CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208085Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 208085
Review #2

Drug Name/Dosage Form	Hydrocodone bitartrate/guaifenesin tablets
Strength	5 mg hydrocodone bitartrate/400 mg guaifenesin/tablet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ECI Pharmaceuticals, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original (rev. 1)	13-APR-2016	
Amendment (rev. 1)	09-MAY-2016	Facilities
Amendment (rev. 1)	19-AUG-2016	Drug substance, drug product, process
Amendment (rev. 1)	27-SEP-2016	Process and drug substance
Amendment (rev. 1)	28-SEP-2016	Biopharmaceutics
Amendment (rev. 1)	13-OCT-2016	Biopharmaceutics
Amendment (rev. 1)	27-OCT-2016	Process and drug substance
Amendment (rev. 1)	01-NOV-2016	Drug product
Amendment (rev. 1)	28-NOV-2016	Biopharmaceutics
Amendment (rev. 1)	14-DEC-2016	Drug product
Amendment (rev. 1)	19-DEC-2016	Drug product
Amendment (rev. 1)	20-DEC-2016	Process and facilities
Amendment (rev. 1)	09-JAN-2017	Facilities
Amendment (rev. 1)	13-JAN-2017	Facilities
Amendment (rev. 2)	30-OCT-2017	Process and facilities, and drug substance
Amendment (rev. 2)	07-MAR-2018	Facilities

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	II/Division of New Drug API
Drug Product	Chris Hough	IV/DNDPII
Process	Xiaoying Zhang	IV/DPAII
Microbiology	Xiaoying Zhang	IV/DPAII
Facility	Cassandra Abellard	II/DIA
Biopharmaceutics	Angela Lu	II/DB
Regulatory Business Process Manager	Florence Aisida/Steve Kinsley	I/Division I

Application Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)	N/A	
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

. DMFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	02-DEC-2016	
	II			Adequate	11-Aug-2016	
	II			Adequate	30-NOV-2016	
	III			Not reviewed		Drug product reviewer indicates that there is sufficient information in the NDA
	III			Not reviewed		"
	III			Not reviewed		"
	III			Not reviewed		"
	III			Not reviewed		"
	IV			Not reviewed		"

. Other D *plications*

DOCUM	NUMBER	DESCRIPTION
IND	109251	ECI's IND for the hydrocodone/guaifenesin product

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews of the resubmission and recommendations from the drug substance, process, and facilities teams outlined below, an overall recommendation of **Approve** is to be forwarded to the clinical Division (DPARP).

II. Summary of Quality Assessments

A. Product Overview

The oral drug product is proposed for "use in symptomatic relief of cough, to (b) (4) loosen (b) (4) (mucus) (b) (4) The dosage form is an immediate release, white, capsule-shaped tablet, embossed with "ECI" and "601" on opposite sides. It is manufactured with compendial grade excipients. The drug product is for occasional use and the maximum daily dose is 30 mg hydrocodone bitartrate and 2.4 g guaifenesin/day (6 tablets).

B. Quality Assessment Overview

The drug product is a fixed-dose combination of 5 mg hydrocodone bitartrate and 400 mg guaifenesin as an immediate-release tablet dosage form (one strength combination). The proposed dissolution specification acceptance criteria for both Hydrocodone Bitartrate and Guaifenesin of not less than (b) (4)% of label claim dissolved in 15 minutes is acceptable. The drug product is formulated with multiple common compendial-grade inactive ingredients. The manufacturing process includes (b) (4) (b) (4)

The first API, hydrocodone bitartrate, USP is a tartrate salt of morphinanone derivative (b) (4) (b) (4) This API is a white-to-yellowish powder and soluble in water. The specification for hydrocodone bitartrate is consistent with USP monograph, and batch analysis data for three batches met this specification. The API is to be stored (b) (4) (b) (4) (b) (4) The retest period is (b) (4) when stored

(b) (4)

(b) (4)

The drug product is manufactured (b) (4)

(b) (4)

During the inspection of the **ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida** manufacturing facility for this NDA, the field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. These issues have been resolved and the facilities team recommends the application be approved.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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Final Drug Product Risk Assessment - Attachment

Drug product attribute/CQA[1]	Factors that can impact the CQA	O[2]	S[2, 3]	D[2]	FMECA RPN #	Comment & considerations
Appearance	• low tablet hardness impacts friability • friability impacts appearance	1	3	2	6	• Tablet hardness tested in-process (b) (4) • Friability tested in-process (b) (4) • Tablets are uncoated, thus friability is possible, which could impact appearance (among other parameters such as assay); friability results well below USP limit of NMT 1.0%
Identification	• incorrect drugs formulated • no drugs formulated • (b) (4)	1	3	5	15	• Probability of occurrence of incorrect or no drug(s) formulated should be relatively low and detectability high if applicant adheres to GMPs; (b) (4) (b) (4) • • (b) (4)
Potency(assay)/ Purity	• input purity of APIs • input purity of excipients • incorrect amounts of API formulated • impurity formation due (b) (4) • degradation of drug	1	3	2	6	• (b) (4) (b) (4) (b) (4) (b) (4) • Residual solvent levels in HC has relatively high limits, but still within Q3C • Excipients are of compendial quality, i.e., suitable for solid oral dosage forms • GMP adherence should prevent incorrect API/excipient amounts formulated

[1] Applicant has not defined CQAs for the drug product
[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[3] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

Final Drug Product Risk Assessment - Attachment

	• substances due to moisture and oxidation (protection from environment) • presence of organic solvents •					• Applicant chose excipients already used in other HB containing tablets to limit potential for compatibility issues (physicochemical) • Guaifenesin and HB have retest periods from their respective suppliers of (b) (4) and the applicant applies a (b) (4) (b) (4) • (b) (4)
Release (dissolution)	• (b) (4) • excipients and APIs • change • tablet hardness variation	2	3	2	12	• (b) (4) • criteria; Guaifenesin was tested for PSD but no acceptance criteria were proposed; considered low risk due to high drug load of this API • (b) (4)
Content uniformity	• lack of blend uniformity (b) (4) • particle size of API	1	3	5	15	• (b) (4)

Final Drug Product Risk Assessment - Attachment

						• (b) (4)
Microbial limits[4]	• microbial load of input materials for formulation	1	3	1	3	• (b) (4) (b) (4) microbial limits testing performed for Mg stearate, (b) (4) (b) (4) microcrystalline cellulose, and talc; no microbial testing of crospovidone and stearic acid; applicant has now established microbial limits testing in the drug product specification for stability testing (not for release, however) • Stability batches were not tested for microbial limits (*vide supra*)

[4] Evaluation done by the process team/reviewer.

Craig Bertha

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Date: 3/12/2018 07:27:40AM
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Recommendation: Complete Response

NDA 208085
Review #1

Drug Name/Dosage Form	Hydrocodone bitartrate/guaifenesin tablets
Strength	5 mg hydrocodone bitartrate/400 mg guaifenesin/tablet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ECI Pharmaceuticals, LLC
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
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Amendment	09-JAN-2017	Facilities
Amendment	13-JAN-2017	Facilities

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Application Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)	N/A	
Environmental Analysis (EA)	N/A	

Quality Review Data Sheet

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	III			Not reviewed		"
	III			Not reviewed		"
	III			Not reviewed		"
	III			Not reviewed		"
	IV			Not reviewed		"

Other D *plications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	109251	ECI's IND for the hydrocodone/guaifenesin product

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, biopharmaceutics, process, and facilities teams outlined in the review below, an overall recommendation of **Complete Response** is to be forwarded to the clinical Division (DPARP). Deficiency comments to be captured in the CR letter are:

1. Provide the following data to the NDA for at least one commercial scale drug product batch:

    a. Data from the (b) (4) (b) (4) (b) (4) per your submission Sections 3.2.P.3.4 and 3.2.P.5.2 (Version 09).

    b. Drug product certificate of analysis against the current release specification.

    c. Certificate of analysis for the APIs [used for that drug product batch(es)] per your current specification for drug substance.

2. During a recent inspection of the **ECI Pharmaceuticals LLC, FEI 3008798439, in Fort Lauderdale, Florida** manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

II. Summary of Quality Assessments

A. Product Overview

The oral drug product is proposed for "use in symptomatic relief of cough, to (b) (4) loosen (b) (4) mucus) (b) (4) The dosage form is an immediate release, white, capsule-shaped tablet, embossed with "ECI" and "601" on opposite sides. It is manufactured with compendial grade excipients. The drug product is for occasional use and the maximum daily dose is 30 mg hydrocodone bitartrate and 2.4 g guaifenesin/day (6 tablets).

B. Quality Assessment Overview

The drug product is a fixed-dose combination of 5 mg hydrocodone bitartrate and 400 mg guaifenesin as an immediate-release tablet dosage form (one strength combination). The proposed dissolution specification acceptance criteria for both Hydrocodone Bitartrate and Guaifenesin of not less than (b) (4)% of label claim dissolved in 15 minutes is acceptable. The drug product is formulated with multiple common compendial-grade inactive ingredients. The manufacturing process (b) (4)

The first API, hydrocodone bitartrate, USP (b) (4) This API is a white-to-yellowish powder and soluble in water. The specification for hydrocodone bitartrate is consistent with USP monograph, and batch analysis data for three batches met this specification. The API is to be stored in tight, (b) (4). The retest period is (b) (4) when stored (b) (4)

(b) (4)

(b) (4)

The facilities team recommends **withhold**, due to inspectional issues identified that require correction, at the drug product manufacturing site.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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BIOPHARMACEUTICS

Product Background:

NDA: 208085

Drug Product Name / Strength: hydrocodone bitartrate/guaifenesin tablets/5 mg hydrocodone bitartrate and 400 mg guaifenesin per tablet

Route of Administration: Oral

Applicant Name: ECI Pharmaceuticals, LLC

Review Summary:

The Applicant submitted a new NDA for (b) (4) (Hydrocodone Bitartrate and Guaifenesin Tablets, 5 mg/400 mg) Tablets by the 505(b)(2) pathway and plans to rely on the FDA's previous finding of safety and effectiveness of the following:

a. Tussigon® (hydrocodone bitartrate 5 mg and homatropine methylbromide 1.5 mg) Tablets of king Pharmaceuticals (ANDA088508) for the hydrocodone component of (b) (4) Tablets.

b. Guaifenesin OTC monograph (21 CFR 314.18) for the guaifenesin component of (b) (4) Tablets.

Hydrocodone Bitartrate and Guaifenesin Tablets, 5 mg/400 mg is indicated for symptomatic relief of cough and to loosen mucus associated with the common cold.

Formulation:

The composition and function of each component in the drug product is listed below:

Table 1: Quantitative Composition and Function of Drug Product Ingredients

Ingredient	Quality Standard	Function	Quantity (mg/tablet)	% w/w	Quantity per batch (kg) [Exhibit Batches]
					(b) (4)
Hydrocodone Bitartrate	USP	API	5		(b) (4)
Crospovidone	NF				(b) (4)
Microcrystalline Cellulose	NF				
Stearic Acid	NF				
Talc	USP				
Magnesium Stearate	NF				
Total Weight			**505**		(b) (4)

Dissolution Method:

The Applicant's proposed dissolution method is as follows:

Stage Name	1, 2 and 3
Dissolution Medium	Deionized (DI) water
Volume	900mL
Apparatus	Apparatus 2 (Paddles)
Speed	50rpm
Temperature	37.0°C ± 0.5°C
Time Points	(b) (4) minutes
Specification	NLT (b) (4) % (Q) at (b) (4) minutes

Dissolution Acceptance Criterion

The proposed dissolution specification for both Hydrocodone Bitartrate and Guaifenesin is NLT (b) (4) % of label claim dissolved in 15 minutes.

List Submissions being reviewed (table):

Application 208085 - Sequence 0000 - 0000 (1) 04/13/2016 ORIG-1 /Multiple Categories/Subcategories

Application 208085 - Sequence 0008 - 0008 (9) 09/28/2016 ORIG-1 /Quality/Response To Information Request

Application 208085 - Sequence 0009 - 0009 (10) 10/13/2016 ORIG-1 /Quality/Response To Information Request

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: The Applicant does not claim BCS designation.

Solubility:

- Guaifenesin: Soluble in water, alcohol, chloroform, propylene glycoland sparingly soluble in glycerine.
- Hydrocodone Bitartrate: Almost insoluble in the ether and chloroform. 1 g dissolves in 16 ml of water. 1 g dissolves in 150 g of ethanol

Permeability: Not provided.

Dissolution:

Stage Name	1, 2 and 3
Dissolution Medium	Deionized (DI) water
Volume	900 mL
Apparatus	Apparatus 2 (Paddles)
Speed	50 RPM
Temperature	37.0°C ± 0.5°C
Time Points	15 minutes
Acceptance Criteria	NLT (b) (4)% at 15 minutes

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

Drug Product

1. Dissolution Method

In vitro dissolution method for (b) (4) tablets (Hydrocodone Bitartrate and Guaifenesin):

Stage Name	1, 2 and 3
Dissolution Medium	Deionized (DI) water
Volume	900 mL
Apparatus	Apparatus 2 (Paddles)
Speed	50 RPM
Temperature	37.0°C ± 0.5°C
Time Points	15 minutes
Acceptance Criteria	NLT (b) (4)% at 15 minutes

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(b) (4)

[redacted]

The proposed dissolution specification for both Hydrocodone Bitartrate and Guaifenesin is NLT (b) (4)% of label claim dissolved in 15 minutes. Figure 1 and Figure 2 show the comparative dissolution profiles for clinical batch in different agitation speed and media for Hydrocodone Bitartrate and Guaifenesin, respectively. For the chosen agitation speed (50 rpm) and medium of DI water, both Hydrocodone Bitartrate and Guaifenesin dissolved more than (b) (4)% of label claim in 15 minutes.

The Applicant conducted the long term stability testing with four batches. The stability testing was not updated with the revised proposed dissolution specification when it was completed (36 months) for the first three batches (originally proposed (b) (4)% (Q) dissolved in (b) (4) minutes). After the Applicant proposed the revised dissolution specification of (b) (4)% (Q) dissolved in 15 minutes for both Hydrocodone Bitartrate and Guaifenesin, the fourth and most recently manufactured submission batch (batch # EJ14-3) was tested at the 24 month time point. It met the acceptance criterion. Long term stability was tested at 25°C ± 2°C /60% ± 5% relative humidity.

Reviewer's comments:

The proposed dissolution specification for both Hydrocodone Bitartrate and Guaifenesin of NLT (b) (4)% of label claim dissolved in 15 minutes is reasonable. Both Hydrocodone Bitartrate and Guaifenesin are immediate release.

2. Analytical Method Validation-Linearity

For both Hydrocodone Bitartrate and Guaifenesin, the linearity was validated over the range from 25% (1.39 µg/mL for Hydrocodone and 110.70 µg/mL for Guaifenesin) of low dosage strength to 200% (11.12 µg/mL for Hydrocodone and 885.61 µg/mL for Guaifenesin) of high dosage strength of test concentration with the correlation coefficient (r) ≥ 0.99. The linearity is adequately validated.

[redacted]

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

Reviewer's Assessment: n/a

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: n/a

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: This is an immediate release drug product, and in vitro alcohol dose dumping study is not needed.

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: n/a

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: n/a

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: n/a

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: n/a

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: n/a

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: n/a

Bridging of Formulations

Reviewer's Assessment: n/a

Biowaiver Request

Reviewer's Assessment: n/a

R Regional Information

Comparability Protocols

Reviewer's Assessment: n/a

Post-Approval Commitments

Reviewer's Assessment: n/a

Lifecycle Management Considerations

Reviewer's Assessment: n/a

List of Deficiencies: None.

Primary Biopharmaceutics Reviewer Name and Date: An-chi (Angela) Lu, Pharm D. 11/29/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Haritha Mandula, PhD., 12/14/2016

Haritha
Mandula

Digitally signed by Haritha Mandula
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Final Drug Product Risk Assessment - Attachment

Drug product attribute/CQA[1]	Factors that can impact the CQA	O[2]	S[2, 3]	D[2]	FMECA RPN #	Comment & considerations
Appearance	• low tablet hardness impacts friability • friability impacts appearance	1	3	2	6	• Tablet hardness tested in-process (b) (4) • Friability tested in-process (b) (4) • Tablets are uncoated, thus friability is possible, which could impact appearance (among other parameters such as assay); friability results well below USP limit of NMT 1.0%
Identification	• incorrect drugs formulated • no drugs formulated • (b) (4)	1	3	5	15	• Probability of occurrence of incorrect or no drug(s) formulated should be relatively low and detectability high if applicant adheres to GMPs; (b) (4) (b) (4) • • (b) (4)
Potency(assay)/ Purity	• input purity of APIs • input purity of excipients • incorrect amounts of API formulated • impurity formation due (b) (4) • degradation of drug	1	3	2	6	• (b) (4) (b) (4) (b) (4) (b) (4) • Residual solvent levels in HC has relatively high limits, but still within Q3C • Excipients are of compendial quality, i.e., suitable for solid oral dosage forms • GMP adherence should prevent incorrect API/excipient amounts formulated

[1] Applicant has not defined CQAs for the drug product
[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[3] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

Final Drug Product Risk Assessment - Attachment

	substances due to moisture and oxidation (protection from environment) • presence of organic • CU problems (*vide*					• Applicant chose excipients already used in other HB containing tablets to limit potential for compatibility issues (physicochemical) • Guaifenesin and HB have retest periods from their respective suppliers of (b) (4) and the applicant applies a (b) (4) (b) (4) • (b) (4)
Release (dissolution)	• (b) (4) • • change • tablet hardness variation	2	3	2	12	• • (b) (4) • • criteria; Guaifenesin was tested for PSD but no acceptance criteria were proposed; considered low risk due to high drug load of this API • (b) (4) •
Content uniformity	• lack of blend uniformity (b) (4) • particle size of API	3	3	5	45	• • • • (b) (4)

Final Drug Product Risk Assessment - Attachment

						• (b) (4)
Microbial limits[4]	• microbial load of input materials for formulation	1	3	1	3	• (b) (4) (b) (4) (b) (4) stearate, (b) (4) microcrystalline cellulose, and talc; no microbial testing of crospovidone and stearic acid; applicant has now established microbial limits testing in the drug product specification for stability testing (not for release, however) • Stability batches were not tested for microbial limits (*vide supra*)

[4] Evaluation done by the process team/reviewer.

Craig
Bertha

Digitally signed by Craig Bertha
Date: 1/26/2017 01:17:13PM
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