CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207999Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **May 24, 2016**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 207999**

Subject: Final Recommendation for NDA 207999

At the time when the CMC Review #1 was completed on April 19, 2016, it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the ONDP perspective.

The revised package insert and immediate container labels were submitted on May 24, 2016. The CMC sections of the package insert and immediate container labels were reviewed by Dr. Hitesh Shroff and found acceptable (**Attachment – 1).**

Recommendation:
This NDA is now recommended for Approval from the ONDP perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
May 24, 2016

Attachment 1:

1. *Package Insert*

(a) "Highlights" Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OCALIVA safely and effectively. See full prescribing information for OCALIVA.

OCALIVA (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

——————DOSAGE FORMS AND STRENGTHS——————

Tablets: 5 mg, 10 mg (3)

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

3 DOSAGE FORMS AND STRENGTHS

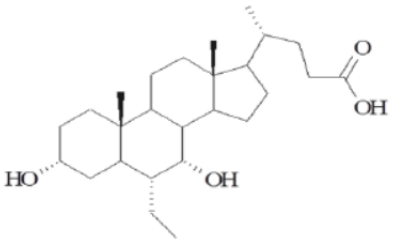
OCALIVA is available as:

- 5 mg tablet: Off white to yellow, round tablet debossed with "INT" on one side and "5" on the other side.
- 10 mg tablet: Off white to yellow, triangular tablet debossed with "INT" on one side and "10" on the other side.

#11. Description

11 DESCRIPTION

OCALIVA is a farnesoid X receptor (FXR) agonist. Chemically, obeticholic acid is 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid. It is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH. Its chemical formula is $C_{26}H_{44}O_4$, the molecular weight is 420.63 g/mol and the chemical structure is:



OCALIVA tablets are supplied in 5 mg and 10 mg strengths for oral administration. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating is Opadry II (Yellow) containing polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

#16 How Supplied/storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

OCALIVA tablets are packaged in a 40 mL high density polyethylene bottle closed with a 33 mm polypropylene child resistant cap containing an induction seal. Each bottle contains 30 tablets.

5 mg Tablets

OCALIVA tablets are available as off-white to yellow, round tablets debossed with INT on one side and 5 on the other side. Each tablet contains 5 mg of obeticholic acid.

- NDC 69516-005-30 5 mg tablets in a bottle (30 count)

10 mg Tablets

OCALIVA tablets are available as off-white to yellow, triangular tablets debossed with INT on one side and 10 on the other side. Each tablet contains 10 mg of obeticholic acid.

- NDC 69516-010-30 10 mg tablets in a bottle (30 count)

Storage and Handling

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C- 30°C (59°F -86°F) [See USP Controlled Room Temperature].

2. ***Labels***

Reviewer's Assessment and Signature:

The final label and labeling submitted on May 24, 2016 are satisfactory from ONDP perspective.

Reviewer's Signature:
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Secondary Review Comments and concurrence:

Supervisor's Signature:
Moo-Jhong Rhee, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Recommendation: This 505(b)(1) application is not deemed ready for approval as of this review in its present form, per 21 CFR 314.125(b)(6).

NDA 207999
Review #1

Drug Name/Dosage Form	Obeticholic Acid Tablets
Strength	5 mg and 10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Intercept Pharmaceuticals, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	29-Jun-2015
Amendment	02-Sep-2015
Amendment	16-Oct-2015
Amendment	19-Oct-2015
Amendment	27-Oct-2015
Amendment	20-Jan-2016

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Stevens	OMPT/CDER/OPQ/ONDP/DND API/NDBII
Drug Product	Hitesh Shroff	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Process	Vaikunth Prabhu	OMPT/CDER/OPQ/OPF/DPAII/PABV
Microbiology	Vaikunth Prabhu	OMPT/CDER/OPQ/OPF/DPAII/PABV
Facility	Bryan Ryan	OMPT/CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Peng (Vincent) Duan	OMPT/CDER/OPQ/ONDP/DB/BBII
Regulatory Business Process Manager	Truong Quach	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	OMPT/CDER/OPQ/ONDP/DND PII/NDPBV
Laboratory (OTR)	Laura Pogue	OMPT/CDER/OPQ/OTR/DPA/PABII
ORA Lead	Paul Perdue	OGROP/ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	James Laurenson	OMPT/CDER/OPQ/ONDP

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

[1] N/A: There is enough data in the application, therefore the DMD did not need to be reviewed

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63307	Tablet

2. CONSULTS:

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

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

The Office of Facility and Process has made a final overall manufacturing Inspection "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the label/labeling issues have ***not*** been completely resolved as of this review

Therefore, from the OPQ perspective this NDA is not deemed ready for approval at this time in its present from per 21 CFR 314.125(b)(6) until the above issues are satisfactorily resolved. **(see the List of Deficiencies on p. 214)**

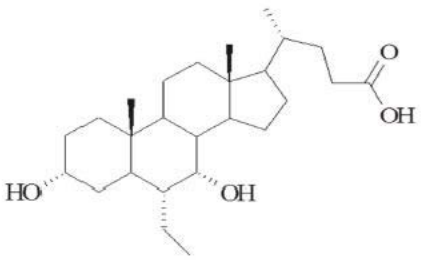
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The active pharmaceutical ingredient in the drug product is Obeticholic acid. It is a white to almost white powder. (b) (4) soluble in (b) (4) (b) (4) such as (b) (4) ethyl acetate, methanol, etc. Its solubility in water is pH dependent. (b) (4) (b) (4)

Obeticholic acid is known chemically as 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid. The chemical formula is $C_{26}H_{44}O_4$, the molecular weight is 420.63 g/mol and the chemical structure is:



Obeticholic acid is manufactured (b) (4)

(b) (4)

Obeticholic acid is manufactured and controlled according to the procedures described and conforms to the requirements for formulation of obeticholic acid tablets described in this NDA.

B. Drug Product [Established Name] Quality Summary

Obeticholic acid tablets, 5 mg and 10 mg are indicated for treatment of primary biliary cirrhosis (PBC) in adults.

The 5 mg tablets containing 5 mg obeticholic acid are yellow, round, debossed with INT on one side and 5 on the other side. The 10 mg tablets containing 10 mg obeticholic acid are yellow, triangular tablets, debossed with INT on one side and 10 on the other side. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating Opadry II (Yellow) contains polyvinyl alcohol-part hydrolyzed, titanium dioxide, Macrogol (polyethylene glycol 3350), talc, and iron oxide yellow. The drug product is supplied in a 40 cc high density polyethylene bottle containing 30 tablets and it is closed with an induction seal and a 33 mm polypropylene child resistant cap.

Obeticholic acid tablets are manufactured (b) (4)

(b) (4)

(b) (4)

Based on the stability data submitted 24-month expiration dating period is well justified when stored in the proposed container closure system at 25ºC. The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable.

The identity, strength, purity and quality of the drug product are assured by the adequate raw material controls, validated manufacturing process and drug product specification.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Ocaliva
Non Proprietary Name of the Drug Product	Obeticholic acid tablets
Non Proprietary Name of the Drug Substance	Obeticholic acid
Proposed Indication(s) including Intended Patient Population	Treatment of primary biliary cirrhosis (PBC) in combination with rsodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA
Duration of Treatment	As needed
Maximum Daily Dose	The recommended starting dose is 5 mg once daily and should be increased after 3 months, if tolerated, to 10 mg once daily to improve response.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: N/A
   - Drug Product: N/A

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: N/A
   - IVIVC: N/A

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Process/Facility Quality Summary (See Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

From the quality perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125 (b)(6), until the label/labeling issues are satisfactorily resolved **(see the List of Deficiencies on p. 214).**

Hitesh Shroff, Ph. D.
Application Team Lead, Branch V
Division of New Drug Products II

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA 207999.

Coverage during the next inspection is recommended for the following facilities:

(b) (4)

Brian J. Ryan 09FEB2016; 29FEB2016
Consumer Safety Officer, OPF/DIA/ Branch III

Secondary Review Comments and Concurrence:
I concur.
Grace E. McNally, Acting Branch Chief, OPF/DIA/Branch 3
February 29, 2016

ASSESSMENT OF THE BIOPHARMACUETICS

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

Applicant's Response:

Obeticholic Acid (OCA) is a farnesoid X receptor (FXR) agonist and is a modified bile acid being developed in the United States (US) and Europe seeking approval for the treatment of primary biliary cirrhosis (PBC) (b) (4) OCA is an NME (new molecular entity).

OCA is proposed as film-coated 5 mg and 10 mg oral tablets as shown below (Table 1).

Table 1. Composition of the commercial formulation of 5 and 10 mg OCA Tablets

Component	Amount Per Tablet (mg)	Function	Reference to Quality Standard
5 mg tablet			
Obeticholic acid[a]	5.0[a]	Active ingredient	(b) (4)
Microcrystalline cellulose	(b) (4)		NF/Ph. Eur.
Sodium starch glycolate			NF/Ph. Eur.
Magnesium stearate			NF/Ph. Eur.
Opadry II Yellow coating material[b]	(b) (4)	Coating material	(b) (4)
	(b) (4)		USP/Ph. Eur.
Total weight	208.0		
10 mg tablet			
Obeticholic acid[a]	10.0[a]	Active ingredient	(b) (4)
Microcrystalline cellulose	(b) (4)		NF/Ph. Eur.
Sodium starch glycolate			NF/ Ph. Eur.
Magnesium stearate			NF/ Ph. Eur.

Component	Amount Per Tablet (mg)	Function	Reference to Quality Standard
10 mg tablet			
Opadry II Yellow coating material[b]	(b) (4)	Coating material	(b) (4)
	(b) (4)		USP/Ph. Eur.
Total weight	208.0		

NF = National Formulary; Ph. Eur. = European Pharmacopeia

[a] OCA drug substance amount added assumes the drug substance content is 100%; actual amount added is adjusted based on the potency of the drug substance lot used; the amount of microcrystalline cellulose is correspondingly decreased.

[b] Refer to Module 3.2.P.4, Control of Excipients, for a summary of the components and composition of Opadry II Yellow (b) (4) Opadry II coating material is manufactured from NF compendial excipients or from colorant meeting compliance with Directive 2008/12/EC (formerly 95/45/EC) and Federal Food, Drug, and Cosmetic Act standards.

(b) (4)

Note: Pilot and clinical formulations of 10 mg, 25 mg, and 50 mg capsule strengths and 25 mg tablet strength were tested previously; however, the Applicant now only seeks approval for the 5 mg and 10 mg tablet strengths.

The proposed dissolution method is as follows (Table 2):

Table 2. Proposed dissolution method

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

1. From the Biopharmaceutics perspective, the proposed dissolution method and dissolution acceptance criterion are acceptable.

2. Clinical batches are properly bridged to commercial batches, and the biowaiver request for the 5 mg OCA tablet is acceptable, pending on the acceptance of the results of BE study 747-115 and 747-116 by OCP.

3. The following dissolution method and acceptance criterion proposed by the Applicant should be implemented for the Release and Shelf Life for drug product quality control once this NDA is approved.

Dissolution method:

Dissolution Apparatus	(b) (4)
Stirring	Paddles (USP Apparatus 2) at 75 rpm
Dissolution Medium	0.08% polysorbate 80 in 50 mM sodium phosphate dibasic buffer pH 6.8.
Volume of Dissolution Medium (mL)	900
Dissolution Medium Temperature (°C)	37.0 ± 0.5
Sampling Time (minutes)	10, 15, 30, 45, 60
Sample Size (mL)	7.5 with medium replacement
	(b) (4)
Quantitation	HPLC (b) (4)

Samples are assayed undiluted. (b) (4)
into an HPLC vial discarding the first 5 mL (b) (4)

Acceptance Criterion: for both 5 and 10 mg tablet strengths

Q= (b) (4) % at 15 min

Vincent (Peng) Duan, Ph.D.
Biopharmaceutics Primary Reviewer, BBII/ DB/ONDP/OPQ
Feb 28, 2016

Secondary Review Comments and Concurrence:

I concur. 12/08/15

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead, BBII/ DB/ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:
The OCA drug product is [redacted] (b) (4) The microbial limit specification for the OCA drug product is provided in Module 3.2.P.5.1, Specification and is tested using USP and Ph. Eur. methodology; details are provided in Module 3.2.P.5.2, Analytical Procedures. *The microbial criteria have been consistently monitored during development at both release and on stability.*

The microbial levels have met specifications for all data collected to date. Details are provided in Module 3.2.P.5.4, Batch Analyses for a batch analyses summary of representative release data. Utilizing the decision tree #6, as described in the ICH guidance Q6A, periodic microbial release testing is proposed for this following successful microbial testing of the first 3 commercial batches of each strength. The microbial testing will be performed on 1 in every 10 commercial batches, or at least 1 batch every 12 months.

Reviewer's Assessment:

Compendial excipients used in the manufacturing process of obeticholic acid (OCA) tablets are listed in Table 1 below. All excipients are tested and released to compendial specifications by [redacted] (b) (4) their contractors. Information on the specification for the non-compendial excipient in OCA tablets is provided in Module 3.2.P.4.1, Specifications Opadry II.

Table 1: Excipients in OCA Tablet Drug Product

Excipient	Quality Reference
Microcrystalline cellulose	NF/Ph. Eur.
Sodium starch glycolate	NF/Ph. Eur.
Magnesium stearate [redacted] (b) (4)	NF/Ph. Eur.
[redacted] (b) (4)	USP/Ph. Eur.

NF = National Formulary; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia

The specification for Opadry II Yellow [redacted] (b) (4) is provided in Table 1. All components of the Opadry II Yellow [redacted] (b) (4) coating material comply with United States Pharmacopeia or National Fomulary requirements, as well as Directive 2008/12/EC.

Table 1: Specification for Opadry II Yellow 85F32351

Attribute	Test Method	Acceptance Criteria
Appearance[a]	Visual	Yellow powder
Identification[a]	IR spectrum	Conforms to standard
Color Difference[b]	Total Color Difference	(b) (4)
Dispersion[b]	Dispersion Test	Pass
Microbial Limits[a]	Ph. Eur. 2.6.12, USP <61>	Total Aerobic Microbial Count: NMT (b) (4) cfu/gram Total Yeasts and Molds Count: NMT (b) (4) cfu/gram *Escherichia coli*: Absent in (b) (4) gram

cfu = colony forming unit; ΔE* = color difference; NMT = not more than; Ph. Eur. = European Pharmacopeia

(b) (4)

Detailed data on microbial tests are provided in Module 3.2.P.5.4, Batch Analyses for a batch analyses summary of representative release data.

Microbial Limits (cfu/g) test is included in drug product release following USP<61> and <62>; Total aerobic microbial count: NMT (b) (4) cfu/g; Total combined yeasts and molds count: NMT (b) (4) cfu/g; E.coli: Should be absent. Method used is QCM859 from Almac analytical method.

Proposed Commercial Specification for 5 mg and 10 mg OCA Tablets

Microbial Limits (cfu/g)[a]	QCM859[c] USP<61> and USP<62>	TAMC (total aerobic microbial count): NMT (b) (4) cfu/g TYMC (total combined yeasts/molds count): NMT (b) (4) cfu/g Absence of *E. coli*

a Test is used for both release and stability
c (b) (4) analytical method

It is noted that in 3.2.R, BSE/TSE Statement on OCA drug substance (Lot # JP1408001, Lot# JP1408002 and Lot # JP1408003) from (b) (4) is provided stating that the drug substance Obeticholic acid (OCA) is free from any risk (b) (4) See Question # 42 for additional details.

It is noted that in 3.2.R section firm has provided the following BSE/TSE statement for OCA tablets:

(b) (4)

Firm's proposal of periodic microbial release testing is acceptable (justification: referenced to decision tree #6, as described in the ICH guidance Q6A). This subject was discussed internally with peer reviewers and an additional consideration was given to the fact that firm has understanding (b) (4) Batch # B08803 (5 mg strength) and Batch # B08805 (10 mg strength)] and microbial limits were monitored successfully and documented in all clinical and registration batches. The microbial criteria have been consistently monitored and complied during development at both release and on stability studies. Provided data [see hold period for bulk tablets 5 mg strength (lot # B03290 and lot# B08803) and 10 mg (lot # B03289 and lot# B08805) studies at 0 and 12 months at CRT conditions; meets Microbial Limits specification requirements; PD Report pp 92-96], indicate that microbial levels are consistently below acceptance criteria levels or testing may not be necessary. Also, firm is proposing successful microbial testing of the first 3 commercial batches of each strength. Based on all the above facts risk level was assessed to be 'low'. So firm's proposal is acceptable.

3.2.P.8.2 Post Approval Stability protocol and Stability Commitment
[OCA, Tablet, Piramal]

Post Approval Commitment for Stability Studies On Commercial Scale Lots

Table 1: Proposed Stability Testing Schedule for Three Commercial Scale Lots of OCA Tablets

(b) (4)

[redacted]

Post Approval Commitment for Annual Stability Studies

.

Micro testing proposal on annual stability is acceptable.

(b) (4)

[redacted]

METHOD REFERENCE:
Validation Protocol and Report: VAL/13/140/P, and VAL/13/140/R
Current European Pharmacopoeia sections 2.6.12 and 2.6.13.
Current United States Pharmacopoeia sections <61> and <62>
Current Japanese Pharmacopoeia section 4.05.

Satisfactory.

2.3.P.7 Container/Closure System

36. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:
A comparison between the clinical and proposed commercial container closure system is provided in Table 105. They are similar.

Table 105: Comparison of Clinical and Commercial Container Closure System for OCA Tablets

Component	Clinical Supplies	Commercial Supplies	Rationale for Change in Commercial Packaging
Bottle	85 cc Round White HDPE	40 cc Round White HDPE	(b) (4)
		(b) (4)	
Child Resistant Cap	33 mm with induction heat seal	33 mm with induction heat seal	
		(b) (4)	
		(b) (4)	

Table 106: Head Space Comparison for Container Closure Systems

Description	Clinical Supplies 30 count, 5 and 10 mg	Commercial Supplies 30 count, 5 mg	Commercial Supplies 30 count, 10 mg
Bottle Size	85 cc	40 cc	40 cc
Empty bottle head space	94 cc	53 cc	53 cc
Tablet Volume (n=30)	3 cc	3 cc	4 cc
Filled bottle head space	91 cc	50 cc	49 cc

Reviewer's Assessment:

Information provided is adequate.

This section may have been covered in Drug Product 3.2.P.7 section.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

37. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product

contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:
See earlier sections.

Reviewer's Assessment:

(b) (4)

(b) (4)

Information provided is adequate.

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:
See earlier sections.

Reviewer's Assessment:

See earlier sections.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The microbial limit specification for the OCA drug product is provided in Module 3.2.P.5.1, Specification and is tested using USP and Ph. Eur. methodology; details are provided in Module 3.2.P.5.2, Analytical Procedures. The microbial criteria have been consistently monitored during development at both release and on stability. Proposed 'Post Approval Commitment for Annual Stability Studies' as documented above is acceptable.

Satisfactory.

Vaikunth S. Prabhu - September 16, 2015; November 20, 2015
Senior CMC Reviewer; OPF/DPA II/BranchV

Secondary Review Comments and Concurrence:
I concur, overall microbiology assessment is acceptable.
Celia N. Cruz, Ph.D. 25-November-2015
Acting Branch Chief, OPF/DPAII/BV

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

39. Is the applicant's claim for categorical exclusion acceptable?

40. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response: The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). Specifically, the expected introduction concentration (EIC) of (b) (4) ppb for obeticholic acid (OCA) was noted as lower than the 1 ppb categorical exclusion value. The nonclinical overview, however, noted that the rat embryo-fetal development study reported evidence of developmental toxicity. Also, recent literature indicates a possible role of nuclear receptors such as FXR in endocrine-related environmental toxicity (e.g., OECD 2012, Detailed Review Paper on the State of the Science on Novel In Vitro and In Vivo Screening and Testing Methods and Endpoints for Evaluating Endocrine Disruptors). Since drugs with endocrine-related activity have been shown to have

potential developmental or reproductive effects in aquatic organisms at environmentally relevant concentrations, FDA requested additional information to determine whether extraordinary circumstances exist, per FDA's recent draft guidance on this subject at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf. The claim for a categorical exclusion also was not accompanied by an adequate statement of no extraordinary circumstances, however, as required per 21 CFR 25.15(a), which also was noted in the information request.

The applicant sent additional information on October 16, 2015 in response to the information request. Briefly, the applicant noted that (1) OCA is a selective FXR agonist and that there is no cross-reactivity of OCA at nuclear receptors other than the target receptor, FXR; (2) there is no evidence that the FXR/RXR heterodimer modulates reproduction- or thyroid-related endocrine processes; (3) FXR is evolutionarily conserved and there is no evidence to indicate that FXR has any functions in non-mammalian vertebrates or invertebrates other than bile acid homeostasis and lipid regulation; and (4) there are no endocrine-related toxicity findings. The applicant concludes that OCA does not have activity in the estrogen, androgen, or thyroid pathways, nor in other endocrine pathways, and there is no indication that the use of OCA will, at the estimated potential environmental exposure of <1 ppb, have any adverse impact on the environment. The applicant also stated that no extraordinary circumstances exist that would significantly affect the quality of the human environment.

Reviewer's Assessment: The expected introduction concentration (EIC) of (b) (4) ppb is approximately two orders of magnitude below the 1 ppb categorical exclusion value. Therefore, the categorical exclusion claim is appropriate for the anticipated amount of drug to be used. The calculation appears accurate and reasonable. Also, an adequate statement of no extraordinary circumstances is now present.

The applicant's explanations and data regarding the FXR receptors and the lack of any endocrine-related toxicity findings also are reasonable and compelling, in particular (1) the data showing that no estrogenic, androgenic, or other nuclear receptors other than FXR were activated by OCA or conjugated OCA; (2) the clinical and nonclinical data showing that specific reproductive and developmental hazards have not been identified for OCA, and that the rat embryo-fetal development study results noted above are explained as effects related to marked maternal toxicity in individual animals and not to a specific developmental effect; and (3) the description of the evolutionarily conserved pathway that is expected to maintain a lack of endocrine activity in non-mammalian species.

While the above information indicates that OCA has no endocrine activity, it is clear that even if there is such activity, it is low relative to drugs with known estrogenic, androgenic, and thyroid activity. In addition, the highest total estimated annual use amount for OCA, (b) (4) kg/year, is similar to the amounts for the most potent known hormonally active drugs (e.g., ethinyl estradiol, methyl-testosterone, levothyroxine), and thus with significantly lower or nonexistent hormonal activity, no significant impact is

expected.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: The claim for a categorical exclusion from an EA is acceptable.

James P. Laurenson, CDER/OPQ/ONDP EA Team, 12/4/2015

Secondary Review Comments and Concurrence: I concur with the above review. Concur

M. Scott Furness, Deputy Director, ONDP

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Container Labels

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug name is presented correctly. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed as 5 mg and 10 mg. **Satisfactory**
Net contents (21 CFR 201.51(a))	Net content displayed correctly. **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement is displayed. **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is indicated properly. **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Displayed **Satisfactory**
Storage conditions	Storage condition is not described properly. **Not Satisfactory**
Bar code (21CFR 201.25)	Barcode is displayed. **Satisfactory**
Name of manufacturer/distributor	The name of the distributor is displayed correctly. **Satisfactory**
And others, if space is available	N/A

Evaluation: Not adequate. The bottle labels for both strength tablets should be revised as follows:

- Store at 20ºC to 25ºC (68ºF to 77ºF) [See USP Controlled Room Temperature]

Labeling Review

The following is a summary of the labeling review.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRADENAME safely and effectively. See full prescribing information for TRADENAME.

TRADENAME® (obeticholic acid) Tablet, for oral use
Initial U.S. Approval: 20xx

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	TRADENAME®(obeticholic acid)	The drug product title is described correctly. **Satisfactory**
Dosage form, route of administration	tablet	**Satisfactory**
Controlled drug substance symbol (if applicable)	N/A	**Not applicable**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Tablets: 5 mg, 10 mg	The dosage form is described correctly as tablets. The strength is described correctly. **Satisfactory**

Whether the drug product is scored (If the product is not scored, do not say "not scored.")		The product is not scored.

Evaluation: Adequate.

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

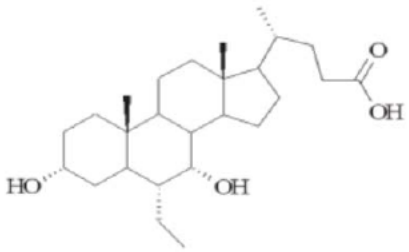
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablet	Dosage form described correctly. **Satisfactory**
Strengths: in metric system	5 mg and 10 mg	The strengths are described correctly. **Satisfactory**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)	The tablets are described correctly. **Satisfactory**

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

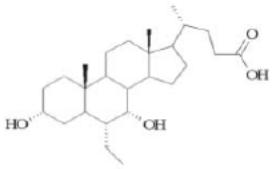
(b) (4)

chemical formula is $C_{26}H_{44}O_4$, the molecular weight is 420.63 g/mol and the chemical structure is:



TRADENAME tablets are supplied in 5 mg and 10 mg strengths for oral administration. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating is Opadry II (Yellow) and contains polyvinyl alcohol-part hydrolyzed, titanium dioxide, Macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	TRADENAME and obeticholic acid	The proprietary name and established name are correct.
Dosage form and route of administration	Tablets	**Satisfactory**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not applicable	Not applicable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Tablet: Microcrystalline cellulose, sodium starch glycolate, magnesium stearate Opadry II Yellow: polyvinyl alcohol – part hydrolyzed, titanium dioxide, Macrogel (PEG 3350), talc and iron oxide yellow	Information for inactive ingredients is provided correctly. **Satisfactory**
Statement of being sterile (if applicable)		**Not applicable**
Pharmacological/ therapeutic class		Will be determined in the labeling meeting. **Satisfactory**

Chemical name, structural formula, molecular weight	Chemical Name: 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid Molecular formula: $C_{26}H_{44}O_4$ Molecular weight: 420.63 g/mol molecular structure is:  	This information is correct. **Satisfactory**
If radioactive, statement of important nuclear characteristics.		Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)		The general properties of the drug substance are not described **Not Satisfactory**

Evaluation: Not adequate. This section should be revised as follows to include chemical or physical properties of the drug substance.

- Obeticholic acid is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	5 mg and 10 mg	Strengths are properly described **Satisfactory**
Available units (e.g., bottles of 100 tablets)	30 tablets	This information provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	The description of tablets and NDC numbers are provided. However, the format is not correct. **Not Satisfactory**
Special handling (e.g., protect from light, do not freeze)		Not applicable
Storage conditions	(b) (4)	Information not provided correctly. **Not Satisfactory**

Evaluation: Not adequate. This section should be revised as follows:

- NDC 69516-005-30 5 mg tablets, 30-count bottle
- NDC 69516-010-30 10 mg tablets, 30-count bottle
- Store at 20ºC to 25ºC (68ºF to 77ºF) [See USP Controlled Room Temperature]
- Add container description as shown below.
  TRADENAME tablets are packaged in 40 cc high density polyethylene bottle closed with a 33 mm polypropylene child resistant cap containing an induction seal.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Intercept Pharmaceuticals, Inc. New York, NY 10011	Information is correctly provided. **Satisfactory**

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

The applicant has provided preliminary labeling and package insert, and request for their revision will be conveyed to the applicant, and as of this review, the labels and labeling have not been finalized..

Reviewer's Signature
Hitesh Shroff, Ph.D.
Branch V
Division of New Drug Products II/ONDP

Secondary Review Comments and Concurrence:
I agree with Dr. Shroff's assessment on the labeling and labels and his request for revision as delineated in the **List of Deficiencies.**

Moo-Jhong Rhee, Ph.D.
Chief, Branch V/DNDP II/ONDP

II. List of Deficiencies To Be Communicated

The following comments should be conveyed to the applicant.

A. Regarding Label/labeling

Immediate container labels:

- The storage conditions on the container labels for both strength tablets should be as shown below:

  Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]

PI

"Highlights" Section

- Display the pharmacological class for this drug product.

#11 Description

- Add chemical or physical properties of the drug substance as shown below.

  Obeticholic acid is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH.

#16 How supplied/storage and handling

- The NDC numbers should be displayed as shown below.

  NDC 69516-005-30 5 mg tablets, 30-count bottle
  NDC 69516-010-30 10 mg tablets, 30-count bottle

- Add container description as shown below.

  TRADENAME tablets are packaged in 40 cc high density polyethylene bottle closed with a 33 mm polypropylene child resistant cap containing an induction seal.

III. Attachments

A. Facilities

OVERALL RECOMMENDATION: "Approve" recommendation was entered in Panorama on December 10, 2015.

B, Lifecycle Knowledge Management

a) Drug Product

Drug Product Risk Assessment

Product attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/Comments
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	The ingredients are compendial or controlled by internal specification. During manufacturing process development critical process parameters were identified and in process controls (IPC) were instituted for a robust manufacturing process and to constistantly produce quality DP. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested. Assay is determined by a validated HPLC method.	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4)	Low to None	None
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4) DP is tested per USP<905> and controlled at release.	Low to None	None
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site Finished product water activity Release/stability testing	L	None of the ingredients in the DP is conducive to microbial contaminatio. The DP is a tablet formulation which is tested for microbial impurities at release.	Low to None	None
Dissolution	• Formulation • Raw materials Exclude major reformulations • Process parameters • Scale/equipment • Site	M	The drug product dissolutions controlled by DP release and stability specification. It is tested per USP<711>	Low to None	None

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REPORT SUMMARY

TO: Danuta Gromek-Woods, ATL, Moo-Jhong Rhee (Branch Chief), Heather Strandberg (CMC Project Manager)
Office of New Drug Products (ONDP), Branch V
E-mail Address: Danuta.Gromek-Woods@fda.hhs.gov
Phone: (301) 796-1217

FROM: FDA
Division of Pharmaceutical Analysis
Laura C. Pogue, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: Michael Trehy, Ph.D., Lab Chief, Branch II
Phone: (314) 539-3815

SUBJECT: Methods Verification Report Summary

Application Number: 207999

Name of Product: Obeticholic Acid Tablets, 5 mg and 10 mg

Applicant: Intercept Pharmaceuticals, Inc.

Applicant's Contact Person: Linda Robertson, PhD, Vice President, Regulatory Affairs and Quality Assurance

Address: 4760 Eastgate Mall, San Diego, CA 92121

Telephone: (858) 652-6805 Email: lrobertson@interceptpharma.com

Date Methods Verification Consult Request Form Received by DPA: 8/11/2015

Date Methods Verification Package Received by DPA: 9/11/2015

Date Samples Received by DPA: 9/11/2015

Date Analytical Completed by DPA: 2/22/2016

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 South Newstead Ave
St. Louis, Missouri 63110
Telephone (314) 539-3822
FAX (314) 539-2113

Date: February 22, 2016

To: Danuta Gromek-Woods, ATL
Moo-Jhong Rhee, Branch Chief
Heather Strandberg, CMC Project Manager

Through: Michael Trehy, Ph.D., Acting Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Jeffrey T. Woodruff, Chemist, CDER/OPQ/OTR/DPA
Kui Zeng, Ph.D., Chemist, CDER/OPQ/OTR/DPA
Nisarga Phatak, Ph.D., Orise Fellow, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 207999: Obeticholic Acid Tablets, 5mg and10 mg

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1) The HPLC assay method for the assay of INT-747 in uniformity of dosage units and content of INT-747 film coated tablets 10 mg
2) Related Substances: Impurities (b) (4) (%w/w) (b) (4)
3) Related Substances: Impurities (b) (4) (%w/w) (b) (4)
4) HPLC method for the determination of impurity (b) (4) and unspecified impurities in OCA film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM1069/01
5) HPLC method for the determination of impurity (b) (4) in INT-747 film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM857/01
6) Assay and Identification (b) (4))

The Division of Pharmaceutical Analysis (DPA) would like to share the following comments to the reviewers regarding several methods:

1) The HPLC method for the determination of impurity (b) (4) in INT-747 film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM857/01

    a) Two calibration data sets are collected in the experiment with 6 standard concentrations. Suggest applicant clarify which data set in the specified sequence is used to determine the quadratic equation constants for system suitability and calculation.
2) The HPLC method for the determination of impurity (b) (4) and unspecified impurities in OCA film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM1069/01

a) In this method only 3 standard concentrations are prepared (see page 3 of this method) and used to generate a quadratic curve which will always result in a correlation coefficient (r) of 1 and always meet the system suitability requirement of (b) (4) It is suggested that more data points are used to build a calibration curve as performed in the method for Impurity (b) (4) point calibration curve).

b) Two calibration data sets are collected in the experiment. Suggest applicant clarify which data set in the specified sequence is used to determine the quadratic equation constants for system suitability and calculation.

3) Assay and (b) (4) (b) (4)

c) In DPA's analysis, the concentration of the standard (b) (4) injection volume lead to overloading of the column resulting in poor peak shape and an inability to meet system suitability (Symmetry Factor). DPA reduced the injection volume by (b) (4) per USP<621> guidelines, and yielded sufficiently quantifiable results with better method performance.

Original analyst worksheets and data can be viewed here:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880c7bbe5

SUMMARY OF RESULTS:

The HPLC assay method for the assay of INT-747 in uniformity of dosage units and content of INT-747 film coated tablets 10 mg

Criteria 1:

(b) (4)

Result

(b) (4)

PASS

Criteria 2:

(b) (4)

Result

(b) (4)

PASS

AV = 2.0
Mean = 100.7%
%RSD = 0.84

Related Substances: Impurities (b) (4) ***(%w/w)*** (b) (4)

Table 4:

Related substances	Requirement	Results
Sum of impurity (b) (4)	NMT (b) (4) %	(b) (4)
impurity (b) (4)	NMT %	
impurity	NMT %	
impurity	NM %	
impurity	NMT %	
Unknown impurity	NMT %	
Total	NM %	

ND= Not detected

Related Substances: Impurities (b) (4) ***(%w/w)*** (b) (4)

% Impurity (b) (4) = (b) (4) %
Requirement = NMT (b) (4) %

HPLC method for the determination of impurity (b) (4) and unspecified impurities in OCA film coated tablets 5mg, 10 mg and 25 mg

Table 1: Impurity 8 and unspecified impurities

Name	% Imp (b) (4)	% Imp, (b) (4)	Avg, % Imp	Report, %	NDA Specification, %	Pass/Fail
unspecified (b) (4)					(b) (4)	Pass
unspecified						Pass
unspecified						Pass
impurity (b) (4)						Pass
unspecified (b) (4)						Pass

HPLC method for the determination of impurity (b) (4) in INT-747 film coated tablets 5mg, 10 mg and 25 mg

Table 2: Impurity (b) (4)

Name	% Imp (b) (4)	% Imp, (b) (4)	Avg, % Imp	Report, %	NDA Specification, %	Pass/Fail
impurity (b) (4)					(b) (4)	Pass

Table 3: Total Specified and Unspecified Impurities by HPLC

Name	% Imp (b) (4)	% Imp (b) (4)	Avg, % Imp	Report, %	NDA Specification, %	Pass/Fail
unspecified (b) (4)					(b) (4)	Pass
unspecified						Pass
unspecified						Pass
impurity (b) (4)						**Pass**
unspecified (b) (4)						Pass
impurity (b) (4)						**Pass**
Total Impurities:						**Pass**

Assay and Identification (b) (4)

Requirement **Results**	(b) (4)

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

/s/

LAURA POGUE
02/23/2016

MICHAEL L TREHY
02/23/2016

<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" tabindex="0"><label></label></td></tr> <tr><td style="font-family:Microsoft Sans Serif;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>
 <FONT SIZE =2><FONT COLOR="#000080"> No active OAI / POAI Alerts are present against the facilities on selected Projects</FONT></FONT>

Facility Status View for NDA 207999 Original 1

Displays information for the facilities that are associated to NDA 207999 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 12/11/2015 3:56:35 PM

Overall Manufacturing Inspection Recommendations for NDA 207999 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207999-Orig1-New - Form 3674/NDA(2)	INTERCEPT PHARMACEUTICALS INC	Approve	Complete	12/10/2015

OPF Facility Recommendations for Facilities on NDA 207999 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 207999-Orig1-New - Form 3674/NDA(2)				(b) (4)	Approve Facility	Complete	8/13/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/24/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/30/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/30/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	12/9/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	12/10/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/29/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/24/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)						Cancelled	7/23/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	7/29/2015
NDA 207999-Orig1-New - Form 3674/NDA(2)					Approve Facility	Complete	12/9/2015

Data refreshed on: 12/11/15 12:15:11 AM