

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207975Orig1s000

CHEMISTRY REVIEW(S)

<table cellspacing=0 width="1100" > <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold,color:#000080,white-space:nowrap" class="TitleCell"> Facility Alerts</td></tr> <tr><td style="text-align:left;font-family:Times New Roman;font-size:25px;font-style:normal;font-weight:bold,color:#000080,white-space:nowrap" class="TitleNameCell"> <td style="text-align:left;font-family:Times New Roman;font-size:11px,color:#8055B7," class="SubtitleCell"> This report displays the Alerts associated with facilities on the selected applications</td></tr> <tr><td style="text-align:left;border-style:none;border-bottom:solid 1px #7f7f7f;font-family:Microsoft Sans Serif;font-size:10px,color:#000080," class="SubtitleCell"></td></tr></tbody> </table> <style type="text/css"> td.ResultLinksCell { } </style>
 <div align="center"> No active OAI / POAI Alerts are present against the facilities on selected Projects</div>

Facility Status View for NDA 207975 Original 1

Displays information for the facilities that are associated to NDA 207975 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

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Overall Manufacturing Inspection Recommendations for NDA 207975 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207975-Orig1-New/NDA(2)	TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC		Complete	9/16/2015

OPF Facility Recommendations for Facilities on NDA 207975 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 207975-Orig1-New/NDA(2)			(b) (4)	CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/13/2015
NDA 207975-Orig1-New/NDA(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/27/2015
NDA 207975-Orig1-New/NDA(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/13/2015
NDA 207975-Orig1-New/NDA(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/13/2015
NDA 207975-Orig1-New/NDA(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/27/2015
NDA 207975-Orig1-New/NDA(2)				CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Approve Facility	Complete	2/13/2015
NDA 207975-Orig1-New/NDA(2)				CTL CONTROL TESTING LABORATORY	Approve Facility	Complete	2/13/2015
NDA 207975-Orig1-New/NDA(2)				(b) (4) TARI FTS, (b) (4)	Approve Facility	Complete	8/26/2015

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NDA 207975
Review # 2
Review Date 10/30/2015

Drug Name/Dosage Form	Vantrela ER (Hydrocodone Bitartrate) Tablets
Strength	15, 30, 45, 60, and 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Branded Pharmaceutical Products R&D, Inc
US agent, if applicable	None

Evaluation of Environmental Assessment

Start of Sponsor Material.

ENVIRONMENTAL ASSESSMENT: CLAIM FOR CATEGORICAL EXCLUSION

Pursuant to 21 CFR 25.30, Teva Pharmaceuticals, Inc. hereby claims a categorical exclusion from the requirement of an Environmental Assessment for hydrocodone bitartrate extended-release tablets (CEP-33237).

Expected Introduction Concentration (EIC)

In accordance with the applicable FDA Guidance for Industry, “Environmental Assessment of Human Drug and Biologics Applications” (July 1998 CMC 6 Revision 1), the EIC of an active moiety of similar annual consumption into the aquatic environment is calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where,

A = kg/year produced for direct use (as active moiety)

B = l/liters per day entering Publicly Owned Treatment Works (POTWs)*

C = year/365 days

D = 109 µg/kg (conversion factor)

* (b)(4) liters per day entering POTWs

The annual amount of hydrocodone bitartrate (kg/year) produced for direct use (i.e., A) was calculated based on Teva’s forecasted need for the peak year in (b)(4). The available doses (15 mg, 30 mg, 45 mg, 60 mg, and 90 mg) were multiplied by the annual projected number of units (b)(4). The sum of these units was then multiplied by 100 doses/unit and converted from mg/yr to kg/yr as shown in the following equation:

$$A = [(15 \text{ mg/dose} \times (b)(4) \text{ units}) + (30 \text{ mg/dose} \times (b)(4) \text{ units}) + (45 \text{ mg/dose} \times (b)(4) \text{ units}) + (60 \text{ mg/dose} \times (b)(4) \text{ units}) + (90 \text{ mg/dose} \times (b)(4) \text{ units})] \times 100 \text{ dose/unit} \times (b)(4) \text{ kg/mg}$$

= (b)(4) kg/year hydrocodone bitartrate produced for direct use. Hydrocodone bitartrate USP is a hemipentahydrate (molecular formula C₁₈H₂₁NO₃ • C₄H₆O₆ • 2.5 H₂O, molecular mass 494.50 g/mol). The active moiety, hydrocodone base, is C₁₈H₂₁NO₃ (molecular mass 299.370). That is, 60.5% the mass of hydrocodone bitartrate is the active moiety, so the mass of hydrocodone bitartrate calculated from the commercial finished product forecast ((b)(4) kg/year) is multiplied by the conversion factor (b)(4) to result in (b)(4) kg/year hydrocodone base.

Accordingly, EIC-Aquatic value for hydrocodone bitartrate is calculated as,

$$\text{EIC-Aquatic} = A \times B \times C \times D = (b)(4) \text{ (kg/year)} \times (b)(4) \text{ (liter/day)} \times 1/365 \text{ (year/day)} \times 109 \text{ (}\mu\text{g/kg)} = (b)(4) \text{ ppb.}$$

In conclusion, hydrocodone bitartrate, the active moiety of hydrocodone bitartrate extended-release tablets (CEP-33237), gives a calculated EIC-Aquatic value of approximately (b)(4) fold lower than the action value of 1 ppb. Since no metabolism effect is factored into this calculation, the actual EIC value will be less. It is unlikely that the product will be a cause of concern for the aquatic environment.

End of Sponsor Material.

Evaluation: Adequate. The sponsor has provided the appropriate justification for categorical exclusion.



QUALITY REVIEW



Reviewer's Signature

Ciby J. Abraham

-A

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
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cn=Ciby J. Abraham -A
Date: 2015.10.30 18:46:25 -0400'

Ciby J. Abraham, Ph.D.

Quality Assessment Lead (Acting)

Application Technical Lead

ONDP/DIVII/Branch IV



**NDA 207975
Review # 1
Review Date 09/18/2015**

Drug Name/Dosage Form	Vantrela ER (Hydrocodone Bitartrate) Tablets
Strength	15, 30, 45, 60, and 90 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Branded Pharmaceutical Products R&D, Inc
US agent, if applicable	None

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission - 0000	12/23/2014
Amendment - 0013	5/4/2015
Amendment - 0018	7/9/2015
Amendment - 0023	8/18/2015

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY	BRANCH/DIVISION
Drug Substance	Erika Englund, Ph.D.	Donna Christner, Ph.D	Branch II/ONDP
Drug Product	Christopher Hough, Ph.D.	Ciby Abraham, Ph.D.	Branch IV/ONDP
Process	Haitao Li, Ph.D.	Ubrani Venkataram, Ph.D.	OPF
Microbiology	Haitao, Ph.D.	Ubrani Venkataram, Ph.D.	OPF
Facility	Michael Shanks	Mahesh Ramanadham, PharmD	OPF
Biopharmaceutics	Fang Wu, Ph.D.	John Duan, Ph.D.	Branch III/ONDP
Project/Business Process Manager	Steven Kinsley, Ph.D.	N/A	OPRO
Application Technical Lead	Ciby Abraham, Ph.D.	N/A	Branch II/ONDP

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:
2. RELATED/SUPPORTING DOCUMENTS:
 - A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	7/16/2015	
	Type II		Active	18-Sept-2014	Adequate	
	Type III		Acitve	Updated 09-Apr-2014		
	Type III		Active	Last updated 06-Jun-2012.		
	Type III		Active	Updated 15-Jan-2014		
	Type III		Active	Updated 15-Aug-2013		

(b) (4)	Type III	(b) (4)	Active	Updated 09-Feb-2015	
	Type III		Active	Updated 25-May-2012	
	Type IV		Active	Updated 10-Oct-2014	

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 105587	

3. CONSULTS:

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

Executive Summary

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the recommendation from the following disciplines, drug substance, process, microbiology, biopharmaceutics, facilities, and drug product, CMC recommends the approval of Vantrela ER 15, 30, 45, 60, and 90 mg tablets.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Product

Drug Substance

The drug substance, hydrocodone bitartrate is manufactured by (b) (4), and is referenced in DMF# (b) (4) (adequate, last reviewed 9/19/2015). Hydrocodone bitartrate is a white to slightly yellow-white crystalline substance which is water soluble. The drug substance has a (b) (4) month retest period when stored in (b) (4)

Drug Product

The drug product Vantrela ER is manufactured by (b) (4). The extended-release tablets are manufactured in five capsule strengths containing 15, 30, 45, 60, and 90 mg of hydrocodone bitartrate. Vantrela ER tablets are packaged in 100-count, high-density polyethylene bottles with induction sealed child-resistant closures. The container closure system contains a 1g of desiccant sachet and rayon coil. The 15

mg, 30 mg, and 45 mg tablets are packaged into 150 cc bottles, while the 60 mg and 90 mg tablets are packaged into 250 cc bottles. Based on the stability data provided, an expiry of 36-months will be granted using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F)." For the in-vitro abuse deterrence studies, the summary of all the studies can be found on page 9.

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

Vantrela ER is an extended-release hydrocodone bitartrate, abuse-deterrent, oral tablet in 15, 30, 45, 60, and 90 mg strengths. The product is to be indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, biopharmaceutics, facilities, and drug product. The application is therefore recommended for approval.

Executive Risk Assessment Summary

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	-	N/A	-
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	-	N/A	-
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Appropriate in process controls are in place	Acceptable	-
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment 	L	-	-	-
Alcohol Dose Dumping	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations <ul style="list-style-type: none"> • Alcohol dose dumping 	H	-	Acceptable	There is no dose dumping detected in the in vitro dose dumping study under the condition tested. In vivo alcohol dose dumping study data confirmed that there is no dose dumping issues.

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.



III. Administrative

A. Reviewer's Signature

Ciby J.
Abraham -A

Digitally signed by Ciby J. Abraham -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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Ciby J. Abraham, Ph.D.
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Application Technical Lead
ONDP/DIVII/Branch IV

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CMC Review for NDA 207975 – Abuse Deterrence studies
(Category 1 Laboratory Manipulation and Extraction Studies)

REVIEW NO.: 1

DATE OF REVIEW: June 30, 2015.

PROPRIETARY NAME: **Vantrela ER™ Tablets**

ALTERNATE NAMES / CODES USED: CEP-33237 (ALO-02)

GENERIC NAME: Hydrocodone Bitartrate Extended Release Tablets.

SPONSOR: Teva Branded Pharmaceutical Products R&D, Inc

DOSAGE STRENGTH(S): 15 mg, 30 mg, 45 mg, 60 mg and 90 mg.

PRIMARY CMC / QUALITY REVIEWER: Christopher Hough, Ph. D;

IN VITRO ABUSE-DETERRENT STUDIES REVIEWER:

Venkateswara Pavuluri, Ph. D., R. Ph.

Branch Chief, ONDP Division II, Branch IV: Julia Pinto, Ph. D;

Quality Assessment Lead: Ciby, Abraham, Ph. D;

Summary:

According to the sponsor, Vantrela ER™ Tablets (Hydrocodone bitartrate extended-release tablets) can deter abuse when subjected to physical manipulations. The sponsor performs the following category 1 laboratory-based in vitro manipulation and extraction studies:

- I. Physical manipulation tool assessment using a variety of household tools, i.e. cutting, crushing, grinding of tablets. Planned physical manipulations were also performed on tablets subjected to heating and frozen conditions prior to manipulation. In vitro dissolution studies using simulated gastric fluid were conducted on manipulated drug products to compare the effectiveness of various manipulation tools.
- II. Simple chemical manipulations include extraction of crushed or ground tablets into solutions representing common household products, e.g. water, aqueous solutions of pH 2 and 8, 20 % and 40 % ethanol for direct oral ingestion.
- III. Extractions using various organic solvents e.g. methanol, isopropyl alcohol, acetone, ethyl acetate etc. for isolation of solid drug substance
- IV. Multiple-step extractions carried out on physically manipulated tablets to assess the extraction efficiency and purity of isolated drug substance using acid/base, polar, non-polar and aromatic organic solvents, under various experimental conditions.

Following overall conclusions were based on review of study results for the above category 1 laboratory-based in vitro manipulation and extraction studies, comparing with either the pure drug substance or one of the two marketed products (Zohydro^(R) ER tablets and immediate release combination product Vicoprofen[®] tablets).

The proposed drug product, Vantrela ER™ Tablets (Hydrocodone bitartrate extended release tablets) is

1. More resistant to abuse by inhalation /insufflation (simulated nasal fluid extraction studies) and injection (small volume aqueous extraction studies) when compared to Zohydro ER.
2. Less susceptible to large volume extractions using aqueous media of varying pH when compared to immediate release Vicoprofen[®].
3. Susceptible to simple solvent and complex liquid/liquid extractions comparable to Zohydro ER, more so upon physical manipulation, for separation of drug substance and/or preparation of concoctions by methodical abusers.
4. Able to reduce the susceptibility of extended release properties to an extent comparable to Zohydro[®] ER, when subjected to physical manipulation followed by simulated oral ingestion and dose dumping studies in presence of alcohol up to 40 % v/v, retaining extended-release properties to some extent.

Overall, the drug product under review has superior abuse-deterrence properties when compared to immediate release combination product Vicoprofen[®] tablets, and has comparable or better resistance to manipulation than Zohydro[®] ER, depending on the mode of abuse. Vantrela ER[™] tablets demonstrated better resistance for abuse by inhalation and injection routes, but data submitted by sponsor is not sufficient to establish any significant abuse-deterrence by oral route or its superiority over approved drug product with Hydrocodone Bitartrate as single ingredient in extended-release form, Zohydro[®] ER. Thus the superiority of Vantrela ER[™] tablets over Zohydro[®] ER capsules for abuse-deterrence by oral route of administration or solvent extraction following physical manipulation, can't be established at this time.

Review of Category 1 Laboratory based Abuse Deterrence studies

Introduction

The scope of this review is for the evaluation of category 1 laboratory-based *in vitro* experiments, consisting of physical and chemical manipulation of the tablets. The review includes a brief discussion on i) physico-chemical properties of hydrocodone bitartrate and functional excipients used in the formulation to confer extended-release properties and resistance to manipulation/abuse of the drug product and ii) properties of intact and manipulated drug product(s) pertinent to abuse-deterrence testing protocols and test reports included by the sponsor. Suitability of analytical methods and dissolution media used for demonstrating the resistance of intact or manipulated drug product to dose dumping (abuse-deterrence) is reviewed by the CMC drug product reviewer and the Biopharmaceutics reviewer. Comparative evaluation on the relevance /adequacy of the physical and chemical manipulations, and simulation methods used by sponsor to determine the abuse-deterrence to those commonly used by abusers are evaluated by Controlled Substance Staff (CSS).

Overview of *in vitro* Abuse-deterrent studies conducted by Sponsor

Several premarket studies were conducted by the sponsor under categories 1, 2 and 3 of the FDA's Draft Guidance for Industry 'Abuse-Deterrent Opioids - Evaluation and Labeling'. The category 1 abuse-deterrent studies are based on *in vitro* characterization of Hydrocodone Bitartrate extracted from Vantrela™ ER tablets by using various manipulations /tampering techniques, in comparison with two marketed products. The two marketed products selected for comparison are Zohydro® ER (hydrocodone) 50 mg capsules, and Vicoprofen® IR tablets, 7.5 mg / 200 mg hydrocodone/ ibuprofen.

A list of all executed *in vitro* manipulation protocols, originally submitted by sponsor to the IND 105587 application, with Type B pre-NDA meeting materials (15 September 2011, in sequence 0047) and additional *in vitro* characterization studies as requested by the Agency (FDA) at Type C (23 January 2014) and Type B pre-NDA (23 July 2014) meetings were consolidate in a table and submitted under section 3.2.P.2.

Study Type	Brief Description	Products Studied ^a
Simulated Oral Ingestion	In vitro dissolution (USP 2, 50 rpm, 37°C) in simulated gastric fluid to simulate ingestion, 500 mL or 900 mL. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance
Particle Size Distribution	Particle size distributions of manipulated materials were characterized by sieve analysis with six screens of mesh sizes ranging from 106 µm to 850 µm. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER
Simulated Nasal Insufflation	Extraction into simulated nasal fluid at 37°C, 10 mL. Heated (150°C) and frozen (-20°C) CEP-33237 were also included.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance

Simulated Intravenous Extraction	Extraction for simulated intravenous (IV) injection, with physical assessment of the feasibility of IV abuse by syringeability and injectability tests (functional tests for viscosity). Per FDA's request, IV extraction experiments included both intact and comminuted tablets and employed multiple pH media (water, pH 6.3 and pH 10.3 buffers), 5 or 10 mL extraction volume.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance
Simple Aqueous Extractions for Ingestion	Simple chemical extractions into 30 mL of solutions that could be directly ingested after extraction, represented by water, pH 2 and pH 8 buffers, 20% ethanol and 40% ethanol solution. Temperatures from ambient to 100°C were explored.	CEP-33237 ZOHYDRO ER Vicoprofen Hydrocodone Bitartrate drug substance
Simple Organic Solvent Extractions	Simple chemical extractions into common organic solvents, represented by methanol, isopropanol, acetone, ethyl acetate, and methylene chloride. After removal of the solvent, the isolated solid residues were characterized for hydrocodone content and purity.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance
Multiple-Step Extractions	Multiple-step, acid/base liquid/liquid extractions to simulate tampering that may be performed by the most sophisticated abusers to attempt isolation of the opioid free base from the excipients. The residual solids obtained were characterized for hydrocodone content and purity.	CEP-33237 ZOHYDRO ER Hydrocodone Bitartrate drug substance

a Note that that CEP-33237 and applicable comparators were studied under the conditions indicated in the referenced summary tables (column 4 above)

Results of category 1 in vitro studies for demonstrating abuse-deterrence of the new Hydrocodone Bitartrate extended release tablets, (Vantrela™ ER) in comparison with the two marketed products, along with details of manipulation equipment selection experiments (multiple (b) (4) protocols and results of the in-vitro manipulation studies) were also included in section 3.2.P.2.2. The titles for various major studies submitted by sponsor are as follows:

- In vitro abuse potential comprehensive high level summary
- Teva Study Report: Tools Selection for Physical Manipulations
- Teva Study Report: Simulated Ingestion Studies
- Teva Study Report: Particle Size Distribution
- Teva Study Report: Simulated Nasal Fluid Extraction Studies
- Teva Study Report: Simulated Intravenous Manipulation and Small Volume Extraction Studies
- Teva Study Report: Larger Volume Extractions

An overall summary of the study results from the Category 1 in vitro manipulation studies was included in section 1.11.4 as a document titled "Abuse Deterrence Assessment". The in vitro studies designed for challenging the controlled release and abuse-deterrent properties of Vantrela™ ER tablets were separated in to sub-sections. These are a) Physical manipulations, b) Simulated oral ingestion (in vitro dissolution) c) Simulated nasal insufflation (in vitro dissolution in simulated nasal fluid) studies, d) Simulated intravenous injection, accompanied by assessments

on injectability and syringability, e) Large volume extractions, using various aqueous media and single organic solvents and f) Multi-step liquid/liquid chemical extractions.

Physicochemical Properties of Hydrocodone Bitartrate and Functional Excipients

Solubility of Hydrocodone Bitartrate (HCBT): Soluble in water; slightly soluble in alcohol; insoluble in ether and in chloroform. (Source: USP/NF accessed online Dt. 4/10/2015). Sparingly soluble in methanol, slightly soluble in acetone and insoluble in hexane (Source: <http://www.swgdrug.org/Monographs/HYDROCODONE.pdf> accessed on 4/28/2015).

Solubility and other relevant properties of functional excipient(s): Information derived from Handbook of Pharmaceutical Excipients, eBook accessed online Dt. 4/3/2015

(b) (4)



Composition and Properties of the Drug Product

All five dose strengths of Hydrocodone Bitartrate extended-release tablets, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg were prepared (b) (4)

hydrocodone bitartrate, (b) (4) The

proposed composition of extended-release tablets is intended to provide release of drug over an extended period of time while limiting dose dumping when tablets are physically manipulated or ingested with alcohol, and to prevent rapid release of drug when the manipulated dosage form (powder) is ingested or administered via nasal insufflation or subjected to small volume extraction in preparations for intravenous injection.

**Table 2: Quantitative Composition of Hydrocodone Bitartrate Extended Release Tablets
15 mg, 30 mg, 45 mg, 60 mg and 90 mg**

Component	Reference to standard	Function	mg /tablet				
			15 mg tablet	30 mg tablet	45 mg tablet	60 mg tablet	90 mg tablet
Hydrocodone bitartrate (b) (4) (u) (v)	USP	Active Ingredient	15.00	30.00	45.00	60.00	90.00
Lactose monohydrate (b) (4)	NF						(b) (4)

Ethyl cellulose (b) (4)	NF	(b) (4)				
Hypermellose (b) (4)	USP					
Glyceryl behenate	NF					
Magnesium stearate. (b) (4) (b) (4)	NF					
(b) (4) (Varies for each strength)	various					
Total weight / Tablet		575	575	575	1150	1150

The sponsor developed the drug product utilizing a combination of release controlling materials to obtain desired extended release profiles suitable for twice daily dosing regimen under normal conditions and to resist misuse or abuse by physical or chemical manipulation. According to sponsor's submission, (b) (4) formulation technology was used in development of the Hydrocodone bitartrate extended-release tablets. Following are the three major processing steps involved in manufacturing of the drug product

- (b) (4)
- (b) (4)
- (b) (4)

According to the sponsor, (b) (4) are critical for reducing the susceptibility of the drug product to physical manipulations and dose dumping in presence of ethanol that may occur during accidental misuse and intentional manipulation.

Reviewer Comment on Small volume Extractions Considering the physico-chemical properties of and functional excipients used together with the manufacturing process described above, the drug product is likely to release hydrocodone bitartrate over an extended period and resist rapid extraction into small volume of aqueous media, either from intact or manipulated tablets. The coating of Hydrocodone (b) (4) granules with a (b) (4) polymer, (b) (4) prevents rapid release of hydrocodone from (b) (4) granules and the tablets. (b) (4) resists rapid extraction of hydrocodone in to small volumes of aqueous media from physically manipulated drug product, (b) (4). Thus the proposed composition and properties of the drug product

may resist small volume extractions using water or other aqueous media, i.e. simulating abuse by insufflation and injection (syringeability and injectability studies) of proposed drug product.

Reviewer Comment on large volume and Solvent Extractions: Hydrocodone bitartrate is soluble in water and slightly soluble in alcohol (b) (4)

(b) (4)
(b) (4)
(b) (4) may not confer any barrier properties to the drug product, (b) (4) and thus may not be effective in preventing drug release from manipulated drug product. Thus hydrocodone bitartrate may be extracted from physically manipulated drug product by methodical abusers, by following a series of extraction and isolation steps as described below.

- a) Extraction of physically manipulated drug with pure ethanol (95%, 190 proof) under hot conditions, facilitating dissolution of (b) (4) and fraction of (b) (4)
- b) Separation of (b) (4) from the hot alcohol extract by filtration.
- c) Separation of (b) (4) from the hot alcohol extract, by precipitation with gradual addition of hot water maintained at temperatures just above 60°C.
- d) Separation of (b) (4) by phase separation and/or solidification, upon cooling the mixture, leaving the drug in hydro alcoholic solution which is suitable for oral consumption (abuse).

Following sponsor's statements also supports the above assumption.

Start of sponsor material

"Unlike some abuse deterrent products with physical barriers, the CEP-33237 tablet itself is not exceptionally hard and is not intended to be physically difficult to manipulate. As previously described, hydrocodone bitartrate is contained within coated (b) (4) granules, and the coated (b) (4) granules are (b) (4) gel-forming polymer in the tablet matrix. The (b) (4) (b) (4) polymers in the (b) (4) granule control drug release and provide mechanical resistance to limit damage to the (b) (4) granule when a tablet is manipulated. The drug release rate from manipulated tablets is expected to increase as a function of physical damage to the coated (b) (4).

"Simple and multiple-step chemical extractions may be used to extract the majority of a dose for methodical abusers willing to invest time to defeat the release controlling mechanism prior to each use. However, doing so required significant time and effort and these techniques did not result in the extraction of a pure opioid drug substance."

End of sponsor material

Evaluation of Physical Manipulation Tools and in vitro Characterization Studies

Physical manipulation experiments were conducted on Hydrocodone extended-release tablets stored at ambient, heated, and frozen conditions to simulate common forms of manipulation of opioid medications. Resultant powders were characterized by particle size distribution, in vitro dissolution in simulated gastric fluid, extraction into simulated nasal fluid, and small volume extraction for simulated intravenous injection. Assessment of the feasibility of abuse by intravenous injection was simulated by syringeability and injectability tests, and assay of the

small volume extracts for content of drug substance when feasible. Different controls were used for comparison during each type of in vitro study conducted on the drug product:

- Hydrocodone bitartrate drug substance for all extraction experiment
- VICOPROFEN[®] (AbbVie) tablets (Immediate-release, containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen) for simulated oral ingestion, simulated insufflation, and simple chemical extraction (pH 2 and 8 buffers) tests after manipulation (two Vicoprofen[®] tablets were used simultaneously to represent a 15 mg hydrocodone dose).
- Zohydro ER tablets were used for additional studies requested by FDA.

The HPLC method is same as the method used for quantitation of the released drug during in vitro dissolution studies from finished drug product. The results presented are mean values for six replicates (with a few exceptions) for study product and three replicated for reference products; and are expressed both as percent of extracted from one dose unit and absolute mass of drug extracted. Much of the in vitro manipulation data for the 15-, 30-, and 45-mg strengths was obtained on development lots containing coated (b) (4) granule (b) (4) (b) (4) while all data for the 60-mg and 90-mg tablets were obtained on tablets with a (b) (4) coated (b) (4), representing the to-be-marketed formulation.

Physical Manipulations – Feasibility Assessment: Initial manipulation tool selection and feasibility assessment was performed by (b) (4) (for (b) (4)) for physical manipulation of tablets from among the several household and pharmacy tools that could potentially be employed for manipulation. The selected manipulation tools include hammer, mortar and pestle, coffee mill and PediPaws as representative of the linear crushing, grinding, rotary cutting, and rotary abrasion mechanisms respectively. The physically manipulated drug product, Vantrela[™] tablets and the comparator Vicoprofen[®] immediate release were used for laboratory based characterization studies and in vitro abuse-deterrence assessment.

Particle size distribution: PSD was measured after manipulation using various tools. Coffee mill manipulation had resulted in more large particles (> 850 µm) and fewer fine particles (< 106 µm) than after tablet manipulation using Powder crusher (15 seconds) and EZYDose crusher. The resulting manipulated drug products were subjected to in vitro drug release study to evaluate the abuse-deterrent properties of drug product upon tampering with various tools, using simulated Gastric fluid without enzymes, or 0.1 N HCl. No direct correlations were found between PSD and drug release rate across the tools tested.

Simulated Oral Ingestion Studies:

Effect Manipulation Tool on Drug Release: In vitro dissolution studies on manipulated tablets resulted in release of drug ranging from 32% to 53% at 120 minutes compared to 11% drug released from intact Vantrela[™] tablets. The cumulative drug release from split tablets was stated to be comparable to intact tablets during initial time points with a gradual increase towards the end of the six hour study. Manipulation by rotary abrasion method (simulating intended abuse) resulted in highest extraction efficiencies among the other manipulation tools used, e.g. 80% release (rotary abrasion tool) compared to the ~20% release from intact and split tablets (accidental / unintended misuse) at 120 minutes for 15 mg dose strength. Among the various dose strengths subjected to manipulation by rotary abrasion, about 74% cumulative drug release was observed in 60 minutes for the 15-mg strength and 39% cumulative drug release in 60 minutes for the 90-mg strength. Vicoprofen[®] drug release values were ≥ 92% within 15 minutes for every tool used.

The effect of temperature extremes on formulated tablets: This was investigated by freezing tablets at about -20°C for 24 hours or heating them to 150°C for 30 minutes before manipulation. While freezing has no impact on the release rate of hydrocodone relative to tablets maintained at room temperature, it was reported that heating of tablets before manipulation resulted in changes in release rate of hydrocodone in some cases, i.e. the release rate for 60 and 90 mg strengths increased upon pre-heating to 150°C for 30 minutes.

Comparison of Manipulated Vantrela™ tablets with Manipulated Zohydro ER: Zohydro® ER capsule, 50 mg containing coated beads of Hydrocodone Bitartrate became commercially available after completion of initially comparative studies with Vicoprofen® tablets. Zohydro® ER did not exhibit comparable resistance to that of Vantrela™ tablets, when subjected to simulated oral ingestion (drug release) studies after manipulation with three different tools. More than 70 % extraction observed for Zohydro® ER after 15 minutes compared to the < 10 % extraction from Vantrela™ tablets.

Reviewer Evaluation: The selected tools represent the mechanisms of crushing, grinding, or chewing of tablets mimicking abusers or patients inadvertently manipulating to make a tablet easier to swallow or to titrate dose. Grinding and abrading/shaving mechanisms affected the formulated tablets differently than direct blunt force or milling mechanisms while grating / abrasion has the highest impact on drug release when compare to intact tablets. Based on the in vitro drug release profiles presented, the crushed Vantrela™ tablets are low compared to Vicoprofen® tablets and Zohydro® ER capsules. Manipulated Zohydro® ER capsules exhibited faster drug release compared to manipulated Vantrela™ tablets. No comparative in vitro dissolution data on intact Vantrela™ tablets to Zohydro® ER capsules was evaluated as part of this review.

In Vitro Alcohol Interaction Studies: The in vitro dissolution profiles of clinical batches were initially evaluated by sponsor with 40% v/v alcohol to verify whether the tablets maintain comparable in vitro release profiles in the presence of ethanol as in the absence of ethanol, and that there is no dose dumping. The 15 mg strength demonstrated the greatest susceptibility to the 40% v/v alcohol challenge, with about 50 percent of drug released in four hours. An interaction study was conducted to evaluate the in vitro release profile of a batch of 15 mg tablets (Lot C62020) in the presence of 0%, 5%, 10%, 20%, and 40% v/v alcohol.

Reviewer Evaluation: This conclusion of sponsor is based on data from the in vitro dissolution profiles of drug product obtained using medium containing different alcohol concentrations below 40% v/v. Additional studies using dissolution medium with different alcohol concentrations above 40% v/v are to be performed by sponsor to justify that alcohol has no dose dumping effect.

IR response: Information request sent to sponsor for additional information on studies using alcohol above 40 %v/v and up to 95 % v/v. Sponsor states that though the Agency requested additional extraction experiments in 20% ethanol and 75% ethanol (on July 18, 2014 Pre-NDA Preliminary Reviewer Comments, page 7), during the July 23, 2014 Pre-NDA (Type-B) meeting the Agency acknowledged that only the 20% ethanol experiments were necessary, to serve as a reference point relative to other products (Meeting Minutes, Type B pre- NDA meeting, IND 105587, p. 11), apart from the studies conducted using 0 % and 40 % v/v ethanol. Sponsor claims that extraction results in (b) (4) are relevant substitutes for the data requested and admits that extractions using concentrations of ethanol above 40% v/v and up to 95% v/v will generate results progressively approaching those from pure organic solvents.

Reviewer comment on IR response: We disagree with sponsor on use of (b) (4) as substitutes for the extraction studies using ethanol above 40 %v/v and up to 95 % v/v. Information requested was to evaluate the oral abuse potential, by defeating the extended release properties, when subjected to physical manipulations in presence of ethanol. Abusers are more likely to use ethanol with little or no water to extract the drug from the intact or manipulated tablet, for direct oral ingestion after diluting with water, but not the other two solvents as claimed by sponsor.

Studies Simulating Abuse by Nasal Insufflation: Abuse potential by nasal insufflation was also assessed by sponsor through extraction of hydrocodone bitartrate from manipulated Vantrela™ tablets, along with controls, drug substance and two comparator products, (Vicoprofen® tablets and Zohydro® ER) in the nasal environment. The quantity of dissolved hydrocodone in 10 mL of simulated nasal fluid at 10 and 30 minutes was measured. The amount of hydrocodone extracted during a 30 minute interval in simulated nasal fluid was highest for Vantrela™ tablets 15 mg strength, i.e. 46% or 7.0 mg among the different strengths, while 91 % (6.9 mg) was recovered from Vicoprofen® tablets under similar extraction condition and ≥ 82% for manipulated Zohydro ER (50 mg) after 10 minutes of extraction.

Reviewer Evaluation: Based on the in vitro drug release profiles presented, the liability of Vantrela™ tablets for abuse by nasal insufflation appears low.

In Vitro Studies simulating Abuse by Intravenous Injection: Abuse potential by intravenous injection was assessed by small volume extraction studies (5 mL) on intact and manipulated dosage forms using water or other aqueous media of different pH as extraction media with and without agitation. Both syringability and injectability of the extracts were assessed as suggested in FDA's Draft Guidance for Industry 'Abuse-Deterrent Opioids - Evaluation and Labeling'. It was reported that gel-forming excipients rendered small volume extraction mixtures visually unappealing and increased the difficulty of filtering and syringing samples from manipulated tablets for intravenous injection.

Reviewer Evaluation: Based on the in vitro drug release profiles presented and because of the gelling of sample, the liability of Vantrela™ tablets for abuse by intravenous injection appears low.

Simple and Complex Drug Extraction studies: Several extraction studies were designed by the sponsor to liberate the drug substance or separate the drug as solid residue from manipulated tablet. Larger volume extractions range from simple aqueous extractions to complex organic solvent extractions. Simple aqueous extractions were carried out using a fixed volume of 30 ml solutions of pH range from 2 to 8, along with 20% ethanol and 40% ethanol, with change of extraction times, temperatures, and/or agitation. It was reported that extraction efficiencies increased with temperature, agitation, extraction time, and ethanol content in the solvent and were higher in general with use of the rotary abrasion tool relative to other tools. The most aggressive conditions used for extraction has more than 80% drug extracted within 30 minutes. The pH of extraction medium had little to no impact on the drug release properties of manipulated tablets.

Organic solvents used by sponsor for simple extraction include isopropanol, methylene chloride, and ethyl acetate. The drug was fully extracted within 30 minutes in methanol while only 40% to 50% was extracted in ethyl acetate in 30 minutes because of the limited solubility of Hydrocodone Bitartrate. Extraction efficiencies of the drug from manipulated Vantrela™ Tablets

(coffee mill) using acetone, isopropanol and methylene chloride relatively high while purity of the residue was reported to be low when compared to Zohydro® ER Capsules. Among the three solvents isopropyl alcohol has the highest extraction efficiency, above 80 % in 30 minutes.

Sponsor also performed complex extractions involving multiple-step, acid/base, liquid/liquid extractions, simulating manipulation that may be performed by the most sophisticated abusers to isolate the opioid free base from the excipients. Solvents used include methylene chloride, hexanes, or toluene. Among the solvents used for multiple-step liquid/liquid extraction by sponsor, methylene chloride was found to be the most efficient solvent, with drug extraction efficiencies in the range of 49 -84 %, with the highest efficiency in 15 mg manipulated tablets using coffee mill. The purities of the isolated materials from manipulated Vantrela™ tablets were generally higher than those obtained from the simple organic extractions.

Reviewer Evaluation: Organic solvent selected represent a wide range of polarities and the tampering methods used for physical manipulations are deemed adequate. However manipulations using aqueous solutions and organic solvent need to be expanded to include alcohol content above 40% v/v and up to 95 % v/v (190 proof, grain alcohol).

Sponsor was advised, through an information request sent on June 29, 2015, to provide additional information to the agency on category 1 in vitro studies comparing the test product and Zohydro® ER capsules under identical in vitro test conditions as described below. Sponsor's responses were noted above, in the review

1. Simple extractions using aqueous media containing alcohol in concentrations above 40% v/v, i.e. 60 % v/v/, 80 % v/v and pure ethanol (95% or 190 proof alcohol).
2. Complex multi-step extractions performed using any combinations of solvents deemed relevant by sponsor or by following the method described here
 - e) Extract physically manipulated drug with pure ethanol (95%, 190 proof) under hot conditions, facilitating dissolution of hydrocodone, (b) (4) and fraction of (b) (4)
 - f) Suspended (b) (4) may be separated from the hot alcohol extract by filtration.
 - g) Separate (b) (4) from the hot alcohol extract, by precipitation with gradual addition of hot water maintained at temperatures just above 60°C.
 - h) Also separated (b) (4) by phase separation and/or solidification, upon cooling the mixture, leaving the drug in hydro alcoholic solution which is suitable for oral consumption (abuse).

IR Responses:

1. Extractions using concentrations of ethanol above 40% v/v and up to 95% v/v will generate results progressively approaching those from pure organic solvents. The extraction results in (b) (4) are relevant substitutes for the data requested. Teva believes that requested experiments at ethanol levels between 40% and 95% v/v are not necessary to characterize the drug product.
2. The sequence of steps proposed by the Agency is designed to achieve high purity of drug by removing the (b) (4) polymers as well as the (b) (4) from the dissolution media. The material obtained at the end of the proposed procedure, if successful, would be a solution of hydrocodone bitartrate in a relatively large volume of ethanol/water of unknown ratio. This solution could be ingested by the abuser. Alternatively, the ethanol and water could be evaporated and the remaining pure drug reconstituted for injection. Both of these procedures represent considerable effort on the

part of an abuser for a marginal potential improvement in yield and purity. Teva has demonstrated that the formulation can be defeated using relatively sophisticated chemical extractions, and believes the requested experiments are not necessary to characterize the drug product.

Reviewer Comment on IR Response:

1. Same as under In Vitro Alcohol Interaction Studies above.
2. Teva agrees that the formulation can be defeated using relatively sophisticated chemical extractions and purification methods for isolation of the drug substance.

Overall Evaluation / Conclusions:

1. The rotary abrasion tool yielded the highest fraction of fine particles (< 106 µm), 45% w/w among the manipulation tools used.
2. Manipulation with a rotary abrasion tool results in more rapid drug release than any of the other tools in the comprehensive in vitro manipulation studies.

Manipulation Tool (CEP-33237 tablet lot no.)	> 850 µm	600-850	425-600	300-425	180-300	106-180	< 106
Hammer (C73181)	1.2	8.6	17.3	15.3	10.7	7.9	39.1
Mortar and Pestle (C73181)	1.5	9.2	19.1	18.2	14.8	11.2	26.1
Coffee Mill (C73181)	1.0	7.7	19.9	18.8	15.8	10.9	25.9
Rotary Tool (C73181)	10.7	7.1	8.8	8.7	9.0	10.7	45.0
Silent Knight (C93274)	3.6	10.5	23.7	19.4	13.2	6.1	23.6
Maxi-Matic Mixer (C93274)	1.5	3.3	19.1	17.1	12.1	8.2	38.6

3. The gel-forming excipients render small volume extraction difficult for filtering and syringing samples from manipulated tablets for intravenous injection.
4. Intact or manipulated tablets clearly resist extraction of hydrocodone in biologically-relevant volumes of simulated nasal fluid when compared to Vicoprofen (IR) and to ZOHYDRO (ER).
5. Extraction of hydrocodone from manipulated tablets into aqueous solutions intended for ingestion varies as a function of the extraction medium, the temperature and the agitation condition.
6. Hydrocodone bitartrate can be readily extracted from comminuted CEP-33237 tablets as well as manipulated Zohydro ER comparator. Solubility limitations in various organic solvents can be overcome with larger volumes of solvent. The purity of the extracted residues after solvent removal varies with the solvents used and comparable or better than Zohydro ER comparator.
7. Hydrocodone bitartrate can be extracted in high yields using liquid/liquid extraction procedures with the appropriate organic solvents. The purity of isolated materials varies with the type and volume of solvent used, apart from the skills and willingness of chronic abusers

Thus, the overall abuse-deterrent properties of Vantrela™ tablet are comparable to Zohydro® ER capsules and superior to the IR combination product Vicoprofen® tablets for abuse by intranasal (insufflation) and intravenous (injection) routes. The information provided by sponsor is not sufficient to establish the superiority of Vantrela™ tablet over Zohydro® ER capsules, when administered by oral route or for isolation of drug substance by using liquid/liquid extraction methods.

ASSESSMENT OF THE BIOPHARMACEUTICS

INTRODUCTION

Hydrocodone bitartrate extended-release tablets (CEP-33237) were developed to provide a twice daily dosing regimen. The formulation technology utilizes well-characterized compendial materials to provide an extended release profile, while providing physical and chemical barriers to misuse and abuse. Five tablet strengths have been developed, including 15, 30, 45, 60, and 90 mg of hydrocodone bitartrate. All strengths of hydrocodone bitartrate extended release tablets contain [REDACTED] (b) (4)

[REDACTED] All tablets are capsule shaped and are differentiated by tablet color and debossing.

CEP-33237 is formulated with hydrocodone bitartrate that is [REDACTED] (b) (4)

The representative formulation composition for 15, 30, 45, 60 and 90 mg Hydrocodone Bitartrate Extended Release Tablet is shown in the following table. [REDACTED] (b) (4)

Biopharm Table 1. 15 mg, 30 mg, 45 mg, 60 mg and 90 mg Extended Release Tablet PK Study Formulation Using Hydrocodone Bitartrate Coated Granules

Component	Reference to Standard	Function	15 mg (Light Red)	30 mg (Yellow)	45 mg (White)	60 mg (Light Blue)	90 mg (Light Green)	
			mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet	
Hydrocodone bitartrate ^a	USP	Active ingredient	15.00	30.00	45.00	60.00	90.00	
(b) (4)	NF						(b) (4)	
lactose monohydrate								
Ethyl cellulose, (b) (4)	NF							
Hypromellose (b) (4)	USP							
Glyceryl behenate	NF							
Magnesium stearate (b) (4)	NF							
Red ferric oxide	NF							
Yellow ferric oxide	NF							
FD&C Blue #2 aluminum lake (b) (4)	FD&C							
(b) (4)	USP/NF							
Total Weight / Tablet			575	575	575	1150	1150	

Nineteen (19) clinical pharmacology studies have been performed to characterize the pharmacokinetics of hydrocodone following administration of CEP-33237. These studies include assessments of the pharmacokinetics of single and multiple doses (up to 90 mg administered every 12 hours) of extended-release hydrocodone tablets and assessments of single-dose pharmacokinetics under various conditions, including when taken with alcohol or when the tablet is crushed.

The biopharmaceutics review focuses on the following issues (1) Dissolution method and acceptance criteria (2) IVIVC model (3) Bridging BE studies (4) ER designation claim (5) Alcohol dosing dumping (6) Abuse deterrent property of this product.

1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

33A. DISSOLUTION METHOD

The originally submitted dissolution method is shown below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	50 rpm	500 mL for the 15, 30 and 45 mg strengths and 900 mL for 60 and 90 mg strengths	37°C	0.1N HCl

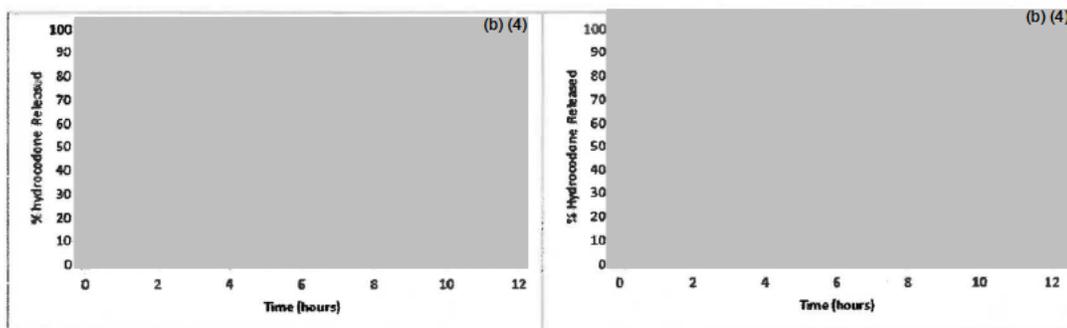
33A.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The Applicant provided the analytical procedure report for the dissolution method in the following link: <\\cdsub1\evsprod\nda207975\0000\m3\32-body-data\32p-drug-prod\c33237-ext-release-tablets\32p5-contr-drug-prod\32p52-analyt-proc\analyt-proc-dissol.pdf>. The following method parameters were evaluated.

Dissolution Media Evaluation

The evaluation of dissolution media (b) (4) is shown in **Biopharm Figure 1**.

Biopharm Figure 1. Effect of pH on the in Vitro Dissolution of Hydrocodone ER Tablets, 15 mg (Batch 200923) and 45 mg (Batch 200916)



The data in **Biopharm Figure 1** demonstrate that drug release from the hydrocodone ER tablets is independent of pH. Please note that the formulation employed in this pH study were not identical to the to-be-marketed formulation. Batch 200916 (45 mg) contained

(b) (4)



whereas the to-be-marketed formulation has (b) (4)

Reviewer's Assessment:

Per this reviewer's point of view, the selection of 0.1 N HCl as proposed QC dissolution method is **ADEQUATE** because the dissolution media pH does not significantly affect the drug release. Selecting one single pH media as QC dissolution method media for Hydrocodone Extended Release Tablet is acceptable.

33A.2 What data are available to support the discriminating power of the method?

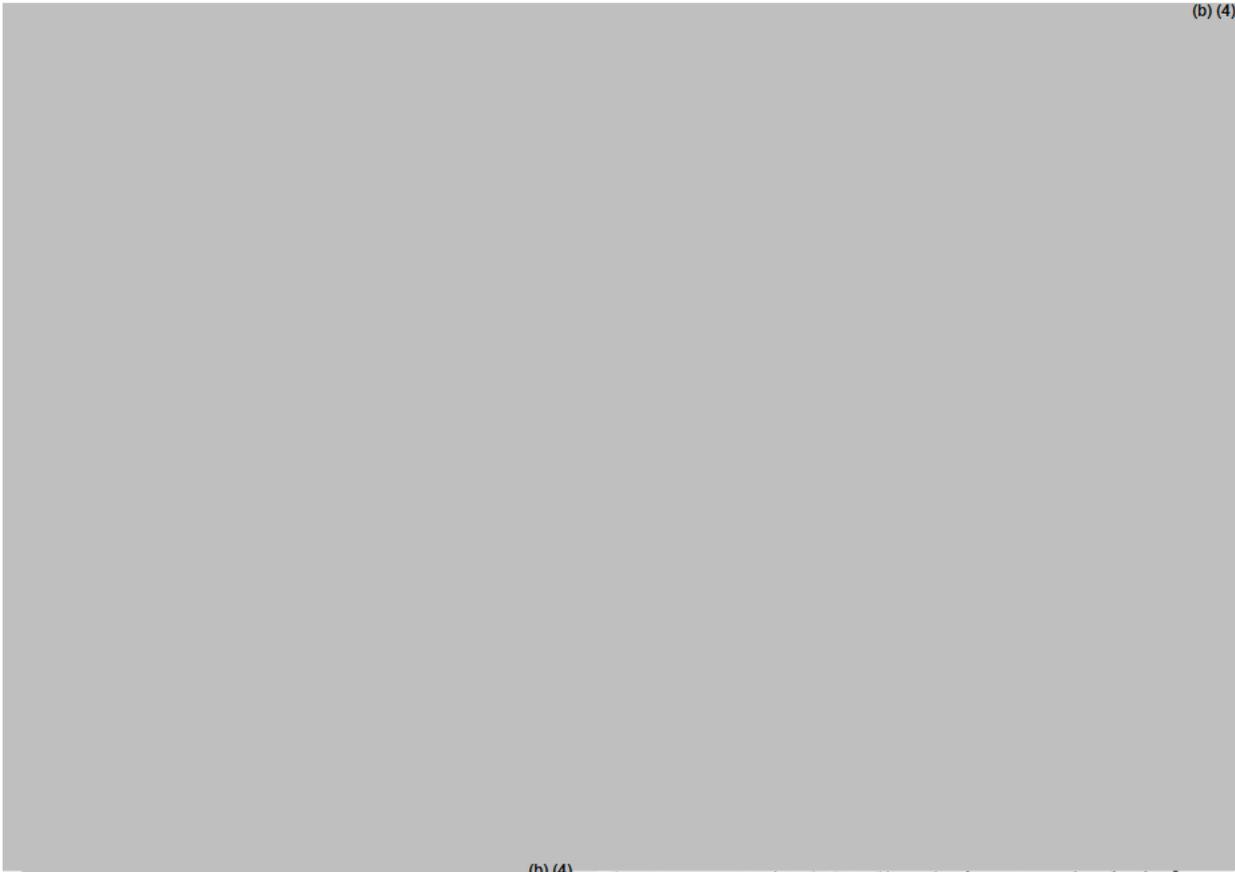
According to the Applicant, the discriminating capability and robustness of the dissolution method as a QC test were established through evaluation of factors that may affect tablet dissolution:

- 1.
- 2.
- 3.
- 4.

(b) (4)

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(b) (4)



(b) (4) The proposed QC dissolution method is ADEQUATE for 15mg, 30 mg, 45 mg, 60 mg and 90 mg Hydrocodone Bitartrate Extended Release Tablet.

33B ACCEPTANCE CRITERION

As agreed upon with FDA (Type B pre-NDA Meeting, 11 Sept, 2011), 3 time points were selected to reflect approximately (b) (4) % release of the drug and were in accordance with FDA guidance. The proposed time points and acceptance ranges for the dissolution specifications are presented in **Biopharm Table 2**.

Biopharm Table 2. Proposed Acceptance Ranges for the Dissolution Specification for Hydrocodone ER Extended-Release Tablets

Time (h)	Acceptance Range (% Hydrocodone Bitartrate Released)				
	15 mg	30 mg	45 mg	60 mg	90 mg
2	(b) (4)				
8					
24					

According to the Applicant, eight batches were selected from the registration/stability batches to set the dissolution specification for the drug product. These batches were manufactured at the commercial facility in (b) (4) and were used in clinical efficacy and safety studies (3103, 3104) or pharmacokinetic studies (1099, 1106) as shown in **Biopharm Table 3**. These batches were manufactured at full commercial scale (b) (4)

Biopharm Table 3. : CEP-33237 Registration Batches Employed in Clinical Efficacy and Bioavailability (BE/PK) Studies and Used to Set the Dissolution Acceptance Criteria

Manufacturing Information	Batch	Strength (mg)	Clinical Use (Study Number)
(b) (4) campaign: 15,30, 45 mg	C89804	15	Efficacy (3103)
	C89805	15	Efficacy (3103, 3104)
	C89806	30	Efficacy (3103, 3104)
	C89807	30	Efficacy (3103), BE/PK (1106)
	C89808	45	Efficacy (3103, 3104)
	C89809	45	Efficacy (3103), BE/PK (1099)
(b) (4) campaign: 60, 90 mg	C91602	60	BE/PK (1106)
	C91605	90	BE/PK (1099)

In the absence of a validated IVIVC model, the recommended dissolution acceptance criterion for extended release products is $\pm 10\%$ (absolute) deviation from the mean dissolution profile of the clinical/bioavailability lots. The mean dissolution profiles from the selected eight batches of CEP-33237 tablets are shown in **Biopharm Table 4**.

Biopharm Table 4. Mean Dissolution Profiles for CEP-33237 Clinical Efficacy and Bioequivalence Batches, Manufactured at Commercial Facility

Time (hr)	% Hydrocodone Bitartrate Released				
	15 mg (2 batches)	30 mg (2 batches)	45 mg (2 batches)	60 mg (1 batch)	90 mg (1 batch)
1	3	4	4	4	4
2	10	10	10	10	10



QUALITY REVIEW



4	23	24	24	21	21
6	37	37	37	33	32
8	51	50	50	44	43
12	70	70	70	63	63
18	84	84	84	81	81
21	88	88	87	86	86
24	90	91	90	89	89

Reviewer's Assessment:

In the submission, a strength dependent dissolution acceptance criteria were proposed. The sampling times for setting the acceptance criteria are adequate because the first acceptance range at the 2 hour time point ensured that there was no dumping of the hydrocodone bitartrate dose. The second acceptance range at the 8 hour time point ensured consistent, controlled drug release (b) (4). The third acceptance range at the 24 hour time point ensured approximately full release of the drug. In addition, the Applicant set the acceptance criteria to (b) (4)% variation around the target value for the middle time point, which is adequate.

A exploratory analysis of an IVIVR model also provides support to the proposed dissolution acceptance criteria (Refer to session 33C.1).

The proposed dissolution specification acceptance criteria are **ADEQUATE**.

33C CLINICAL RELEVANCE OF THE DISSOLUTION METHOD

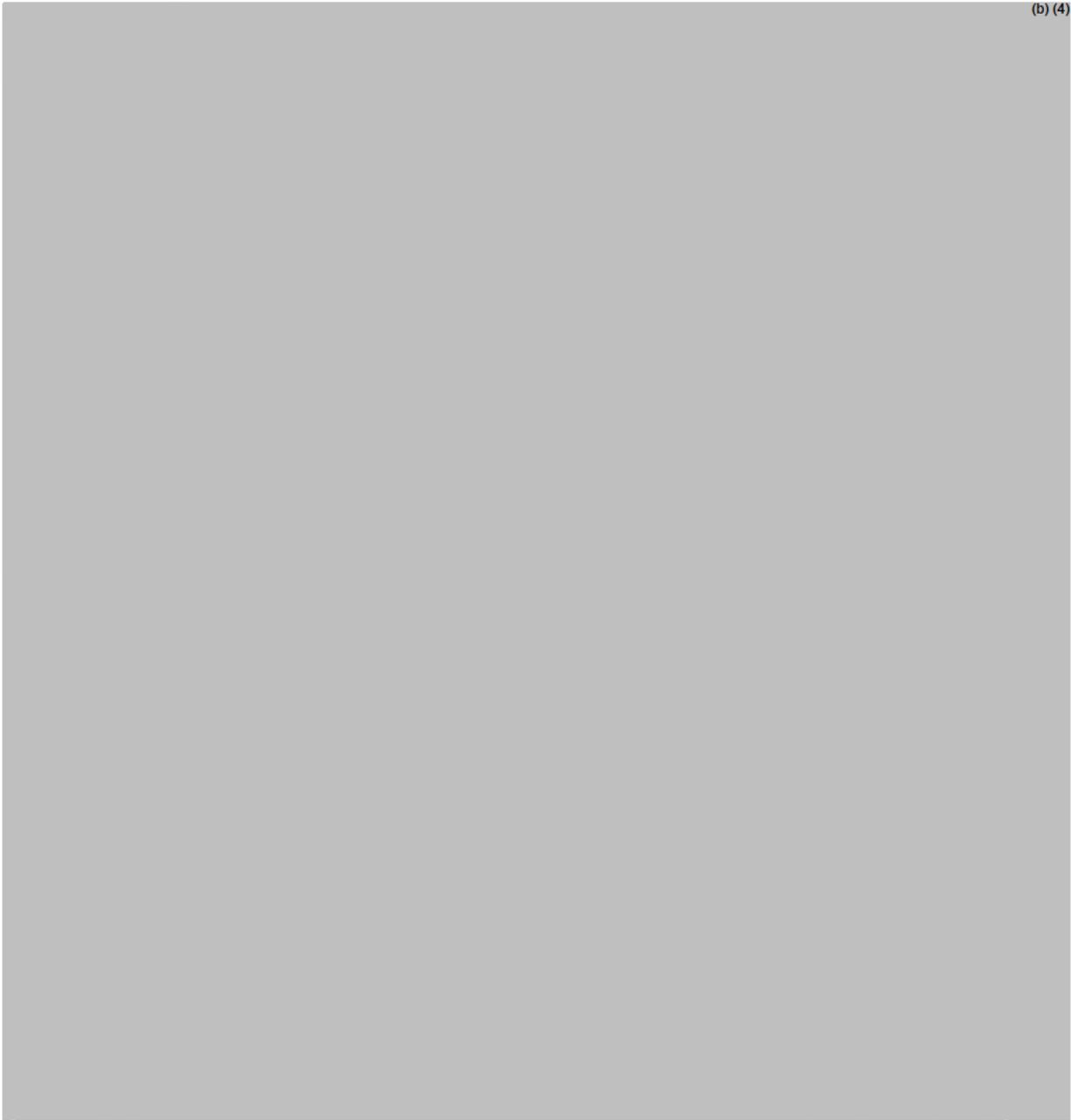
33C.1 Is the proposed dissolution/release method clinically relevant? What data including but not limited to IVIVC are available to support this claim?

The Applicant submitted an *in vitro-in vivo* correlation (IVIVC) analysis of hydrocodone bitartrate ER tablet with the aim to develop a (b) (4) IVIVC model.

The establishment of the IVIVC model and the validation are summarized below:

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(b) (4)



Based on the reviewer's model, the IVIVC model could not pass

(b) (4)

However, there is a rank order existing between the coating level and drug exposure. With the increase of the coating level on the granules, drug exposure decreases. This rank order is reflected in the failed IVIVC analysis, in which although the validation criteria

were not met, a trend did exist. The trend may not be used for dissolution specification setting due to the quantitative restrictions of the specification. However, in a broader sense, it may be used to get further insight about the dissolution time point selection. Therefore, an interest arises for an exploratory analysis in this regard, which is detailed in the next section.

8. Application of the IVIVR model: an exploratory analysis

To determine which time point (21 hr or 24 hr) should be used for the dissolution specification criteria, an exploratory analysis was performed.

Two dissolution profiles were generated based on the dissolution specification criteria, one with the last time point set at 21 hour and another at 24 hour, as shown in **Biopharm Table 15** for the 45 mg strength. The dissolution profile data were fit to a Weibull model and then used as an input into the reviewer’s model to generate the in-vivo absorption profiles. The Oxycodone dissolution profiles data simulated by Weibull model and the predicted pharmacokinetics parameters based on the reviewer’s model are shown in **Biopharm Table 16**.

Biopharm Table 15. Assumed Dissolution Profiles for 45 mg Oxycodone Tablets Based on Different Dissolution Specification Time Point Selections

Time (hrs)	Target specification (% Dissolved)	Predicted (Weibull model)	Target specification (% Dissolved)	Predicted (Weibull model)
0	(b) (4)	0	(b) (4)	0
2	(b) (4)	10.05	(b) (4)	10.05
8	(b) (4)	40.17	(b) (4)	40.17
21	(b) (4)	80.20	(b) (4)	76.07
24	(b) (4)	85.47	(b) (4)	80.14

Biopharm Table 16. Oxycodone Dissolution Profile Data Simulated by the Weibull Model and the Predicted Oxycodone Pharmacokinetic Parameters based on the Reviewer’s Model

In Vitro Dissolution		
	IVIVC Predicted Dissolution By fitting assumed dissolution data (using NLT (b) (4) % at 21 hr as spec)	IVIVC Predicted Dissolution By fitting assumed dissolution data (using NLT (b) (4) % at 24 hr as spec)
Time (Hr)	Mean	Mean
0	0	0
2	10.05	10.05
8	40.17	40.17

21	80.20	76.07
24	85.47	80.14
PK parameters		
AUC _{last} (ng·h/mL), simulated	597.40	548.52
C _{max} (ng/mL), simulated	20.92	20.7

Reviewer's Note:

(b) (4)

The rank order observed may imply a broader limit quantitatively to interpret the dissolution difference. As seen from the reviewer's analysis, although there are some difference of AUC (597.4 vs. 548.5 ng·h/mL), it is only 8.2% differences between these two AUCs. On the other hand, the C_{max}'s are very similar (20.92 vs. 20.7 ng/mL) between the in vivo estimates generated by the two dissolution profiles. This indicates that the differences between the last time point set at 21 and 24 hours may not have an implication for C_{max} differences.

From the *in vitro* perspective, the difference for the last time point between 21 h and 24 h may not significantly affect the shape of the profile. As seen from the table above, the mean dissolution differences between the two dissolution profiles, predicted by Weibull model, are less than 10% at both 21 hours and 24 hours implying the dissolution profile similarity.

Therefore, from both the in vivo (predicted) and in vitro perspectives, the proposed acceptance criterion for the last time point "NLT $\frac{(b)}{(4)}\%$ at 24 hour" is acceptable. The full acceptance criteria for dissolution are shown as **Biopharm Table 2**.

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

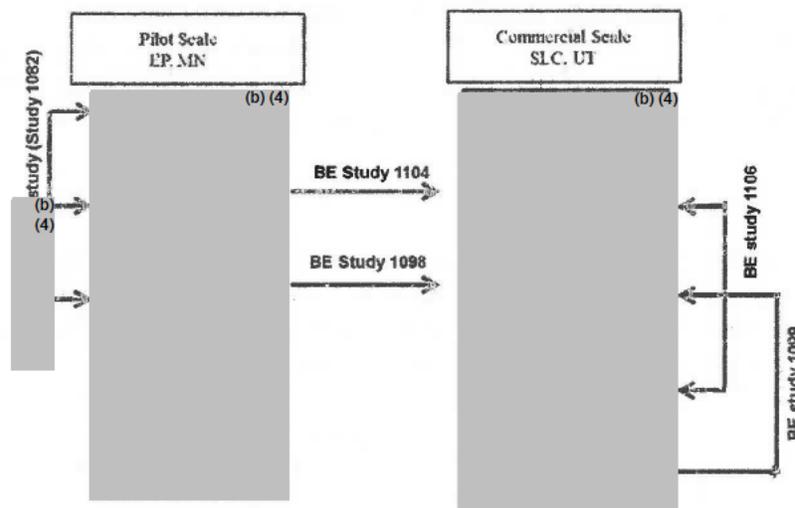
34A. FORMULATION

Eight batches were selected from the registration stability batches manufactured in SLC to set the dissolution specification for the drug formulation. These batches are listed in Section 3.2.P.5.6, Justification of Specifications, and were used in clinical efficacy and safety studies (Study 3103 and Study 3104) and/or pharmacokinetic studies (Study 1099 and Study 1106). These batches were manufactured at full commercial scale for the

(b) (4) and at >1/10th scale for the (b) (4). These eight batches represent the to-be-marketed formulation with respect to formulation, scale, manufacturability, and clinical efficacy.

34A.1 If applicable, how are the formulations used in different phases and/or in different sites are bridged?

The review team created the following chart to demonstrate the bridging studies between formulation used at the pilot scale manufacturing site and the commercial site. The sponsor conducted a series of BE study to support the changes from Pilot Scale manufacturing site and the commercial scale site. BE study **1104** and **1098** demonstrated that 30 mg and 45 mg strength ER tablets are bioequivalent between the pilot scale batch and commercial batch. Study 1082 demonstrated (b) (4) among 15 mg, 30 mg and 45 mg ER tablet manufactured at the pilot scale site. BE study 1106 demonstrated that 60 mg strength is bioequivalent to 2*30 mg strength ER tablets manufactured at the commercial site. Similarly, BE study 1099 demonstrated that 90 mg strength is bioequivalent to 2*45 mg strength ER tablets manufactured at the commercial site.



Biopharm Figure 18. Formulation Development

Reviewer's Assessment:

The performed BE studies shown in Biopharm Figure 18 are sufficient to bridge the formulations in different development stage as well as the manufacturing sites (changed from pilot scale site to commercial scale site). Refer to 34B.1 for the review of the bridging BE studies.

34B. BA/BE STUDIES

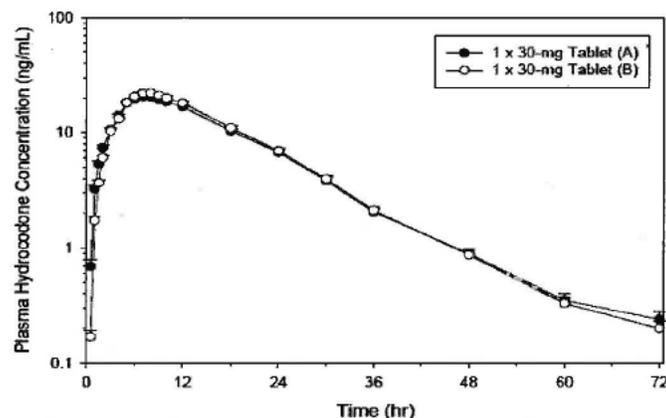
34B.1 What bioavailability (BA)/bioequivalence (BE) data are available for both pre- and post-approval process? Is associated bioanalytical method submitted?

The initial clinical studies (C33237/3079 and C33237/3080) were conducted using the 15 mg, 30 mg, and 45 mg tablets, which required dosing with multiple lower strength tablets (two 30 mg tablets or two 45 mg tablets) to achieve the 60 mg and 90 mg clinical doses. Tablets with higher strengths were developed in an effort to better meet the needs of opioid-experienced patients who may require higher therapeutic doses. The 90 mg strength tablet formula (b) (4) the 45 mg strength EP pilot tablet formula (b) (4). The 60 mg strength tablet formulation (b) (4) the 30 mg strength tablet, however the (b) (4)

According to the SUPAC guidance, the sponsor conducted a series of BE study to support the site changes. BE study 1104 and 1098 demonstrated that 30 mg and 45 mg strength ER tablets are bioequivalent between the pilot scale batch and commercial batch. Study 1082 demonstrated (b) (4) among 15 mg, 30 mg and 45 mg ER tablet manufactured at the pilot scale site. BE study 1106 demonstrated that 60 mg strength is bioequivalent to 2*30 mg strength ER tablets manufactured at the commercial site. Similarly, BE study 1099 demonstrated that 90 mg strength is bioequivalent to 2*45 mg strength ER tablets manufactured at the commercial site.

BE Study 1104

Biopharm Figure 19 presents the mean (+SE) plasma concentration-time profiles for hydrocodone ER 30 mg tablets manufactured at 2 different facilities. The bioequivalence assessment of 30 mg hydrocodone ER tablets manufactured at the pilot and commercial facilities are presented in **Biopharm Table 17** (Applicant calculated).



Biopharm Figure 19. Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following Administration of a Single 30 mg Dose of Hydrocodone ER in Healthy Subjects Using Tablets Manufactured at 2 Different Facilities (Pilot Scale Site and Commercial Site)

Biopharm Table 17. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 30 mg Dose of Hydrocodone ER in Healthy Subjects Using Tablets Manufactured at 2 Different Facilities (Applicant calculated)

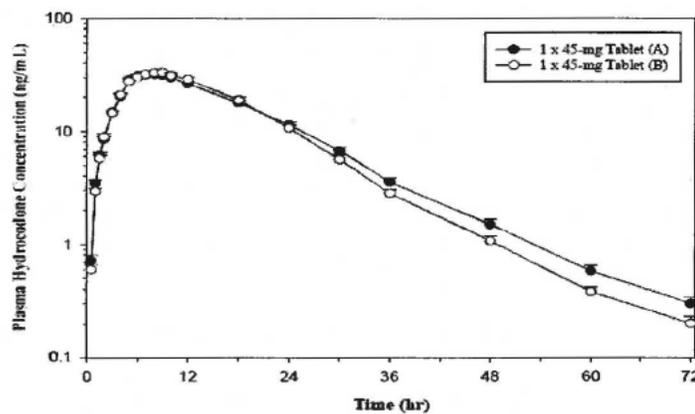
Parameter (unit)	Hydrocodone ER 30 mg Tablet (Reference) ^a (N=43)	Hydrocodone ER 30mg (Test) ^b (N=43)	Hydrocodone ER 30mg Test/Reference Ratio	90% CI
C _{max} (ng/mL)	21.58 (0.68)	22.56 (0.77)	1.0473	0.9967, 1.1005
AUC _{0-∞} (ng·h/mL)	380 (15)	390 (16)	1.0225	0.9692, 1.0851
AUC ₀₋₇₂ (ng·h/mL)	374 (15)	386 (16)	1.0291	0.9724, 1.0891

a. Reference product manufactured at the pilot facility in EP, MN (which is referred to in the study protocol as CIMA Labs).

b. Test product manufactured at commercial facility in SLC, UT (which is referred to in the study protocol as Cephalon).

BE Study 1098

Biopharm Figure 20 presents the mean (+SE) plasma concentration-time profiles for hydrocodone ER 45 mg tablets manufactured at 2 different facilities. The bioequivalence assessment of 45 mg hydrocodone ER tablets manufactured at the pilot and commercial facilities assessed in Study 1098 are presented in **Biopharm Table 18** (Applicant calculated).



Biopharm Figure 20. Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following Administration of a Single 45 mg Dose of Hydrocodone ER in Healthy Subjects Using Tablets Manufactured at 2 Different Facilities

Biopharm Table 18. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 45 mg Dose of Hydrocodone ER in Healthy Subjects in Study 1098 Using Tablets Manufactured at Two Different Facilities (Applicant calculated)

Parameter (unit)	Hydrocodone ER 45 mg (Reference) ^a (N=44)	Hydrocodone ER 45 mg (Test) ^b (N=44)	Hydrocodone ER 45 mg Test/Reference Ratio	90% CI
C _{max} (ng/mL)	32.95 (1.34)	34.05 (1.35)	1.0333	0.9940, 1.0742
AUC _{0-∞} (ng·h/mL)	605 (28)	596 (27)	0.9838	0.9425, 1.0270
AUC ₀₋₇₂ (ng·h/mL)	600 (27)	592 (27)	0.9855	0.9439, 1.0289

Reviewer's Assessment:

Reviewer's analysis on BE study 1104 and 1098 confirmed the Applicant's results, which demonstrated that the ER tablets (30 mg and 45 mg strengths) are bioequivalent between the batches manufactured at the pilot and commercial facilities. The reviewer's analysis results are shown in the following two tables.

Biopharm Table 19. Geometric Means and 90% Confidence Intervals - Reviewer Calculated using Phoenix 6.4

Hydrocodone ER 30 mg Tablet 1 x 30 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Bioequivalence Study, Study No. 1104							
Parameter (units)	RLD ^a	N	Test ^b	N	Ratio	90% C.I.	
C _{max} (ng/ml)	21.6	43	22.6	43	1.04	0.9917	1.0824
AUC _∞ (hr *ng/ml)	379	43	390	43	1.02	0.9692	1.0851
AUC ₀₋₇₂ (hr *ng/ml)	374	43	385	43	1.03	0.9724	1.0891

a Reference product manufactured at the pilot facility in EP, MN (which is referred to in the study protocol as CIMA Labs).

b Test product manufactured at commercial facility in SLC, UT (which is referred to in the study protocol as Cephalon).

Biopharm Table 20. Geometric Means and 90% Confidence Intervals – Reviewer Calculated using Phoenix 6.4

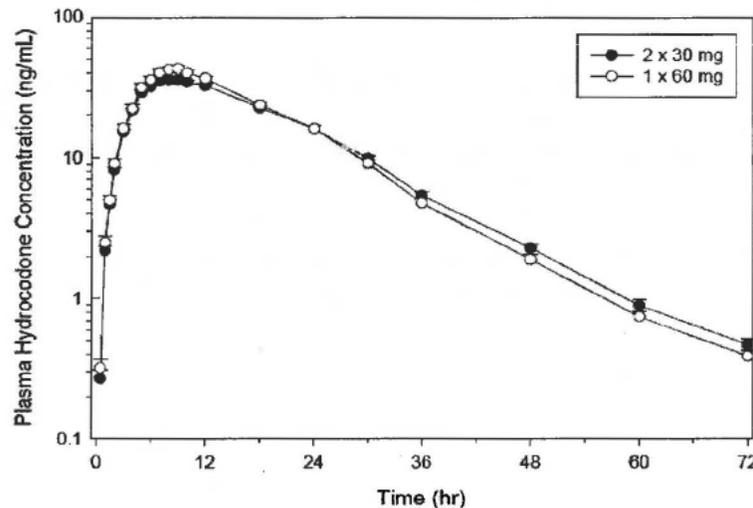
Hydrocodone ER 45 mg Tablet 1 x 45 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Bioequivalence Study, Study No. 1098							
Parameter (units)	RLD ^a	N	Test ^b	N	Ratio	90% C.I.	
C _{max} (ng/ml)	32.9	44	34.0	44	1.0333	0.9940	1.074
AUC _∞ (hr *ng/ml)	605.2	44	595.4	44	0.9838	0.9425	1.0270
AUC ₀₋₇₂ (hr *ng/ml)	600.0	44	591.3	44	0.9855	0.9439	1.0289

a Reference product manufactured at the pilot facility in EP, MN (which is referred to in the study protocol as CIMA Labs).

b Test product manufactured at commercial facility in SLC, UT (which is referred to in the study protocol as Cephalon).

BE Study 1106

After a change in manufacturing facility (EP to SLC) as well as an increase in the ^{(b)(4)} for the 60 mg tablet (from ^{(b)(4)} a bioequivalence study was undertaken to assess the bioequivalence of two 30 mg hydrocodone ER tablets and one 60 mg hydrocodone ER tablet (Study 1106). Biopharm Figure 21 presents the mean (+SE) plasma concentration-time profiles from Study 1106.



Biopharm Figure 21. Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following a Single 60 mg Dose of Hydrocodone ER Administered as Two 30 mg Tablets and as One 60 mg Tablet in Healthy Subjects in Study 1106

The bioequivalence assessment of one 60 mg hydrocodone ER tablet (test) and two 30 mg hydrocodone ER tablets (reference) for study 1106 is presented in **Biopharm Table 21** (Applicant Analysis).

Biopharm Table 21. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following a Single 60 mg Dose of Hydrocodone ER Administered as Two 30 mg Tablets Versus One 60 mg Tablet in Healthy Subjects in Study 1106 (Applicant's analysis)

Parameter (unit)	Two 30 mg Hydrocodone ER tablets (N=46)	One 60 mg Hydrocodone ER tablet (N=46)	Ratio of One 60 mg Tablet: Two 30 mg Tablets	90% CI
C _{max} (ng/mL)	37.62 (1.09)	43.30 (2.51)	1.1488	1.0932, 1.2072
AUC _{0-∞} (ng·h/mL)	766 (26)	801 (29)	1.0431	1.000, 1.0881
AUC ₀₋₇₂ (ng·h/mL)	758 (26)	795 (29)	1.0459	1.0028, 1.0908

SOURCE: Study 1106, Table 9; Ad hoc Summary 1- Study 1106

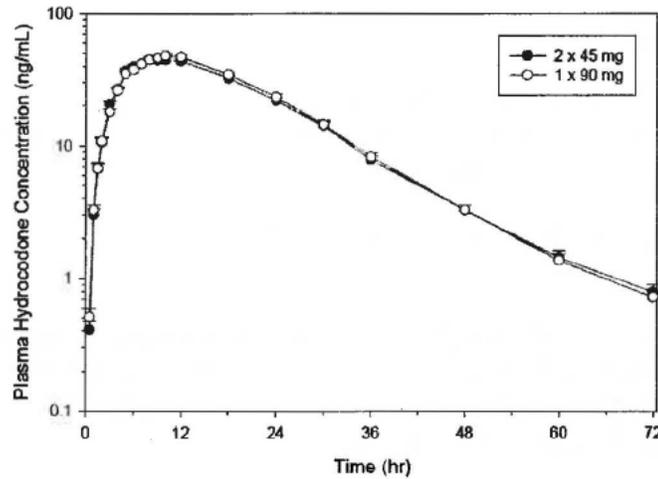
NOTE: Values for C_{max}, AUC_{0-∞}, and AUC_{0-t} are geometric mean (standard error of the mean).

CI=Confidence Interval; C_{max}=maximum observed plasma drug concentration; AUC_{0-∞}=area under the plasma concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration.

BE Study 1099

After a change in manufacturing facility (EP to SLC) as well as a modification in the ^{(b) (4)} for the 90 mg tablet ^{(b) (4)} a bioequivalence study was undertaken to assess the bioequivalence of two 45 mg hydrocodone ER tablets and one 90 mg hydrocodone ER tablet (Study 1099).

The mean (+SE) plasma concentration-time profiles for two 45 mg hydrocodone ER tablets and one 90 mg hydrocodone ER tablet in Study 1099 is shown in **Biopharm Figure 22**.



Biopharm Figure 22. Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following Administration of a Single 90 mg Dose of Hydrocodone ER Administered as Two 45 mg Tablets and as One 90 mg Tablet in Healthy Subjects in Study 1099

The bioequivalence assessment of one 90 mg hydrocodone ER tablet and two 45 mg hydrocodone ER tablets assessed in Study 1099 is presented in Biopharm Table 22 (Applicant Analysis).

Biopharm Table 22. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 90 mg Dose of Hydrocodone ER Administered as Two 45 mg Tablets Versus One 90 mg Tablet in Healthy Subjects in Study 1099 (Applicant’s analysis)

Parameter (unit)	Two 45 mg Hydrocodone ER Tablets (N=42)	One 90 mg Hydrocodone ER Tablet (N=42)	Ratio of One 90 mg Hydrocodone ER Tablet: Two 45 mg Hydrocodone ER Tablets	90% CI
C _{max} (ng/mL)	47.93 (2.06)	50.68 (1.84)	1.0559	0.9918, 1.1241
AUC _{0-∞} (ng·h/mL)	1044 (45)	1079 (45)	1.0317	0.9805, 1.0856
AUC ₀₋₇₂ (ng·h/mL)	1030 (44)	1068 (44)	1.0352	0.9840, 1.0891

Reviewer's assessment:

The reviewer's BE analysis confirmed the Applicant's results, which demonstrated that 60mg tablet was bioequivalent to two 30 mg tablets and that 90mg tablet is bioequivalent to two 45 mg tablets.

The reviewer's BE analysis results for study 1106 and study 1099 are shown in the following tables.

Biopharm Table 23. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following a Single 60 mg Dose of Hydrocodone ER Administered as Two 30 mg Tablets Versus One 60 mg Tablet in Healthy Subjects in Study 1106 (Reviewer's analysis using Phoenix 6.4)

Parameter (unit)	Two 30 mg Hydrocodone ER tablets (N=46)	One 60 mg Hydrocodone ER tablet	Ratio of One 60 mg Tablet: Two 30 mg Tablets	90% CI
C _{max} (ng/mL)	37.60	43.2	1.1488	1.0932, 1.2072
AUC _{0-∞} (ng·h/mL)	766.5	799.6	1.0431	1.000, 1.0881
AUC ₀₋₇₂ (ng·h/mL)	758.2	793.0	1.0459	1.0028, 1.0908

Note: Values for C_{max}, AUC_{0-∞}, and AUC_{0-t} are geometric mean.

Biopharm Table 24. Comparison of Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 90 mg Dose of Hydrocodone ER Administered as Two 45 mg Tablets Versus One 90 mg Tablet in Healthy Subjects in Study 1099 (Reviewer's analysis using Phoenix 6.4)

Parameter (unit)	Two 45 mg Hydrocodone ER Tablets (N=42)	One 90 mg Hydrocodone ER Tablet (N=42)	Ratio of One 90 mg Hydrocodone ER Tablet: Two 45 mg Hydrocodone ER Tablets	90% CI
C _{max} (ng/mL)	46.9	50.1	1.0682	1.0021, 1.1387
AUC _{0-∞} (ng·h/mL)	1006	1044.2	1.0375	0.9852, 1.0926
AUC ₀₋₇₂ (ng·h/mL)	992.5	1052.0	1.0600	0.9954, 1.1287

Note: Values for C_{max}, AUC_{0-∞}, and AUC_{0-t} are geometric mean.

34C ER DESIGNATION CLAIM

34C.1 If it is a modified release (MR) oral formulation, how has the MR claim been established?

The applicant assessed the relative bioavailability of hydrocodone following administration of hydrocodone ER and immediate-release hydrocodone component of VICOPROFEN (NDA 020716) as reference product. The relative bioavailability of hydrocodone ER to the reference listed drug, VICOPROFEN, has been assessed in two studies. In one study, a 15 mg dose of hydrocodone ER was assessed (Study 1079). In the other study, a 90 mg dose of hydrocodone ER was assessed (Study 1090). Given the demonstrated proportionality of hydrocodone ER over the dose range of 15 through 90 mg, data following administration of a 90 mg dose of hydrocodone ER were normalized to 15 mg for the purpose of this characterization.

The Study 1090 results demonstrated that $AUC_{0-\infty}$ was comparable following administration of an equal dose of hydrocodone within hydrocodone ER and VICOPROFEN. The comparisons of mean pharmacokinetic parameter values following administration of hydrocodone ER (dose normalized to 15 mg) and a 15 mg dose of hydrocodone within VICOPROFEN are presented in the following table. The overall systemic exposure ($AUC_{0-\infty}$) was generally similar following administration of the hydrocodone ER and VICOPROFEN. Dose normalized C_{max} was higher (approximately 3-fold) following administration of an equal dose of VICOPROFEN as compared to hydrocodone ER, as would be expected for an IR product.

Biopharm Table 25. Comparison of Mean Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER (Dose Normalized to 15 mg) and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Healthy Subjects (Pharmacokinetic Analysis Set, Bioavailability Subset, Study 1090).

Parameter (unit)	VICOPROFEN (N=60)	Hydrocodone ER (N=60)	Ratio of Hydrocodone ER:VICOPROFEN	90% CI
C_{max} (ng/mL)	34.0 (8.33)	10.8 (2.72)	0.319	0.297, 0.342
$AUC_{0-\infty}$ (ng·h/mL)	227 (53.45)	190.8 (48.11)	0.840	0.783, 0.902

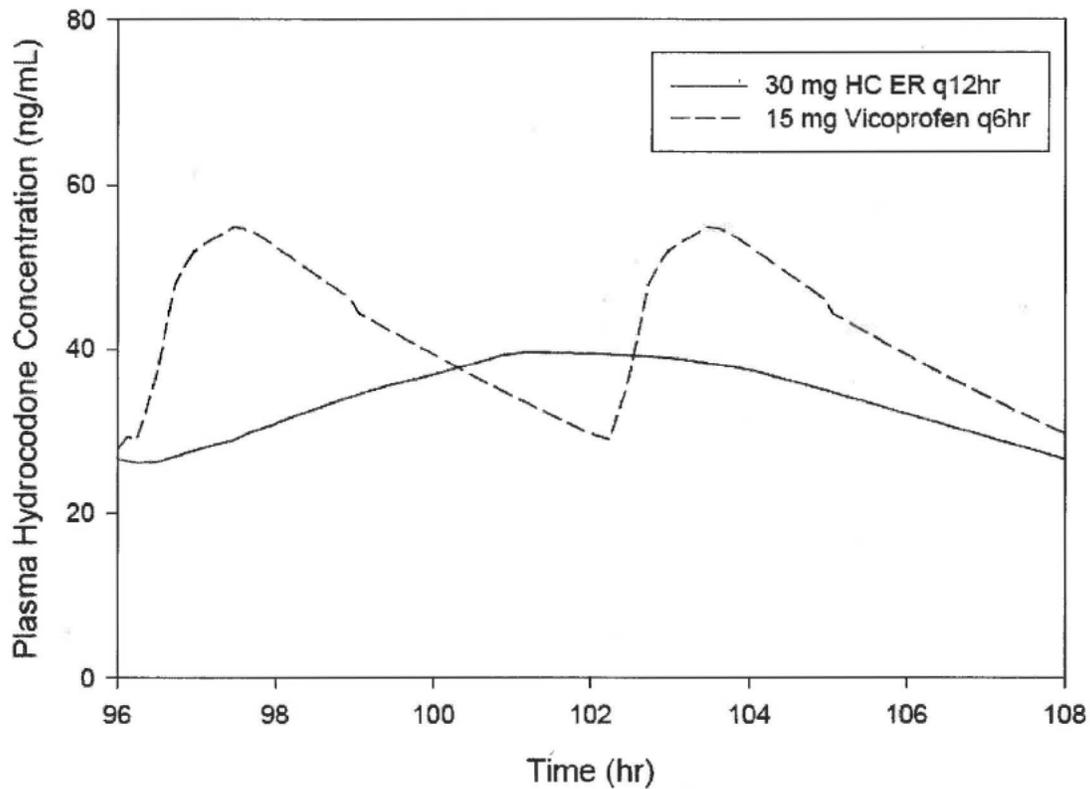
SOURCE: Pharmacokinetic Analysis, Bioavailability Subset, Summary 11.1

NOTE: Values for C_{max} and $AUC_{0-\infty}$ are geometric mean (standard error of the mean).

CI=Confidence Interval; C_{max} =maximum observed plasma drug; $AUC_{0-\infty}$ =area under the plasma drug concentration versus time curve (AUC) from time zero to infinity.

Simulated steady state profiles of hydrocodone ER and VICOPROFEN indicated that systemic exposure to hydrocodone following administration of hydrocodone ER is

expected to be within the range of simulated steady state exposures following administration of VICOPROFEN every 6 hours (**Biopharm Figure 23**).



SOURCE: Ad hoc Summary 3-1079
HC ER=Hydrocodone ER

Biopharm Figure 23. Simulated Mean Plasma Concentration versus Time Profiles for Hydrocodone at Steady State Following Administration of a 30 mg Dose of Hydrocodone ER Every 12 Hours and a 15 mg Dose of Hydrocodone within VICOPROFEN Every 6 Hours in Healthy Subjects

Reviewer's Assessment

The submitted data SUPPORT the ER designation claim because of the following reasons:

1. Hydrocodone ER Tablets has a less dosing frequency (twice daily, once every 12 hours) compared to a currently marketed non-controlled release drug product, VICOPROFEN (once every 6 hours).

2. As shown in **Figure 23** for the drug product's steady-state performance, the fluctuation index is less than currently marketed non-controlled release product, VICOPROFEN, which is supported by the following evidence.

In the responses to the IR dated Sep 9, 2015, the Applicant submitted input and output data for steady state simulation in Figure 23, this reviewer confirmed the Applicant's the steady state simulation using nonparametric superposition function in Phoenix 6.4. In the steady state simulation, the Test Product (hydrocodone ER tablets) was modeled to have a dosing regimen of twice a day (q12 hr) for 5 days (15 mg hydrocodone per dose) and the Reference Product was modeled to have a dosing regimen of four times (q 6 hr) a day for 5 days (15 mg hydrocodone per dose). The fluctuation index was then estimated using a non-compartmental approach (Biopharm Table 26).

Biopharm Table 26 : Percent Fluctuation of hydrocodone for Test and Reference Products at Steady State

	Test Product (Hydrocodone ER tablet)	Reference Product (VICOPROFEN)
Fluctuation (%)	39.2	65.2

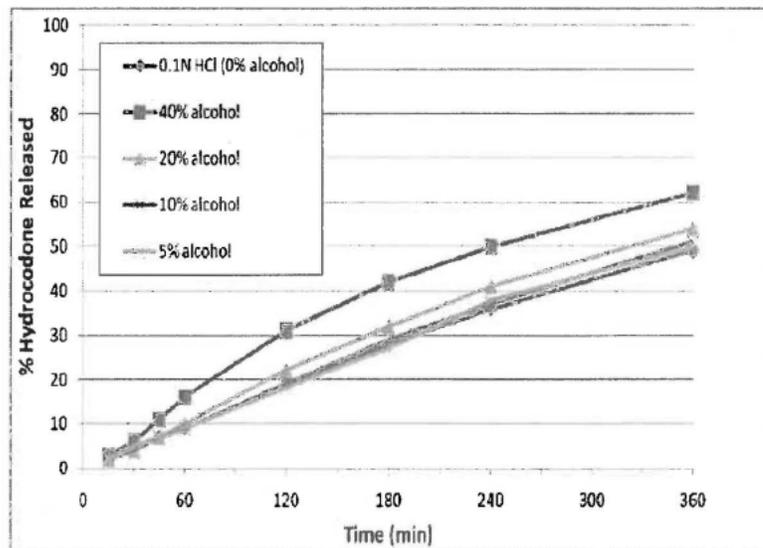
3. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units, Standard Error for Cmax and AUC0-∞ for Hydrocodone ER is all less than that for the currently marketed IR formulation, VICOPROFEN (**Biopharm Table 25**).

Therefore, based on the provided data in the submission, the ER claim is **ADEQUATE**.

34D ALCOHOL DOSE DUMPING

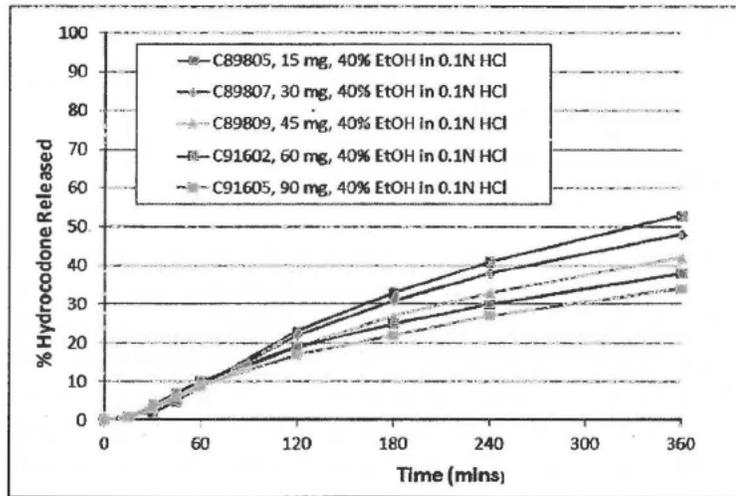
34D.1 If it is a modified release (MR) oral formulation, has an in-vitro alcohol dose dumping study submitted?

The potential for dose dumping was evaluated in in vitro settings using ethanolic media at different concentrations (0%, 5%, 10%, 20% and 40%). **Biopharm Figure 24** shows the in vitro alcohol interaction profile at five alcohol concentrations (0, 5, 10, 20 and 40%) for phase 3 EP pilot scale Hydrocodone Bitartrate Extended Release Tablets (15 mg).



Biopharm Figure 24. In Vitro Alcohol Interaction Profile at Five Alcohol Concentrations (0, 5, 10, 20 and 40%) for Phase 3 EP Pilot Scale Hydrocodone Bitartrate Extended Release Tablets (15 mg lot C62020)

F2 comparisons were made between the dissolution profiles obtained in 0.1 N HCl with 0% ethanol and in 0.1 N HCl with 40% ethanol for all the strengths (15 mg, 30 mg, 45 mg, 60 mg and 90 mg), the results are shown in **Biopharm Table 25** (3.2.p.2 pharmaceutical development [\cdsesub1\evsprod\nda207975\0000\m3\32-body-data\32p-drug-prod\c33237-ext-release-tablets\32p2-pharm-dev\pharm-devel.pdf](#)). According to the Applicant, the data indicate that the intact CEP-33237 tablets do not dump their dose of hydrocodone bitartrate in the presence of up to 40% ethanol for 45, 60 and 90 mg strengths. In two cases (15 mg and 30 mg strengths) the f2 values are just below 50, indicating that the profiles may be statistically different. The data also indicate that the impact of ethanol on the drug release profile decreases as the drug loading increases. The f2 values increase monotonically from 41–44 for 15 mg tablets, to 47 for 30 mg tablets, to 55–57 for 45 mg tablets. Also, the impact of ethanol on the drug release profile decreases as the tablet size increases. These trends result in the higher strengths being less affected by the presence of alcohol than the lower strengths. The same trend can be seen from **Biopharm Figure 25** showing that 15 mg strength exhibited a faster drug release profile in the 40% ethanol medium than any of the higher dose strengths. Therefore, 15 mg tablet has the greatest susceptibility to the 40% alcohol dose dumping. Thus the sponsor performed in vivo PK study (**study 1076**) to further test if there is alcohol dose dumping in vivo.



NOTE: Batch C89805 (15 mg), batch C89807 (30 mg), and batch C89809 (45 mg) are the to-be-marketed formulations, with (b) (4) Batch C91602 (60 mg) and batch C91605 (90 mg) are the to-be marked formulations, with (b) (4)

Biopharm Figure 25. 40% Ethanol Dissolution Profiles for Five Strengths of Hydrocodone ER Tablets

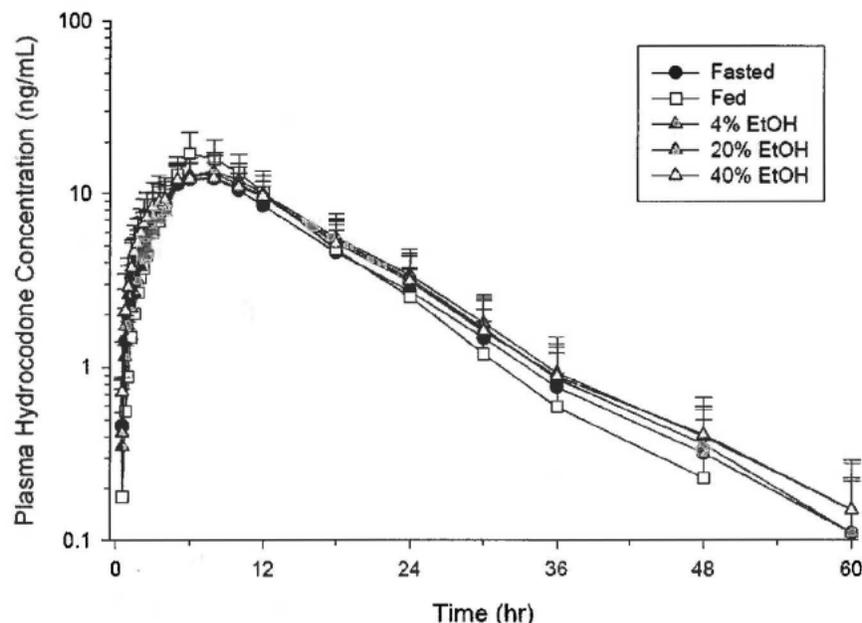
Biopharm Table 27. F2 Values for In Vitro Alcohol Interaction Studies

Lot	Strength (mg)	F2 values at 6 hour dissolution time point ¹
C89804	15	43.5
C89805	15	40.9
C89806	30	47.0
C89807	30	46.7
C89808	45	56.7
C89809	45	55.3
C91602	60	56.2
C91603	60	55.9
C91604	90	63.6
C91605	90	63.3
C93275	15	41.9

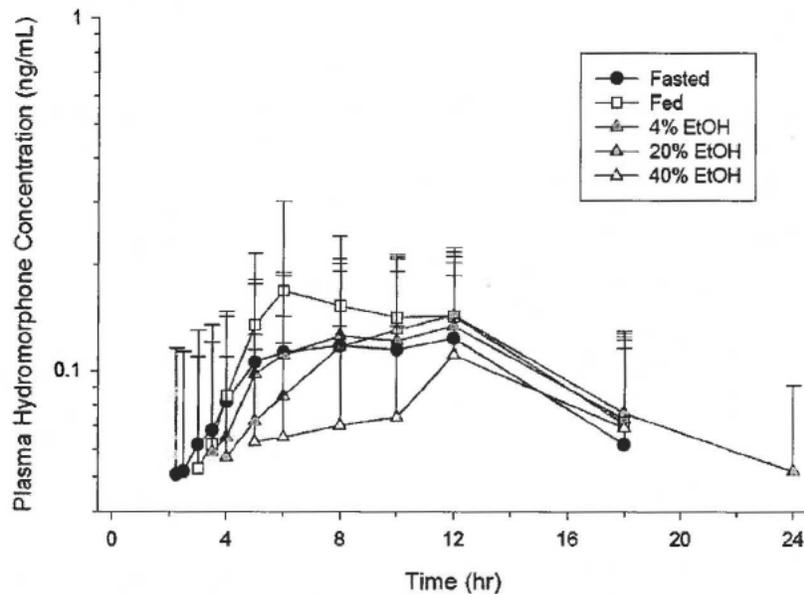
¹ F2 values based on four time points (1, 2, 4 and 6 hours)

For the strength 15 mg and 30 mg, f_2 values are lower than 50 reflecting that the dissolution profiles were statistically different under alcohol condition vs normal condition. As stated by the applicant, for 15 mg strength tablet, in 0.1 N HCl (0% ethanol), average dissolution ranged from (b) (4)% at 1 hour, (b) (4)% at 2 hours, (b) (4)% at 4 hours, and (b) (4)% at 6 hours. In 40% alcohol in 0.1 N HCl, average dissolution was 9% at 1 hour, 23% at 2 hours, ranged from 41-42% at 4 hours, and from 53-55% at 6 hours. Drug release in alcohol was more rapid than that seen under normal conditions with roughly 10% of the drug released during the first hour in the presence of alcohol. Similarly, for 30 mg tablets, in 0.1 N HCl (0% ethanol), average dissolution was (b) (4)% at 1 hour, (b) (4)% at 2 hours, (b) (4)% at 4 hours, and (b) (4)% at 6 hours. In 40% alcohol in 0.1 N HCl, average dissolution at 1 hour ranged from 9-10%, from 22-23% at 2 hours, 38% at 4 hours, and from 48-49% at 6 hours. Roughly 10% of the drug released during the first hour in the presence of alcohol. The data also indicate that the impact of ethanol on the drug release profile decreases as the drug loading increases.

For further assessing the alcohol dose dumping potential, (in vivo) PK study 1076 was conducted to characterize the effect of alcohol on the pharmacokinetic and safety profiles of a 15-mg dose of a hydrocodone bitartrate ER prototype (b) (4) when administered to naltrexone-blocked healthy volunteers. There did not appear to be a substantive effect of alcohol on the systemic exposure to hydrocodone and hydromorphone from the tested extended-release formulation (Figure 26 and Figure 27).



Biopharm Figure 26. Mean (+ SD) Plasma Concentration-versus-Time Profiles for Hydrocodone in Healthy Volunteers Administered Single Doses of 15-mg Hydrocodone ER Tablets under Fasted or Fed Conditions or with Ethanol



Biopharm Figure 27: Mean (+ SD) Plasma Concentration-versus-Time Profiles for Hydromorphone, an Active Metabolite in Healthy Volunteers Administered Single Doses of 15-mg Hydrocodone ER Tablets under Fasted or Fed Conditions or with Ethanol

Reviewer's Assessment:

Based on the in vitro study, there was a potential of dose dumping in the presence of alcohol for the 15 mg and 30 mg tablets based on f2 test. However, the in vivo PK study (study 1076) showed no substantive effect of alcohol on the systemic exposure to hydrocodone and hydromorphone from the tested extended-release formulation (15 mg tablet). OCP has evaluated the in vivo alcohol interaction study and agrees that there is no dose dumping with 15 mg tablet at the presence of alcohol.

34E ABUSE DETERRENT PROPERTY OF THE PRODUCT

34E.1. Does the product have a drug abuse deterrent properties? If Yes, what supporting dissolution data are provided?

The simulated oral tampering (SOT) in vitro test was designed to mimic mechanical manipulation of the tablet, such as crushing, grinding, or chewing, before oral ingestion. For this test, a tool that roughly mimicked crushing, grinding, or chewing was used to mechanically comminute the tablet to a powder. The resulting powder was transferred to a dissolution vessel for in vitro drug release. The in vitro release profile of the crushed tablet samples was obtained in 500 mL (15, 30, 45 mg strengths) or 900 mL (60, 90 mg strengths) of 0.1 N HCl dissolution medium. The samples were agitated at 50 rpm with USP apparatus 2 (paddles) at 37°C. Vicoprofen and ZOXYDRO (n = 6 replicates)

comparator data were generated for the comminution tools. The results are shown in the following table.

Biopharm Table 28. Summary of Simulated Oral Ingestion Results (Experiments Conducted in 500 mL of 0.1 N HCl at 37°C using USP Apparatus 2 at 50 rpm): Ranges of % Hydrocodone Bitartrate Released

Simulated Oral Ingestion Studies		% Hydrocodone Bitartrate Released ^a				
Manipulation Tool	Test Article: Strength (coated intermediate)	15min	30min	60 min	120min	360min
None (intact)	CEP-33237: 15 mg (37.5%)	NA	NA	4-6	10-15	32-50
	CEP-33237: 90 mg (40%)					
Pill Splitter	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	1-2	2-4	5-8	12-19	38-61
	CEP-33237: 60, 90 mg (40%)					
Rotary Abrasion Tool	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	38-59	51-65	64-74	<u>75-80</u>	85-88
	CEP-33237: 15 mg, 30 mg, 45 mg (40%) ^b	32-61	44-68	56-75	66-81	78-86
	CEP-33237: 60, 90 mg (40%)	18-25	27-34	39-48	55-65	77-83
Hammer	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	16-18	24-28	41-45	63-65	83-86
	CEP-33237: 60, 90 mg (40%)	7-9	15-18	29-34	47-53	72-76
Mortar & Pestle	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	11-23	19-34	34-50	57-66	78-81
	CEP-33237: 15 mg, 30 mg, 45 mg (40%) ^b	9-28	18-42	31-56	47-69	69-82
	CEP-33237: 60, 90 mg (40%)	6-10	14-20	28-37	48-54	74-75
Silent Knight	CEP-33237: 15 mg (37.5)	22	35	53	72	89
	CEP-33237: 15 mg, 30 mg, 45 mg (40%) ^c	5-22	11-31	21-45	36-60	65-79
	CEP-33237: 60, 90 mg (40%)	7	17	33-34	54-56	80-82
Coffee Mill	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	13-19	22-30	38-46	58-65	82-83
	CEP-33237: 15 mg, 30 mg, 45 mg (40%) ^b	4-8	9-15	19-26	35-40	61-64
	CEP-33237: 60, 90 mg (40%)	4-7	9-15	20-29	38-48	69-72
Coffee Mill (-20°C tablets)	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	12-18	20-28	37-43	57-61	81-82
	CEP-33237: 60, 90 mg (40%)	3-8	8-16	18-30	36-48	67-73

Coffee Mill (150°C tablets)	CEP-33237: 15 mg, 30 mg, 45 mg (37.5%)	19-26	29-36	44-49	57-63	68-71
	CEP-33237: 60, 90 mg (40%)	21-27	35-41	53-57	67-71	75-79
Hammer, Mortar/Pestle, Coffee Mill, Silent Knight	ZOHYDRO: 50 mg	<u>71-97</u>	76-97	79-98	84-99	93-100
All tools	Vicoprofen: two 7.5 mg tablets	<u>92-101</u>	93-101	94-102	NA	NA
None	Hydrocodone Bitartrate drug substance: 15 mg, 45 mg, 90 mg	101-102	101-102	101-102	NA	NA

Six manipulation tools were employed to study all five strengths of CEP-33237 tablets under simulated ingestion conditions. None of the tools rendered the manipulated tablet into an immediate release dosage form. In general, the tablets exhibited increased resistance to extraction as the dose strength increased. The rotary abrasion tool inflicted the most damage to the release mechanism of CEP-33237 tablets, generating drug release values higher than any of the other tools, reflecting its different comminution mechanism. Using the rotary abrasion tool, the % drug released reached 80% in two hours for the 15 and 30 mg strengths and reached 77-88% after six hours (all strengths). Silent Knight and coffee mill exhibit release rates similar to each other and slower than the rotary tool. The comparator Vicoprofen generated 90-100% drug release within 15 minutes, as expected for an immediate release dosage form. The comparator ZOHYDRO ER behaved as an immediate release dosage form upon manipulation with all tools, generating 71% - 97% drug release within 15 minutes.

In addition, according to the particle size distribution results shown in **Biopharm Table 29**, the rotary abrasion tool is the most efficient manipulating method to reduce the particle size during the crushing, thus generating drug release values higher than any of the other tools.

Biopharm Table 29. Summary of Results for Particle Size Distribution

Tool	Test Article: Strength (coated intermediate)	Amount per Sieve Fraction (w/w%)						
		> 850 µm	600-850 µm	425-600 µm	300-425 µm	180-300 µm	106-180 µm	< 106 µm
Hammer	CEP-33237: 15 mg (37.5)	3.9	4.6	8.3	9.2	10.8	17.1	46.1
	CEP-33237: 30 mg (37.5)	1.9	6.4	12.5	12.0	10.5	11.9	44.8
	CEP-33237: 45 mg (37.5)	1.2	8.6	17.3	15.3	10.7	7.9	39.1
	CEP-33237: 60 mg (40)	1.4	7.8	14.9	13.2	8.2	9.2	45.3
	CEP-33237: 90 mg (40)	1.6	9.8	18.3	17.3	10.1	6.6	36.4
	ZOHYDRO ER: 50 mg	4.2	13.8	7.5	11.4	14.4	15.1	33.6
Mortar & Pestle	CEP-33237: 15 mg (37.5)	2.0	4.9	10.1	12.5	14.8	14.7	41.1
	CEP-33237: 30 mg (37.5)	1.3	6.6	15.7	17.6	16.4	13.2	29.2
	CEP-33237: 45 mg (37.5)	1.5	9.2	19.1	18.2	14.8	11.2	26.1
	CEP-33237: 60 mg (40)	1.1	7.1	17.2	17.9	13.1	11.8	31.7
	CEP-33237: 90 mg (40)	0.9	9.7	20.8	20.1	13.1	10.5	24.8
	ZOHYDRO ER: 50 mg	0.3	1.6	2.1	11.4	21.0	22.7	40.9
Coffee Mill	CEP-33237: 15 mg (37.5)	1.6	5.4	13.1	13.3	13.4	13.0	40.2
	CEP-33237: 30 mg (37.5)	1.8	7.5	17.3	16.6	15.0	12.2	29.5
	CEP-33237: 45 mg (37.5)	1.0	7.7	19.9	18.8	15.8	10.9	25.9
	CEP-33237: 60 mg (40)	3.4	10.5	17.7	15.9	12.2	11.2	29.2
	CEP-33237: 90 mg (40)	1.2	11.0	19.6	18.2	13.2	10.9	25.9
	ZOHYDRO ER: 50 mg	0.0	0.1	1.7	12.6	26.1	26.1	33.3
Coffee Mill (-20°C)	CEP-33237: 15, 30, 45 mg (37.5) CEP-33237: 60, 90 mg (40)	0.8-3.2	6.1-10.1	13.4-19.5	13.2-19.0	11.9-16.0	10.9-13.3	26.4-38.4
Coffee Mill (150°C)	CEP-33237: 15, 30, 45 mg (37.5) CEP-33237: 60, 90 mg (40)	3.4-6.1	10.1-16.0	16.2-20.5	13.7-16.0	9.5-13.8	10.0-13.5	22.3-29.0

Tool	Test Article: Strength (coated intermediate)	Amount per Sieve Fraction (w/w%)						
		> 850 µm	600-850 µm	425-600 µm	300-425 µm	180-300 µm	106-180 µm	< 106 µm
Silent Knight	CEP-33237: 15 mg (37.5)	27.1	7.8	9.7	8.2	7.7	9.7	29.8
	CEP-33237: 15 mg (40) ^a	13.1	14.2	12.1	9.9	10.5	11.8	28.3
	CEP-33237: 15 mg (40) ^b	15.7	14.0	13.3	10.7	11.3	11.3	23.7
	CEP-33237: 30 mg (40) ^b	4.1	12.1	18.5	15.8	13.4	9.7	26.5
	CEP-33237: 45 mg (40) ^c	6.0	16.4	17.0	13.7	11.9	6.8	28.4
	CEP-33237: 45 mg (40) ^b	2.3	11.2	22.5	18.4	13.9	7.7	23.9
	CEP-33237: 45 mg (40) ^b	3.6	10.5	23.7	19.4	13.2	6.1	23.6
	CEP-33237: 60 mg (40) ^b	23.0	13.3	16.1	11.7	8.0	7.5	20.4
	CEP-33237: 90 mg (40) ^b	6.3	14.1	21.8	16.7	11.3	6.0	23.8
	ZOHYDRO ER: 50 mg	1.6	53.8	11.6	6.7	8.1	8.7	9.4
Rotary Abrasion Tool	CEP-33237: 15 mg (37.5)	6.3	3.3	5.0	5.1	6.2	12.3	61.7
	CEP-33237: 30 mg (37.5)	7.9	5.6	7.3	6.7	7.5	10.9	54.1
	CEP-33237: 45 mg (37.5)	10.7	7.1	8.8	8.7	9.0	10.7	45.0
	CEP-33237: 60 mg (40)	5.1	3.8	5.2	6.0	8.1	15.8	55.9
	CEP-33237: 90 mg (40)	5.3	6.0	8.5	10.2	11.0	14.1	45.0

Reviewer's Assessment:

As demonstrated by the studies described above, CEP-33237 tablets present a barrier to manipulation for drug abuse compared with the reference product, ZOHYDRO® ER (Zogenix) and IR product Vicoprofen. Extended-release properties were retained to a significant degree when the tablets were physically manipulated with a variety of tools

and subjected to simulated oral ingestion and simulated nasal extractions.

Using Rotary Abrasion Tool, the most efficient particle size reducing method, Hydrocodone Bitartrate Tablets release 56-75% and 66-81% respectively at 1 hour and 2 hours. However, the comparator Vicoprofen generated 90-100% drug release within 15 minutes, as expected for an immediate release dosage form. Another comparator ZOHYDRO ER behaved as an immediate release dosage form upon manipulation with all tools, generating 71%- 97% drug release within 15 minutes.

The CEP-33237 tablet has certain degree of abuse deterrent properties compared to ZOHYDRO® ER (Zogenix) and IR product Vicoprofen.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACUETICS**

Reviewer's Assessment and Signature:

1. The data submitted support the proposed dissolution method and dissolution acceptance criteria (shown in the following tables), which are ADEQUATE.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	50 rpm	500 mL for the 15, 30 and 45 mg strengths and 900 mL for 60 and 90 mg strengths	37°C	0.1N HCl

Time (h)	Acceptance Range (% Hydrocodone Bitartrate Released)				
	15 mg	30 mg	45 mg	60 mg	90 mg
2	(b) (4)				
8					
24					



QUALITY REVIEW



2. The proposed IVIVC did not pass the internal and external validations and therefore is not acceptable. However, a rank order exists between the fraction of the in vitro released and the fraction of the in vivo absorbed, which may be used for justification under appropriate circumstances.
3. The BE bridging analyses shown in Biopharm Figure 18 were confirmed by the reviewer. The to-be-marketed formulations are adequately linked to those used in the pivotal clinical studies. The higher strengths are adequately bridged to the lower strengths by the BE study (60 mg vs 30 mg and 90 mg vs 45 mg).
4. The ER designation claim is ADEQUATE for the proposed products.
5. Although the in vitro dissolution study showed a potential of dose dumping in the presence of alcohol for the 15 mg and 30 mg tablets (15 mg has more potential of dosing dumping compared with 30mg tablet), the in vivo PK study indicated no substantive effect of alcohol on the systemic exposure to hydrocodone and hydromorphone. OCP evaluated the in vivo alcohol interaction study and agrees that there is no dose dumping in the presence of alcohol for the 15 mg tablet.
6. Based on the data provided, the CEP-33237 tablets showed abuse deterrent properties compared to ZOHYDRO® ER (Zogenix) and IR product Vicoprofen.

Fang Wu, Ph.D.
Primary Biopharmaceutics Reviewer
CDER/OPQ/ONDP/Division of Biopharmaceutics
Date: Sep 15, 2015

John Duan, Ph.D.
Secondary Biopharmaceutics Reviewer&Branch Chief (Acting)
CDER/OPQ/ONDP/Division of Biopharmaceutics

cc Sandra Suarez, Paul Seo

Supervisor Comments and Concurrence: Concur. John Z Duan

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207975

Submission Type: NDA 505b(2)

Established/Proper Name:
Vantrela ER - Hydrocodone
Bitartrate Extended-release
Tablet

Applicant: Teva

Letter Date:12/23/2014

Dosage Form: Tablet

Chemical Type: Non-
NME

Stamp Date:12/23/2014

Strength: 15, 30, 45, 60, and 90 mg

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?			CMC: Yes Biopharmaceutics: Yes
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			Biopharmaceutics: There are no potential review issues identified. Refer to page 10 for comments to be conveyed to the Applicant as part of the 74-Day Letter.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	x	
2.	Botanical ¹	<input type="checkbox"/>	x	
3.	Naturally-derived Product	<input type="checkbox"/>	x	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	x	
5.	PET Drug	<input type="checkbox"/>	x	
6.	PEPFAR Drug	<input type="checkbox"/>	x	
7.	Sterile Drug Product	<input type="checkbox"/>	x	
8.	Transdermal ¹	<input type="checkbox"/>	x	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	x	
10.	Locally acting drug ¹	<input type="checkbox"/>	x	
11.	Lyophilized product ¹	<input type="checkbox"/>	x	
12.	First generic ¹	<input type="checkbox"/>	x	
13.	Solid dispersion product ¹	<input type="checkbox"/>	x	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	x	
15.	Modified release product ¹	x	<input type="checkbox"/>	Extended release product with potential abuse deterrent properties

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FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
16.	Liposome product ¹	<input type="checkbox"/>	x	
17.	Biosimilar product ¹	<input type="checkbox"/>	x	
18.	Combination Product	<input type="checkbox"/>	x	
19.	Other	<input type="checkbox"/>	x	

Regulatory Considerations					
20.	USAN Name Assigned		x	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements		x	<input type="checkbox"/>	
22.	SPOTS (Special Products On-line Tracking System)		<input type="checkbox"/>	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		<input type="checkbox"/>	x	
24.	Comparability Protocol(s) ²		x	<input type="checkbox"/>	
25.	Other		<input type="checkbox"/>	x	
Quality Considerations					
26.	Drug Substance Overage		<input type="checkbox"/>	x	
27.	Design Space	Formulation	<input type="checkbox"/>	x	
28.		Process	<input type="checkbox"/>	x	
29.		Analytical Methods	<input type="checkbox"/>	x	
30.		Other	<input type="checkbox"/>	x	
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	x	
33.	Alternative Microbiological Test Methods		<input type="checkbox"/>	x	
34.	Process Analytical Technology ¹		<input type="checkbox"/>	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	x	
36.		Excipients	<input type="checkbox"/>	x	
37.		Microbial	<input type="checkbox"/>	x	
38.	Unique analytical methodology ¹		<input type="checkbox"/>	x	
39.	Excipients of Human or Animal Origin		x	<input type="checkbox"/>	Lactose monohydrate NF (b) (4)
40.	Novel Excipients		<input type="checkbox"/>	x	
41.	Nanomaterials ¹		<input type="checkbox"/>	x	
42.	Hold Times Exceeding 30 Days		<input type="checkbox"/>	x	
43.	Genotoxic Impurities or Structural Alerts		x	<input type="checkbox"/>	(b) (4) is a degradant
44.	Continuous Manufacturing		<input type="checkbox"/>	x	
45.	Other unique manufacturing process ¹		<input type="checkbox"/>	x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹		<input type="checkbox"/>	x	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹		<input type="checkbox"/>	x	
50.	Other		<input type="checkbox"/>	x	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	x	<input type="checkbox"/>	<input type="checkbox"/>	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? 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? For each site, does the application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)	x	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	x	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 	x	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the 	x	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<p style="margin-left: 20px;">manufacturing process from material used in clinical to commercial production lots</p> <ul style="list-style-type: none"> ○ Includes complete description of product lots and their uses during development <p><input type="checkbox"/> Manufacture</p> <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <p><input type="checkbox"/> Control of Excipients</p> <p><input type="checkbox"/> Control of Drug Product</p> <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <p><input type="checkbox"/> Reference Standards or Materials</p> <p><input type="checkbox"/> Container Closure System</p> <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <p><input type="checkbox"/> Stability</p> <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <p><input type="checkbox"/> APPENDICES</p> <p><input type="checkbox"/> REGIONAL INFORMATION</p>				
BIOPHARMACEUTICS					
8.	<p>Does the application contain dissolution data?</p> <ul style="list-style-type: none"> • Is the dissolution test part of the DP specifications? • Does the application contain the dissolution method development report including data supporting the discriminating ability? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Yes. Dissolution test is part of the DP specification. The proposed dissolution method is as follows:</p>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS																																																																																																		
					<table border="1" style="width: 100%; border-collapse: collapse; font-size: 8px;"> <tr> <td style="width: 20%;">Instrumentation</td> <td colspan="5">Dissolution system equipped with a temperature controller</td> </tr> <tr> <td>Apparatus</td> <td colspan="5">USP Apparatus 2, paddles</td> </tr> <tr> <td>Paddle Speed</td> <td colspan="5">50 rpm</td> </tr> <tr> <td>Medium</td> <td colspan="5">0.1 N hydrochloric acid</td> </tr> <tr> <td rowspan="2">Median Volume</td> <td colspan="5">500 mL (35, 50, 45 mg strengths)</td> </tr> <tr> <td colspan="5">500 mL (60 and 90 mg strengths)</td> </tr> <tr> <td>Median Temperature</td> <td colspan="5">37.0 °C ± 0.5 °C</td> </tr> <tr> <td>Sample Time Points</td> <td colspan="5">2, 8 and 24 hours</td> </tr> <tr> <td rowspan="3">Sample Volume</td> <td colspan="5">5 mL (manual)</td> </tr> <tr> <td colspan="5">8 mL (Waters 269D Transfer Module)</td> </tr> <tr> <td colspan="5">21 mL (Vintan VK 8000 Transfer Module)</td> </tr> <tr> <td colspan="6" style="text-align: center;">Acceptance Range (% Hydrocodone Bitartrate Released)</td> </tr> <tr> <td style="text-align: center;">Time (h)</td> <td style="text-align: center;">15 mg</td> <td style="text-align: center;">30 mg</td> <td style="text-align: center;">45 mg</td> <td style="text-align: center;">60 mg</td> <td style="text-align: center;">90 mg</td> </tr> <tr> <td style="text-align: center;">2</td> <td colspan="4" style="background-color: #cccccc;"></td> <td style="text-align: center;">(b) (4)</td> </tr> <tr> <td style="text-align: center;">8</td> <td colspan="4" style="background-color: #cccccc;"></td> <td></td> </tr> <tr> <td style="text-align: center;">24</td> <td colspan="4" style="background-color: #cccccc;"></td> <td></td> </tr> </table> <p>Yes, the Dissolution Method contains data supporting the discriminating ability.</p>	Instrumentation	Dissolution system equipped with a temperature controller					Apparatus	USP Apparatus 2, paddles					Paddle Speed	50 rpm					Medium	0.1 N hydrochloric acid					Median Volume	500 mL (35, 50, 45 mg strengths)					500 mL (60 and 90 mg strengths)					Median Temperature	37.0 °C ± 0.5 °C					Sample Time Points	2, 8 and 24 hours					Sample Volume	5 mL (manual)					8 mL (Waters 269D Transfer Module)					21 mL (Vintan VK 8000 Transfer Module)					Acceptance Range (% Hydrocodone Bitartrate Released)						Time (h)	15 mg	30 mg	45 mg	60 mg	90 mg	2					(b) (4)	8						24					
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24																																																																																																		
9.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>The application contains five phase 1 BE studies. These studies will be reviewed by division of biopharmaceutics.</p> <p>The PK files are not in the format for ease of use, a request will be made to provide SAS transport files for the 5 BE studies.</p> <p>Inspection may be necessary for some of these phase 1 studies bridging the clinical batch to the TBM formulation.</p>																																																																																													
10.	<p>Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Several BE studies were conducted to bridge across the phases of drug product development. Five of these studies are considered relevant and will be reviewed by Biopharmaceutics.</p> <p>It is noted that BE study 1090 was not conducted with the final formulation. Additional internal bridging analysis will be needed to assess the clinical relevance of its modification.</p>																																																																																													
11.	<p>Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																																																																																														
12.	<p>For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Refer to \\cdsesub1\evsprod\NDA207975\0001\m2\27-clin-sum</p>																																																																																													
13.	<p>For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																																																																														

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C. FILING CONSIDERATIONS					
14.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
15.	Does the application include in vitro in vivo correlation? If yes, is there sufficient data to support the model?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Refer to ICON Report IVIVC-652004
REGIONAL INFORMATION AND APPENDICES					
16.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	x	<input type="checkbox"/>	
17.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	<input type="checkbox"/>	<input type="checkbox"/>	
18.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<input type="checkbox"/>	<input type="checkbox"/>	x	
19.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			x	

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Risk Assessment

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	3	2	Release (1) Stability (3)	Release (6) Stability (18) (low)	The drug product has a 3 year proposed shelf life at 25 °C. Impurity trend for degradant (b) (4) 2 analytical methods are used to determine (b) (4) (significant difference in results)
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	2	4	24 (low)	Hydrocodone Bitartrate is stable at 25 °C for 3 years.
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	2	4	16 (low)	(b) (4) % API load
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	1	2	3	(low)	(b) (4)
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • 	4	4	4	64 (high)	Alcohol dose dumping - opioid

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	Scale/equipments • Site • Exclude major reformulations • Alcohol dose dumping					
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CMC Assessment

Vantrela ER is an extended-release hydrocodone bitartrate, abuse-deterrent, oral tablet in 15, 30, 45, 60, and 90 mg strengths. The product is to be indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Review Issues Identified:

No review issues have been identified at this time.

CMC has no comments for 74-Day Letter

BIOPHARMACEUTICS ASSESSMENT

SUMMARY OF BIOPHARMACEUTICS FINDINGS

Submission:

The biopharmaceutics review portion of this NDA consists of 5 phase 1 bioequivalence studies, an IVIVC, in vitro alcohol dose-dumping, and *in vitro* release profiles of the drug product.

Review Issues Identified:

No review issues have been identified at this time.

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Biopharmaceutics Comments for 74-Day Letter:

1. Provide SAS transport files of the pharmacokinetics parameters for the bioequivalence studies, , 1097, 1098, 1099, 1104, and 1106 in the following column format:

SUBJ SEQ PER TRT C1 C2 C3...Cn KE_FIRST KE_LAST T1 T2 T3...Tn

where KE_FIRST and KE_LAST are the first and last time points, respectively, used to estimate the elimination constant (Kel) for each subject/period. Also submit the pharmacokinetic dataset in the following format:

SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf

2. Submit the WinNonlin project report generated in the construction and validation of the IVIVC.
3. We acknowledge the data submitted to determine the impact of several particle size reduction (PSR) techniques on the release of your proposed product. It is also noted that the proposed QC method was used to assess the percent release over time. Provide data justifying the suitability of the dissolution method used for assessing the dissolution rate of the “pulverized” drug product. Specifically, provide data demonstrating that the in vitro release results submitted are not confined by the use of an inappropriate dissolution technique.

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Noory, PhD.**

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Assadollah Noory, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Products

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