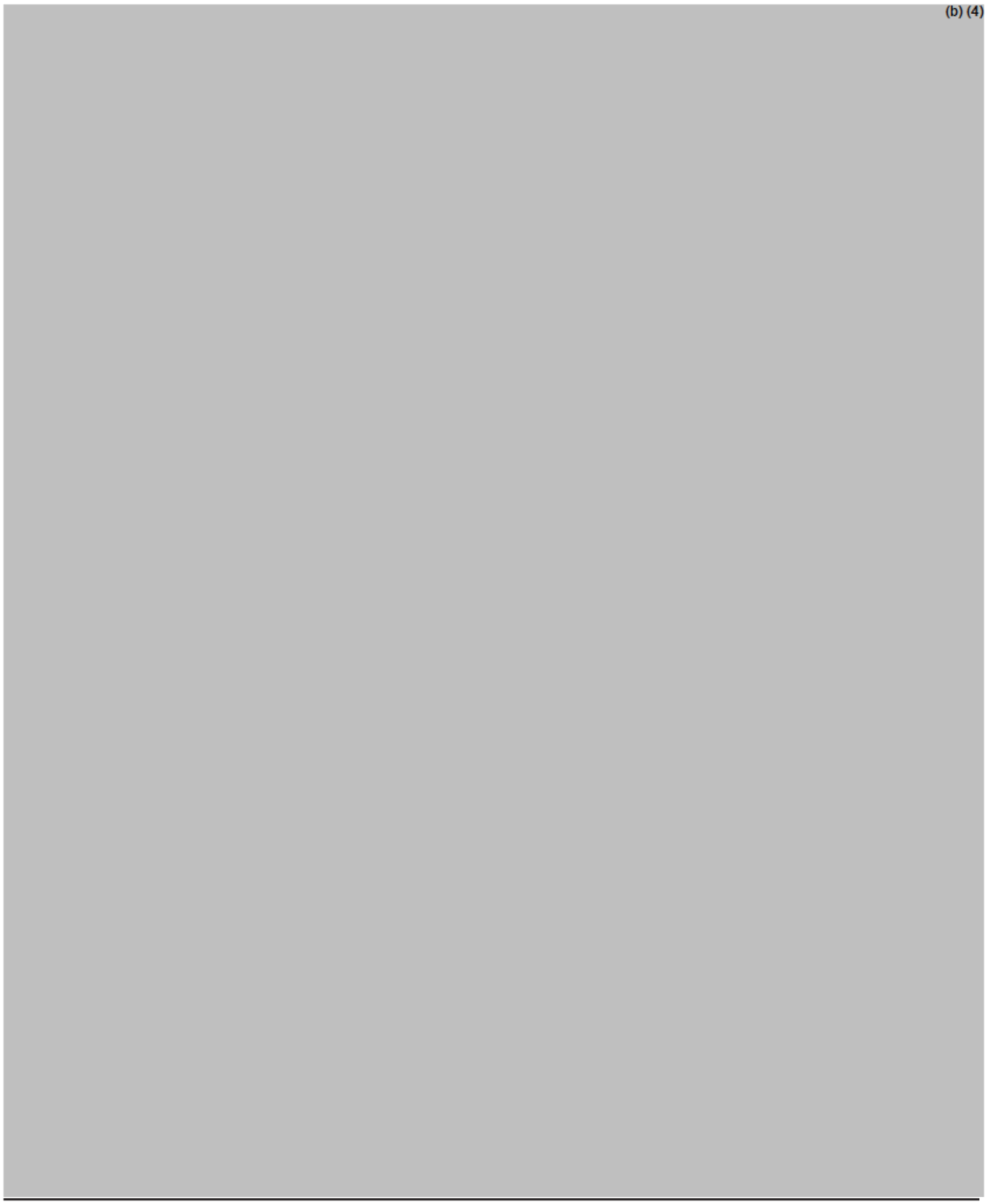
Labeling

(Only new and updated blister related labeling information are summarized and evaluated below)

1. Container and Carton Labeling

1) Immediate Container Label – Blister Label

Start of Sponsor Material



End of Sponsor Material

Conclusion: ADEQUATE

The blister label contains all the required information in the acceptable format.

Xiaobin Shen

Digitally signed by Xiaobin Shen
Date: 1/03/2018 08:20:16PM
GUID: 508da71f00029eecfb90bd87e5a608ab
Comments: I approve the review.

Julia Pinto

Digitally signed by Julia Pinto
Date: 1/04/2018 12:13:04PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

QUALITY ASSESSMENT

Recommendation: Approval

NDA 208653
Review 1

Drug Name/Dosage Form	**KP201/APAP(Benzhydrocodone Hydrochloride/Acetaminophen)/Tablet**
Strength	**6.67 mg/ 325 mg**
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	**KemPharm, Inc.**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*Dec 9 2015*	*OPQ all*
Amendment	*Feb 8 2016*	
Amendment	*Feb 24 2016* *Mar 23, 2016* *April 15 2016* *May 6 2016*	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Ben Stevens**	**OPQ/ONDP/DNDPAPI/BII**
Drug Product	**Ben Stevens**	**OPQ/ONDP/DNDPAPI/BII**
Process	**Shujun Chen/Pei-I Chu**	**OPQ/OPF/DPAII/BVI**
Microbiology	**Shujun Chen/Pei-I Chu**	**OPQ/OPF/DPAII/BVI**
Facility	**Christina Capacci-Daniel**	**OPQ/OPF/DIA/BII**
Biopharmaceutics	**Mei Ou/Haritha Mandula**	**OPQ/ONDP/DB/BII**
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	**Julia Pinto**	**OPQ/ONDP/DNDPAPI/BII**
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	**Ben Stevens**	**OPQ/ONDP/DNDPAPI/BII**

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	May 2016	(b) (4)
	Type II			Adequate	Feb. 2016	Adequate
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This application is recommended for approval. We acknowledge that the applicant submitted a correspondence on June 7th proposing an alternate commercial packaging of the drug product. The proposed container closure system is (b) (4) blister pack for the product. No stability data was provided for the blister packs on the June 7th 2016 correspondence.

II. Summary of Quality Assessments

A. Product Overview

The drug product, KP201 Tablets 6.67mg/325mg, comprises Benzhydrocodone HCl, a benzyl ester prodrug of hydrocodone and Acetaminophen (APAP). The drug product tablet, is an immediate release product, that has been submitted as an abuse deterrant composition, based on the prodrug form of hydrocodone. Benzhydrocodone will hydrolyze to the active hydrocodone and benzoic acid. The two APIs are referenced to DMFs which have been reviewed as adequate. Benzhydrocodone API has a retest period o (b) (4) years (based on the most recent DMF holder amendment) and APAP has a retest period o (b) (4) years.

The tablets are stored in HDPE bottle (b) (4) (b) (4) Sufficient data is provided to support an expiry o (b) (4) months when stored at 20 – 25 °C (68 –77 °F) with excursions permitted between 15 – 30 °C (59 – 86°F).

Sufficient data is provided to support the quality and safety of the manufacture and release of the drug substance and drug product.

Proposed Indication(s) including Intended Patient Population	***Management of pain***
Duration of Treatment	***Short term, no more than 14 days***
Maximum Daily Dose	
Alternative Methods of Administration	***None***

Special Product Quality Labeling Recommendations (NDA only) : NONE

B. Final Risk Assessment

Product Attribute CQA	Factors that can impact CQA	Probability	Severity of Effect	Detectability	FMECA RPN #	Comment
Assay , stability	Formulation • Raw materials • Process parameters • Scale/equipments • Site	**3**	**4**	Release (1) Stability (3)	Release (6) Stability (18) (low)	
Content Uniformity	Formulation • Raw materials • Process parameters •Scale/equipment • Site	4	4	4	64 (high)	
Dissolution	Immediate release • Slow release	1	2	4	15 (low)	IR tablets

Signature:
Julia C.Pinto, Ph.D.
ATL and (Acting) Branch Chief, ONDP/Division II/Branch IV

Signing on behalf of Julia C. Pinto, Ph.D.:

Ciby J. Abraham -A

Digitally signed by Ciby J. Abraham -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000827346, cn=Ciby J. Abraham -A
Date: 2016.06.08 07:37:57 -04'00'

Ciby J. Abraham, Ph.D.
Quality Assessment Lead (Acting)
ONDP/Division II/Branch IV

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CHAPTER IV: BIOPHARMACEUTICS

BIOPHARMACEUTICS

Product Background: The Applicant, KemPharm, submitted this **NDA 208653** on 12/09/2015 for their proposed drug product, Benzhydrocodone Hydrochloride/Acetaminophen (KP201/APAP) Tablet, 6.67 mg/ 325 mg. This drug product is indicated for the short-term (no more than 14 days) management of acute pain. This NDA is a 505(b)(2) application. The Division of Biopharmaceutics (DB) focuses on the review of in vitro dissolution test and acceptance criteria of the proposed drug product.

NDA: 208653

Drug Product Name / Strength: Benzhydrocodone Hydrochloride /Acetaminophen (KP201/APAP) Tablet, 6.67 mg/325 mg

Route of Administration: Oral

Applicant Name: KemPharm, Inc.

Review Summary:

List of submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	09-Dec-2015	Biopharmaceutics
Amendment	24-Feb-2016	Biopharmaceutics

The in vitro dissolution method for drug product, KP201/APAP tablet, 6.67 mg/325 mg, was derived directly from the USP monograph for Hydrocodone Bitartrate and Acetaminophen Tablets. The dissolution method of KP201 had been determined (b) (4) (b) (4) This method also showed that the dissolving conditions of APAP matched those in the USP monograph. Therefore, the proposed dissolution method as Apparatus II (paddle), 0.1N HCl, 900 mL, 50 rpm, is acceptable for the drug product.

The dissolution method was validated in terms of specificity, linearity, accuracy, precision, robustness, solution stability, system suitability, and repeatability. The in vitro dissolution data are confirmed to be within the linearity range (b) (4) % for both of KP201 and APAP) as established during the method validation. Therefore, the in vitro dissolution method validation is acceptable.

The mean and individual dissolution data of drug product were provided. Based on the totality of submitted data, the proposed dissolution specification of NLT (b)(4)% (Q) of the label claim of KP201 and APAP in 30 minutes is acceptable for the drug product, KP201/APAP tablet, 6.67 mg/325 mg.
The in vitro dissolution method and specification for the proposed drug product are summarized as below:

USP Apparatus	II (Paddle)
Dissolution Medium	0.1N Hydrochloric Acid (HCl)
Volume	900 mL
Agitation speed	50 rpm
Temperature	37°C ± 0.5°C
Sampling time points	5, 10, 15, 20, 30, and 45 minutes
Specification	NL (b)(4)% (Q) of the labeled amount of KP201 and APAP is dissolved in 30 minutes

OVERALL COMMENTS:

This NDA 208653 for drug product, Benzhydrocodone Hydrochloride /Acetaminophen (KP201/APAP) Tablet, 6.67 mg/325 mg, is reviewed and found acceptable from the Biopharmaceutics perspective; therefore, this NDA 208653 is recommended for APPROVAL.

BCS Designation
Reviewer's Assessment: I

Note: From Module 2.3.P, drug substance KP201 is considered to have high solubility in all the buffers. The permeability of KP201 could not be determined directly as the KP201 molecule is metabolized by the cell systems, however, the metabolite of KP201, hydrocodone, is believed to be a BCS I product (high solubility, high permeability). The BCS class of drug substance of APAP is not mentioned in this submission.

Solubility: KP201 has high solubility in all the buffers. APAP is soluble in water and some common solvents.

Permeability: The permeability of KP201 could not be determined directly as the KP201 molecule is metabolized by the cell systems. The permeability of APAP is not mentioned in submission.

Dissolution: KP201/APAP tablet is an immediate release product (M.3.2.P.2).

Dissolution Method and Acceptance Criteria
Reviewer's Assessment:

(1) The composition of the drug product

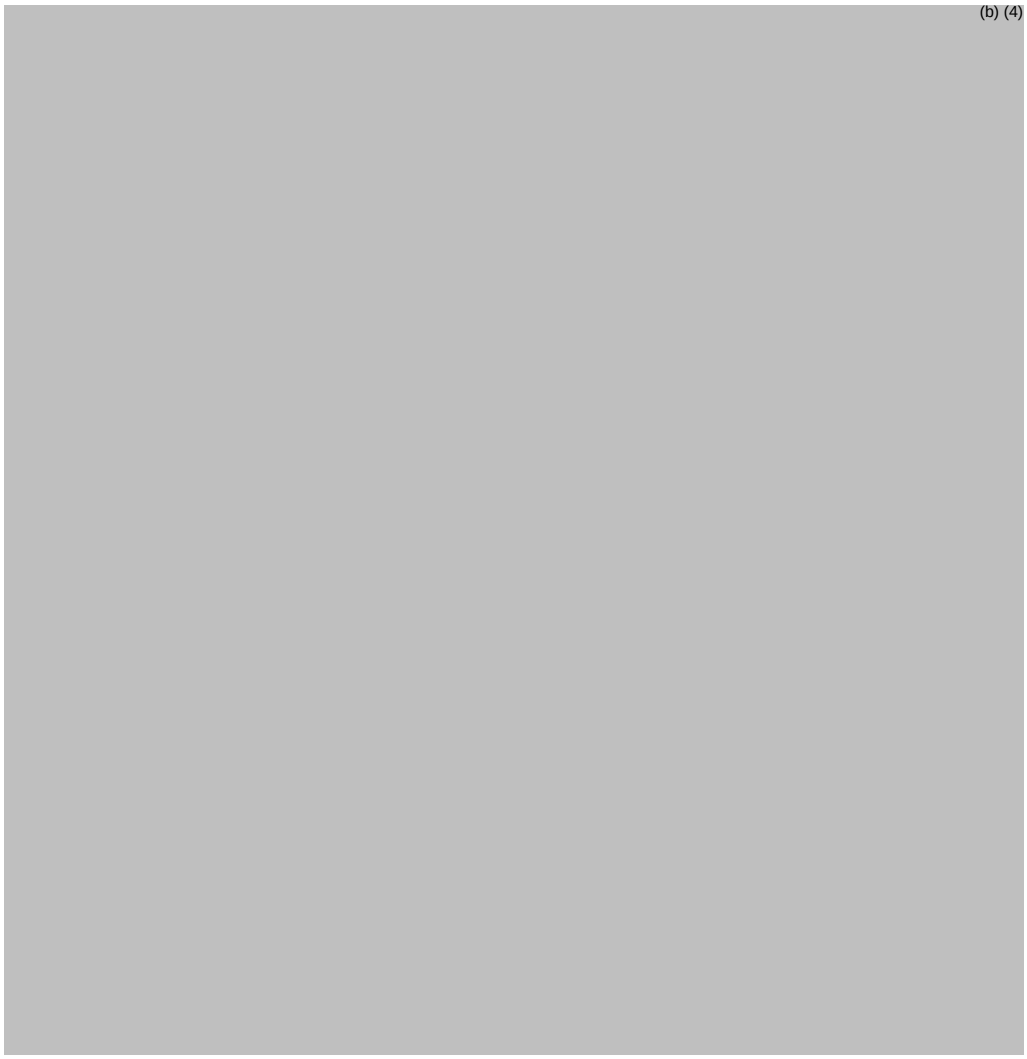
The drug product, KP201/APAP tablet, 6.67 mg/325 mg, is an immediate release fixed-dose combination product (equivalent to 4.54 mg of hydrocodone base and 7.5 mg of hydrocodone bitartrate and 325 mg of acetaminophen). The composition of the commercial formulation along with the function of the excipients used for KP201/APAP tablet is given in Table 1. The Biopharmaceutics review focuses on the in vitro dissolution testing and acceptance criteria of this to-be-marketed formulation drug product.

Table 1: Composition KP201/APAP Tablet, 6.67 mg/325 mg (from M.3.2.P)

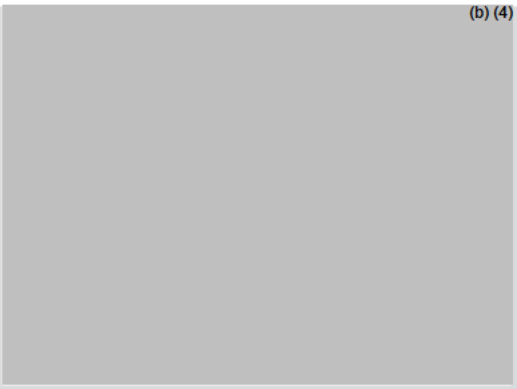
Component	Quantity (mg/tablet)	% w/w	Function	Reference To Quality Standard
Benzhydrocodone hydrochloride	6.67	(b) (4)	Active	In-house
Acetaminophen	325.0		Active	USP
Microcrystalline cellulose			(b) (4)	NF
Pregelatinized starch				NF
Crospovidone				NF
Povidone K30				NF
Stearic acid				NF
(b) (4)				(b) (4)
	(b) (4)			

(2) In vitro dissolution method development

(b) (4)


(b) (4)

(b) (4)



(3) In vitro dissolution m

The detailed in vitro dissolution method for the drug product was provided in M.3.2.P.5.2 (**Method# 929932**). The dissolution method parameters and proposed specification were given in Table 2 below. The dissolution method was effective on 11/05/2015.

Table 2: In vitro dissolution method parameters and proposed specification for the drug product, KP201/APAP tablets, 6.67 mg/325 mg (from M.3.2.P.5.1 and M.3.2.P.5.2)

USP Apparatus	II (Paddle)
Dissolution Medium	0.1N Hydrochloric Acid (HCl)
Volume	900 mL
Agitation speed	50 rpm
Temperature	37°C ± 0.5°C
Sampling time points	5, 10, 15, 20, 30, and 45 minutes
Proposed Specification	NL (b) (4) % (Q) of the labeled amount of KP201 and APAP is dissolved in 30 minutes

(4) In vitro dissolution method validation

The detailed in vitro dissolution method validation reports for the drug product were submitted in M.3.2.P.5.3, listed as:

(b) (4)

The dissolution method was validated in terms of specificity, linearity, accuracy, precision, robustness, solution stability, system suitability, and repeatability. The in vitro dissolution data

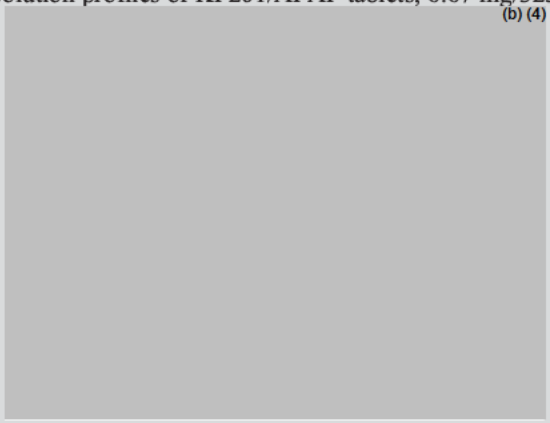
are confirmed to be within the linearity range (b) (4)% for both of KP201 and APAP) as established during the method validation. Therefore, the in vitro dissolution method validation for drug product is acceptable.

(5) In vitro dissolution data and specification of drug product

The in vitro dissolution data of three GMP registration batches of drug product, KP201/APAP tablets, 6.67 mg/325 mg (Batch No. **3108732R**, **3108733R**, and **3108734R** for clinical and stability studies), were provided in M.2.7.1 and M.3.2.P.8.3. The mean dissolution profiles of these three batche (b) (4) (b) (4) was given in Figure 4 below (from M.2.7.1). The individual dissolution data of the three batches at long-term, intermediate, and accelerated storage conditions up to 24 months (b) (4) were given in M.3.2.P.8.3.

Figure 4: Mean dissolution profiles of KP201/APAP tablets, 6.67 mg/325 mg (from M.2.7.1)

(b) (4)



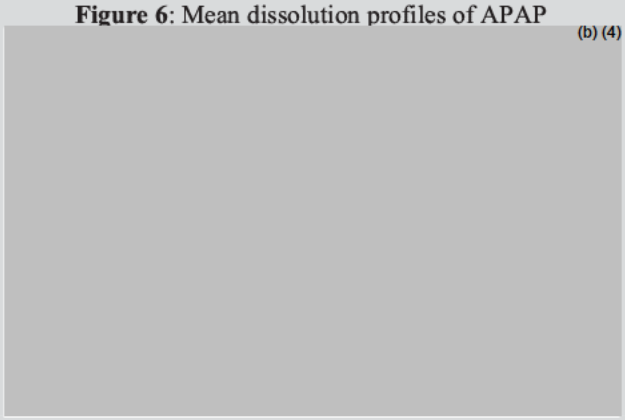
Based on the submitted dissolution data, the Biopharmaceutics reviewer plotted the dissolution profiles of KP201 and APAP of three batches of the drug produc (b) (4) (b) (4) given in Figure 5 and 6 below. Because the proposed drug product exhibits dissolutio (b) (4) of the label amount of KP201 and APAP i (b) (4) per *FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, the dissolution profile comparison with a similarity factor (f2) of KP201 and APAP need not be calculated among these three batches.

Figure 5: Mean dissolution profiles of KP201

(b) (4)

Figure 6: Mean dissolution profiles of APAP

(b) (4)



The Applicant used the dissolution dat (b) (4)
(b) (4) for setting the dissolution specification (b) (4)
(b) (4)
(b) (4) Based on the above consideration, the review team had one Information Request (IR) about dissolution data, which was conveyed to the Applicant in NDA Filing Review Issues Identified Letter (74-day letter) on 02/08/2016 as below. The applicant was asked to clarif (b) (4)
(b) (4)

Biopharmaceutics Information Request:

Provide the complete dissolution profile data (individual, mean, RSD, N=12 units/batch) of your drug product for both Benzhydrocodone Hydrochloride (KP201) and Acetaminophen (APAP) for the three GMP registration batches (Batch No. 3018732R, 3018733R, and 3018734R), with sampling time of 5, 10, 15, 20, 30 and 45 minutes, by using your proposed dissolution QC method (Apparatus 2 Paddle, in 900 mL of 0.1 N HCl, 50 rpm). Your proposed dissolution acceptance criteria [NLT (b) (4)% (Q) of the labeled amount of KP201 and APAP is dissolved in 30 minutes] for both release and stability (b) (4) for your drug product. The final determination of dissolution acceptance criteria will be made after you submit the individual dissolution data profiles.

The Applicant's Responses:

On 02/17/2016, the Applicant responded the above IR comments via email. On 02/24/2016, the Applicant submitted the official copy via formal eCTD submission. The responses are summarized as followed; the detailed additional dissolution data was included in M.1.11.1, Response to Request – Potential CMC Issues.

(b) (4)

Reviewer's comments:

Based on the totality of submitted dissolution data, we consider the proposed dissolution specification of NL (b) (4)% (Q) of the labeled amount of KP201 and APAP in 30 minutes is acceptable for the drug product, KP201/APAP tablets, 6.67 mg/325 mg.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD
Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping
Reviewer's Assessment: n/a

In-Vitro Soft-food Interaction Study
Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products
Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products
Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products
Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products
Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim
Reviewer's Assessment: n/a

Bridging of Formulations
Reviewer's Assessment: n/a

Biowaiver Request
Reviewer's Assessment: n/a

R Regional Information

Comparability Protocols
Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

n/a

List of Deficiencies: [i]

Primary Biopharmaceutics Reviewer Name and Date:

Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products
04/28/2016

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

I have reviewed the biopharmaceutics portion of the review and concur with the reviewers' assessment and conclusion.

Haritha Mandula, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

CHAPTER V: MICROBIOLOGY

Product Background:

Drug product is an abuse-deterrent form of hydrocodone bitartrate/acetaminophen (APAP) immediate release combination product. KP201/APAP tablets are a fixed-dose combination of 6.67 mg of KP201 HCl (equivalent to 4.54 mg of hydrocodone base and 7.5 mg of hydrocodone bitartrate) and 325 mg of acetaminophen.

NDA: 208653

Drug Product Name/Strength: Benzhydrocodone Hydrochloride/Acetaminophen Tablet (KP201/APAP), 6.67 mg/325 mg

Route of Administration: Solid Oral, Immediate Release

Applicant Name: KemPharm, Inc.

Manufacturing Site (b) (4)

FEI # (b) (4)

Method of Sterilization: N/A

Review Summary: ***Adequate***

Drug product is a low microbial risk solid oral table (b) (4) (b) (4) **Firm proposes waiver of microbial limit testing (MLT) specifications for drug product release and stability specifications. Firm provided satisfactory MLT (no growth) and** (b) (4) **data** (b) (4) **for three registration stability batches up to 24 months under long-term storage conditions. MLT test methods are per USP <61>, <62> and validated. MLT acceptance criteria are per USP <1111>.**

Additionally, firm proposes the following (b) (4) **microbial controls:**

(b) (4)

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE

Original, [0001]	**12/09/2015**
Quality Response to Information Request, [0005]	**02/08/2016**
Quality Response to Information Request, [0007]	**02/24/2016**
Quality Response to Information Request, [0009]	**03/23/2016**
Quality Response to Information Request, [0015]	**05/06/2016**

Highlight Key Outstanding Issues from Last Cycle:

1. **No provision of MLT methods or method validation/verification**
2. **Lack of details of MLT specification for Povidone K30**

Concise Description Outstanding Issues Remaining: None

S Drug Substance

Reviewer's Assessment: N/A

Drug product is a non-sterile IR solid oral drug. No sterile drug substance is required.

S.2 Manufacture: N/A

S.2.1 Manufacturers: N/A

S.2.2 Description of the Manufacturing Process and Process Controls: N/A

S.2.5 Process Validation and/or Evaluation: N/A

S.4 Control of Drug Substance: N/A

S.4.1 Specification: N/A

S.4.2 Analytical Procedures: N/A

S.6 Container Closure System: N/A

S.7 Stability: N/A

P.1 Description of the Composition of the Drug Product

Table 3.2.P.1:1 Composition KP201/APAP Tablet, 6.67 mg/325 mg

Component	Quantity (mg/tablet)	% w/w	Function	Reference To Quality Standard
Benzhydrocodone hydrochloride	6.67	(b) (4)	Active	In-house
Acetaminophen	325.0		Active	USP
Microcrystalline cellulose			(b) (4)	NF
Pregelatinized starch				NF
Crospovidone				NF
Povidone K30				NF

Stearic acid	(b) (4)	NF

(b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: Satisfactory

The composition of the drug product is provided in Table 3.2.P.1:1 above. It contains (b) (4) in its formulation, including Acetaminophen, Microcrystalline Cellulose, Pregelatinized Starch, Crospovidone, and Povidone K30. Acetaminophen, Povidone K30 (b) (4) are per USP. All other excipients are per NF. Note that NF for Povidone K30 is a typo, as there is no NF monograph for povidone.

The proposed primary container closure system consists of a white high density polyethylene (HDPE) bottl (b) (4) (b) (4) It provides appropriate storage and protection of the dosage form.

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

P.5.3 Validation of Analytical Procedures

Reviewer's Assessment: Refer to P.5.2 section above.

Endotoxins: N/A
Sterility: N/A

P.7 Container Closure

Summary table of the container closure system proposed

Table 3.2.P.7:1 KP201/APAP Tablets, 6.67 mg/325 mg Container Closure System (100 count configuration)

Component	Description	Materials of Construction
Bottle	100 mL bottl (b) (4) finish, white, high density polyethylene (HDPE), wide mouth round	(b) (4)
Cap Closure	(b) (4)	

(b) (4)

Reviewer's Assessment: Refer to P.1 section above.

P.8 Stability

Reviewer's Assessment: Refer to P.5.1 section above.

P.8.1 Stability Summary and Conclusion

Reviewer's Assessment: Refer to P.5.1 section above.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Table 3.2.P.8.1:3 Stability Test Protocol for Registration Batches of KP201/APAP Tablets, 6.67 mg/325 mg

(b) (4)

(b) (4)

Reviewer's Assessment: Satisfactory

(b) (4)

P.8.3 Stability Data

Reviewer's Assessment: Refer to P.5.1 section above.

A Appendices

Reviewer's Assessment: Satisfactory

(b) (4)

A.2 Adventitious Agents Safety Evaluation: N/A
A.2.1 Materials of Biological Origin: N/A
A.2.2 Testing at Appropriate Stages of Production: N/A
A.2.3 Viral Testing of Unprocessed Bulk: N/A
A.2.4 Viral Clearance Studies: N/A

R Regional Information

Executed Batch Records: N/A
Comparability Protocols: N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A Package Insert: N/A
Post-Approval Commitments: N/A
Lifecycle Management Considerations: N/A
List of Deficiencies: None
Primary Microbiology Reviewer: Shujun Chen, 03/02/2016 (IR #2), 05/11/2016
Secondary Reviewer: Pei-I Chu, Concur, 03/02/2016 (IR #2), 05/11/2016

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