CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209500Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209500

Review # 1

Drug Name/Dosage Form	CAPLYTA (lumateperone) capsules
Strength	(b) (4) 42mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Intra-Cellular Therapies, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001	*06/05/2018*	*All CMC – Rolling Submission*
0002	*06/22/2018*	*Environmental Assessment*
0003	*08/09/2018*	*Process*
0004	*09/21/2018*	*Drug Substance/Facilities*
0009	*10/22/2018*	*Facilities*
0017	*11/16/2018*	*Facilities*
0023	*12/19/2018*	*Drug Substance/Facilities*
0031	*01/30/2019*	*Drug Product/Process/Facilities*
0033	*02/14/2019*	*Process*
0037	*03/08/2019*	*Biopharm*
0041	*04/03/2019*	*Biopharm*
0045	*05/09/2019*	*Environmental Assessment*
0048	*05/16/2019*	*Drug Product - Labeling*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Suong Tran
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee
Process	Zhong Li	Bogdan Kurtyka
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	Mei Ou	Ta-Chen Wu
Environmental Assessment	Ranaan Bloom	
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status
(b) (4)	Type III		(b) (4)	Adequate
	Type III			Adequate

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 79690		
(b) (4)		

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend approval from a product quality perspective based on the approval recommendations from each of the OPQ review team members.

II. Summary of Quality Assessments

A. Product Overview

The proposed drug product CAPLYTA™ (lumateperone) capsules has (b) (4) 42 mg. It is an immediate-release hard gelatin capsule for the treatment of schizophrenia. The labeled strengths are based on lumateperone free base. The capsules contain (b) (4) 60 mg of lumateperone tosylate, a new molecular entity (NME), and the following excipients: mannitol (b) (4), sodium croscarmellose (b) (4), talc (b) (4) and magnesium stearate (b) (4). (b) (4) The proposed commercial formulation is the same as that used for Phase II and Phase III. (b) (4)

The container closure system is a standard blister package used for solid oral dosage form (b) (4). Commercial presentation will be a 30-count carton (3 blisters per carton) and the physician sample (b) (4). Stability data support the proposed 24-month room temperature expiry period.

Proposed Indication(s) including Intended Patient Population	Treatment of schizophrenia
Duration of Treatment	Chronic
Maximum Daily Dose	42 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: The drug substance lumateperone tosylate is a new molecular entity (NME). It is slightly soluble in water - 1 mg/ml at pH 1 and 0.3 mg/ml at pH 7. One polymorphic form was identified, and amorphous material could be produced from a methanol/water mixture. The absolute/relative stereochemistry and structure was

confirmed by single crystal x-ray analysis. The nonclinical reviewer was forwarded the justification for impurity control submitted by the firm to the CMC section and no concerns were communicated back. Potentially (b) (4) are controlled at drug substance release and on stability.

The starting material designation was a review issue and the applicant agreed to designate (b) (4) as regulatory starting materials. The drug substance is (b) (4).

Batch analysis data for three primary (pilot) and the first three commercial-scale batches were comparable and met specification. The data support the proposed (b) (4) retest period (b) (4).

Drug Product: The drug product is formulated as immediate-release capsules in (b) (4) 42 mg. The labeled strengths are based on lumateperone free base. The capsules contain (b) (4) 60 mg of lumateperone tosylate and the following excipients: mannitol (b) (4), sodium croscarmellose (b) (4), talc (b) (4) and magnesium stearate (b) (4). Except for the capsule shell and the imprint ink, all the excipients are compendial grade. (b) (4). The proposed commercial formulation is the same as that used for Phase II and Phase III. (b) (4) The proposed drug product specification was found adequate to control the quality of the capsules. The acceptance criteria for the attributes are in accordance with the appropriate ICH guidances and USP monographs. The lack of chiral purity and elemental impurities tests in the drug product specification was adequately justified. The noncompendial methods used for testing the drug product were adequately validated. Batch data for the primary stability batches show that they consistently met the specification.

The container closure system is a standard blister package used for solid oral dosage form (b) (4). Commercial presentation will be a 30-count carton (3 blisters per carton) and the physician sample (b) (4). There are minor differences between the primary packaging components used in the primary stability batches and those proposed for the commercial batches. The stability batches were packaged in 2x7 blister configuration whereas the proposed commercial batches will have 2x5 blister configuration. Additionally, the foil layer for the commercial batches will have a paper peel-push layer, which is not present in the stability batches. These changes are not expected to affect the protective performance of the primary container closure system. 18 months of long-term data and six-months of accelerated stability data were provided for the primary stability batches. All the batches met the specification with no significant changes at the long-term storage condition. However, under the accelerated condition, the assay and dissolution decreased slightly by the six-month time point. Lumateperone capsules are not light sensitive. (b) (4). The data support the proposed 24-month room temperature expiry period.

Manufacturing: The drug product manufacturing employs (b) (4) [redacted] Following the review of the application's unsolicited amendment of 4/3/2019, there is no outstanding process risk that prevents approval of this application.

Facilities: No significant outstanding manufacturing risks that prevent approval of this application were found. Each of the manufacturing facilities were found to be acceptable based on their inspection histories, pre-approval inspections, and EIR reviews.

Biopharmaceutics: The drug substance exhibits some solubility in aqueous buffer from pH 1.0 to 7.4 and high permeability in Caco-2 cells. The permeation appears to be concentration-independent and primarily by passive diffusion. The dissolution method used a USP Apparatus II (Paddle) with helix sinker at 50 rpm, in 500mL of 0.1 N HCl, 37±0.5°C with an acceptance criterion of Q= (b) (4)% in 15 minutes. Due to the very rapid dissolution in the QC medium, the method has limited discriminating ability toward (b) (4) [redacted]
The Phase 3 pivotal clinical formulation is the same as commercial formulation; therefore, studies to bridge these two formulations were not needed. Since the dissolution for each of the strengths was comparable, bridging across the proposed strengths is considered established.

Environmental Assessment: Based on the expected low exposure concentrations, model results indicate a low environmental risk is expected due to approval of this application; therefore, the applicant's claim of categorical exclusion under 21 CFR 25.31(b) and statement of no extraordinary circumstance are acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	CAPLYTA (lumateperone)
Dosage form, route of administration	capsules, for oral use
Controlled drug substance symbol (if applicable)	n/a
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	n/a

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	n/a
Statement of being sterile (if applicable)	n/a
Pharmacological/ therapeutic class	The clinical review team has not yet determined the therapeutic class for this drug.
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	n/a
Other important chemical or physical properties (such as pKa or pH)	Adequate

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	n/a
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***

The Clinical Division has not yet determined the therapeutic class of this drug. This will be addressed during the labeling negotiation. Otherwise the Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	Adequate	Adequate
Net contents	Absent. But acceptable for small labels.	Adequate
"Rx only" displayed prominently on the main panel	Absent. But acceptable for small labels.	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	Adequate
Lot number and expiration date (21 CFR 201.17)	Adequate	Adequate
Storage conditions		Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available	n/a	n/a

Reviewer's Assessment of Labels: ***Adequate***

The container and carton labels meet the appropriate requirements from a CMC perspective.

List of Deficiencies: none

Overall Assessment and Recommendation: Adequate

Primary Reviewer: Mariappan Chelliah

Secondary Reviewer: Wendy Wilson-Lee

Mariappan Chelliah

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
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BIOPHARMACEUTICS

NDA: **209500 [505(b)(1)], NME**
Drug Product Name / Strength: CAPLYTA™ (lumateperone) Capsules, (b) (4) 42 mg
Route of Administration: Oral
Applicant Name: Intra-Cellular Therapies, Inc.
Proposed Indication: Treatment of schizophrenia.
Submission Dates:
06/05/2018 (Pre-submission of rolling application, CMC section)
08/09/2018 (CMC IR response)
09/27/2018 (NDA complete application)
01/30/2019 (Biopharmaceutics IR response)
03/08/2019 (Biopharmaceutics IR response)
04/03//2019 (CMC IR response)
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, CAPLYTA™ (lumateperone) Capsules, (b) (4) 42 mg, is an immediate-release hard gelatin capsule for oral administration for the treatment of schizophrenia.

For this 505(b)(1) NDA submission, the Biopharmaceutics Review focuses on the evaluation of (1) Solubility and Permeability, (2) the proposed dissolution method as a quality control (QC) test and acceptance criterion of the proposed drug product, (3) *in vitro* bridging between the pivotal clinical formulations and the commercial formulations, as well as across the proposed strengths. Note that the required information with regards to the dissolution method development, setting the dissolution acceptance criterion, and bridging between the pivotal clinical formulations and the to-be-marketed/commercial formulations have been conveyed to the Applicant (cross-referenced to IND 079690[1, 2, 3]). Biopharmaceutics review finding are summarized below.

[1] IND 079690, a Type B, End-of-Phase 2 Meeting on 10/21/2015, preliminary comments on 10/15/2015
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af803b689e&_afrRedirect=3003348568338002
[2] IND 079690, a Type B, pre-NDA Meeting on 11/04/2016, preliminary comments on 11/10/2016
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80410667&_afrRedirect=3003455849791180
[3] IND 079690, a Type B, pre-NDA Meeting on 03/07/2018, meeting minutes on 04/05/2018
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8048ecf1&_afrRedirect=3003546232821242

Solubility and Permeability:
The drug substance exhibited high solubility in aqueous buffer from pH 1.0 to 7.4. In addition, the drug substance showed characteristics of high permeability in Caco-2 cells based on transport study results and comparing to high permeability marker. The permeation appears to be concentration-independent and primarily by passive diffusion.

In Vitro Dissolution Testing of the Finished Product:
The Applicant proposed USP Apparatus II (Paddle) with helix sinker at 50 rpm, in 500 mL of 0.1 N HCl, 37±0.5°C, as the dissolution method for quality control (QC) and stability testing. The proposed dissolution method resulted in very rapid dissolution (b) (4) in 15 minutes) in the QC medium and has limited discriminating ability toward (b) (4) This Reviewer considers that the proposed dissolution method is acceptable and adequate to serve as a QC test for the proposed drug product for batch release and stability testing, considering (i) high solubility and high permeability of the drug substance, and (ii) very rapid and consistent dissolution behavior of the drug product under QC medium and different dissolution conditions.

Dissolution Acceptance Criterion:
The originally proposed dissolution acceptance criterion for the proposed CAPLYTA™ (lumateperone) Capsules is "Q= (b) (4)% in (b) (4) minutes". The Applicant has accepted the recommendation by the Division of Biopharmaceutics during the review cycle for a tighter dissolution acceptance criterion of "Q= (b) (4)% in 15 minutes", based on the totality of the data submitted, including the "very rapid" dissolution, (b) (4) in 15 minutes, in the QC medium.

Formulation Bridging:
The Phase 3 pivotal clinical formulation is the same as commercial formulation; therefore, studies to bridge these two formulations are not needed. Since dissolution profile data are comparable across the proposed all strengths of the proposed capsule formulations, bridging across the proposed strengths are considered established.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 209500 for the CAPLYTA™ (lumateperone) Capsules, (b) (4) 42 mg, is recommended for **APPROVAL**.

The approved *in vitro* dissolution method and acceptance criterion for the proposed drug product are as follows:

USP Apparatus	II (Paddle) with helix sinker
Rotation Speed	50 rpm
Medium and Volume	500 mL of 0.1 N HCl
Temperature	37 ± 0.5°C
Acceptance Criterion	Q (b) (4)% in 15 minutes

BIOPHARMACEUTICS REVIEW

1. Drug Substance Solubility and Permeability

Solubility:
Based on the study results from Study 15INTRP1R3GLPS323[4], drug substance shows high solubility in aqueous buffer from pH 1.0 to 7.4 (Table 1) and characteristics of high permeability in Caco-2 cells (Tables 2 and 3).

Table 1: The solubility of lumateperone tosylate salt in aqueous buffer

pH	Buffer	Measured Concentration (nM)	Measured Concentration (mg/mL)	Mean (mg/mL)	SD (mg/mL)	CV (%)	Volume to Dissolve HDS (mL)[a]
1.0	HCl	1860000	1.05	1.03	0.0507	4.92	< 58.2*
		1800000	1.02				
		1710000	0.97				
		1920000	1.09				
3.0	Acid phthalate	1400000	0.79	0.791	0.0385	4.87	< 75.9*
		1330000	0.752				
		1490000	0.843				
		1370000	0.78				
5.0	Neutralized phthalate	1380000	0.78	0.728	0.0356	4.89	< 82.4*
		1240000	0.70				
		1260000	0.713				
		1270000	0.718				
6.8	Phosphate	930000	0.526	0.649	0.0993	15.3	92.4
		1330000	0.752				
		1090000	0.617				
		1240000	0.701				
7.4	Phosphate	615000	0.348	0.310	0.0282	9.09	194
		498000	0.282				
		549000	0.311				
		527000	0.298				

SD: standard deviation; CV: coefficient of variation (SD/mean*100); HDS: highest dose strength
[a] Volume to dissolve HDS (mL) = HDS (mg) / mean measured dissolved concentration (mg/mL).
* The value is reported as < the calculated volume because the solution was clear at the end of the incubation; the true solubility is higher than the reported value in each case.

Permeability:
In vitro Caco-2 cell monolayers model was used to evaluate the permeability of drug substance. The reported unidirectional and bidirectional permeability data (Tables 2 and 3) showed that: (a) lumateperone has concentration-independent permeability [e.g., 0.01, 0.1, and 1 times the highest dose strength (60 mg of lumateperone tosylate salt) dissolved in 250 mL of aqueous medium, which equals 4.24, 42.4 µM, and 424 µM]; (b) lumateperone (at all three concentrations tested) has higher permeability than minoxidil (the high permeability reference drug) and atenolol (the moderate/low permeability as well as Caco-2 monolayer integrity reference drug); (c) lumateperone is mediated by passive transport mechanism based on efflux ratios and the lack of concentration-dependence of permeability; (d) lumateperone was stable for the duration of the

[4] M.3.2.P.2 of NDA 209500: Application 209500 - Sequence 0001 - Pharmaceutical Development

permeability assay as reflected by mean recovery being greater than 85% at all three concentrations.

The Applicant did not submit any formal BCS designation request. Although the in vitro permeability study was not conducted based on requirements described in the FDA's BCS guidance (*Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, December 2017*), for exampling, using twenty model drugs, it is this Reviewer's view that data suggest the high permeability characteristics of lumateperone.

Table 2: Unidirectional (A-to-B) permeability of lumateperone (ITI-007) and reference drugs

Nominal ITI-007 Dosing Concentration		**4.24 µM**	**42.4 µM**	**424 µM**
ITI-007	P_{app} (10^{-6} cm/s)	24.3 ± 1.07	38.4 ± 0.449[a]	40.6 ± 3.32
	Recovery (%)	75.2 ± 6.18	81.2 ± 3.51	91.9 ± 4.43
	Mass Balance (%)	104 ± 4.78	93.9 ± 4.20	103 ± 3.41
Minoxidil (10 µM)	P_{app} (10^{-6} cm/s)	3.24 ± 0.0902	3.75 ± 0.417	5.92 ± 0.305
	Recovery (%)	89.6 ± 6.44	93.1 ± 7.44	115± 0.562
Atenolol (100 µM)	P_{app} (10^{-6} cm/s)	0.316 ± 0.220	0.191 ± 0.0253	0.217 ± 0.0362
	Recovery (%)	83.8 ± 7.23	92.2 ± 6.03	98.9 ± 6.13

The results are presented as mean ± standard deviation (SD); n=4 for P_{app} and recovery, n=3 for mass balance (see Table A19, Table A20, and Table A21).
[a] One replicate was excluded as a statistical outlier; n=3 for P_{app} only.

Table 3: Bidirectional permeability of lumateperone (ITI-007)

Parameter	**Direction**	**Nominal ITI-007 Dosing Concentration**		
		4.24 µM	**42.4 µM**	**424 µM**
P_{app} (10^{-6} cm/s)	**A-to-B**	23.6 ± 2.34	33.6 ± 2.57	39.6 ± 5.13
Recovery (%)		68.4 ± 4.00	75.7 ± 1.94	82.0 ± 1.26
Mass Balance (%)		127 ± 3.54	97.4 ± 3.54	90.7 ± 0.895
P_{app} (10^{-6} cm/s)	**B-to-A**	23.0 ± 2.46	29.3 ± 5.03	32.3 ± 2.08
Recovery (%)		76.9 ± 3.35	81.3 ± 5.18	81.0 ± 3.70
Mass Balance (%)		82.5 ± 1.59	86.9 ± 4.37	81.1 ± 4.97
Efflux Ratio*		0.975	0.873	0.815

The results are presented as mean ± standard deviation (SD); n=6 (P_{app} and recovery) or n=3 (mass balance).
* Efflux ratios were calculated using the mean A-to-B and B-to-A P_{app} values.

2. In Vitro Dissolution Method

The proposed dissolution QC method is presented as follows:

USP Apparatus	II (paddle) with helix sinker
Rotation Speed	50 rpm
Medium and Volume	500 mL of 0.1 N HCl
Temperature	37°C ± 0.5°C

The following conditions were evaluated during the dissolution method development:

(b) (4)

[redacted]

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Note that the drug substance is highly soluble and highly permeable, and the proposed drug product showed consistently very rapid dissolution behavior under various conditions. Therefore, although the proposed dissolution method is lack of adequate discriminating ability toward the tested critical parameters/attributes, this Reviewer considers it acceptable that the proposed dissolution method (USP apparatus II paddle with helix sinker, 50 rpm, 500 mL of 0.1 N HCl) is adequate to serve as a QC test for the proposed drug product.

Reviewer's Comment:
The proposed drug product cannot dissolve more than (b) (4) buffer (Table 4), i.e., not having rapid dissolution in multi-media, to meet the criterion described in FDA's BCS Guidance (*December 2017*) as a BCS Class I drug product and for BCS-based biowaiver purpose.

3. *In Vitro* Dissolution Data and Acceptance Criterion

Dissolution profiles of nine (9) registration batches are presented in Figure 5, while the detailed data are presented in **Appendix 1**. The proposed dissolution acceptance criterion for the proposed CAPLYTATM (lumateperone) Capsules is "Q= (b) (4)% in (b) (4) minutes".

(b) (4)

The dissolution data of all registration batches under various stability conditions (long-term 25°C/60% RH and accelerated 40°C/75% RH) demonstrated that almost all batches have very rapid and consistent dissolution behavior (**Appendix 1**). The dissolution data under long-term and accelerated stability conditions showed the complete (more than 90%) and consistent/plateaued dissolution from 15 to 45 minutes. (b) (4)

(b) (4)

Since all registration batches showed very rapid dissolution ((b) (4) in 15 minutes, presented in **Figure 5**), proposed drug products across all strengths are considered to have similar dissolution profiles so that the similarity factor (*f2*) calculation is not necessary.

The provided dissolution data support a tighter dissolution acceptance criterion of "Q= (b) (4) % in 15 minutes", which was conveyed to the Applicant in Biopharmaceutics 2nd IR dated 03/04/2019 (**Appendix 2**). In the response dated on 03/08/2019, the Applicant agreed to the FDA's recommendation. In the response dated on 04/03/2019, the Applicant re ed the dissolution acceptance criterion from the originally proposed "*Q= (b) (4) % in (b) (4) minutes*" to the recommended "*Q= (b) (4) % in 15 minutes*" and updated the relevant sections accordingly.

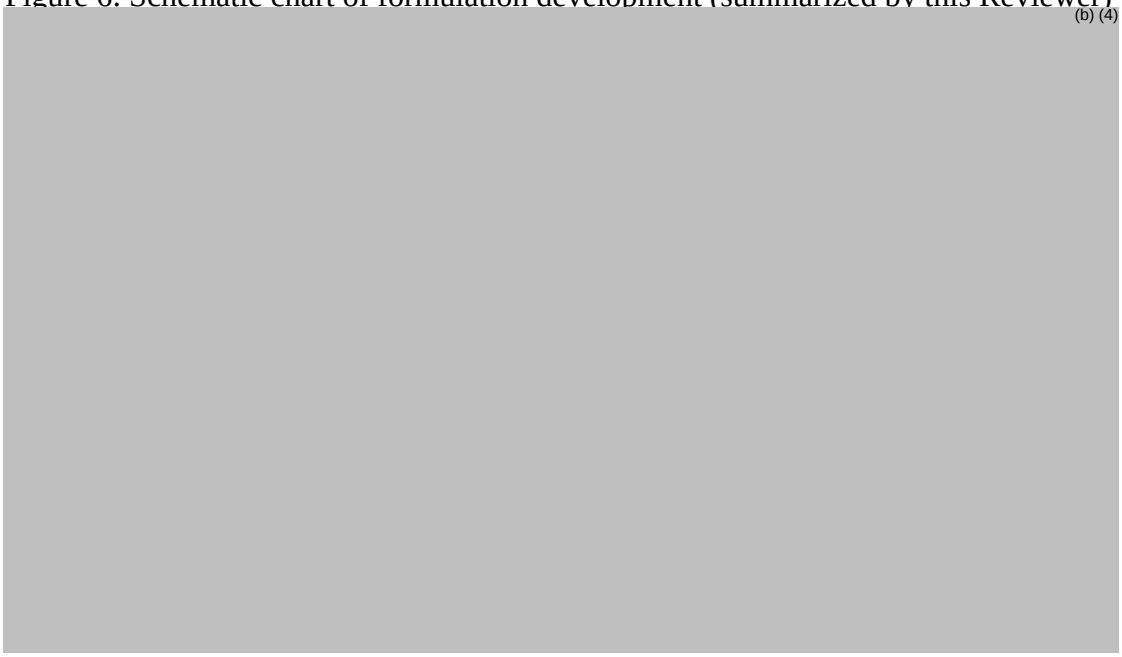
This Reviewer considers that the dissolution method and acceptance criterion (USP apparatus II paddle with helix sinker, 50 rpm, 500 mL of 0.1 N HCl, Q= (b) (4) % in 15 minutes) are acceptable as a QC test for the proposed drug product at release and on stability.

4. Formulation Bridging

In vivo:
Per the Applicant, early clinical studies employed oral solution to allow dosing flexibility. (b) (4) capsule formulation (14, 28, and 42 mg) was studied in clinical trials (b) (4) the capsule formulation did not change during the pharmaceutical development. In addition, (b) (4) capsules used in pivotal clinical studies are the same as the proposed commercial formulation/strengths. Therefore, no further BA/BE study or biowaiver request is needed.

Note that the *in vivo* PK data supporting the formulation bridging (b) (4) is under the purview of the Office of Clinical Pharmacology (OCP).

Figure 6: Schematic chart of formulation development (summarized by this Reviewer)



In vitro:

This Reviewer considered that (i) no additional *in vitro* bridging between pivotal clinical formulation and commercial formulation is needed, and (ii) the *in vitro* bridging (b) (4) capsules is established, thus no additional *in vitro* bridging studies are needed, based on the following information/data:

- As profiles presented in Figure 5 above, (b) (4) capsules have very rapid and comparable dissolution profiles/behavior.
- The manufacturing site for the proposed drug product has no change.
- The batch size increase from clinical capsule formulations to registration/commercial capsule formulations is less than (b) (4) difference.
- The batch size between registration batches and commercial bathes is same.
- The manufacturing process between clinical capsule formulations and registration/commercial capsule formulations (b) (4) is minor, which is considered within Level 1 change per FDA SUPAC-IR guidance.

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Appendix 2
Biopharmaceutics Information Requests

1st IR (conveyed on 01/18/2019):

(b) (4)

2nd IR (conveyed on 03/04/2019):

Based on the totality of dissolution data, FDA recommends a dissolution acceptance criterion of "Q= (b) (4)% in 15 minutes" for your proposed Lumateperone Capsules, (b) (4) 42 mg, for batch release and stability testing. Note that the dissolution acceptance criterion is set based on n=12, therefore, sometimes stage 2 and occasional stage 3 testing may be needed. Update the dissolution acceptance criterion in the drug product release and stability specifications and other relevant sections of your NDA accordingly. In addition, all batches are expected to meet the revised dissolution acceptance criterion in your stability program through your proposed expiry period. If dissolution failures are observed on stability, the failures should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Mei Ou

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Ta-Chen Wu

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ENVIRONMENTAL REVIEW

1. Regional Information
1.12.14: Environmental Analysis

Application: NDA 209500

Drug product: Caplyta

API: Lumateperone Tosylate

Indication: Treatment of schizophrenia

Mode of action: Modulator of serotonin, dopamine, and glutamate neurotransmission. The mechanism of action of lumateperone in schizophrenia is unclear. The efficacy of lumateperone could be mediated through a combination of serotonin, dopamine, and glutamate modulation. Lumateperone is a potent serotonin 5-HT2A receptor antagonist, a dopamine D2 receptor pre-synaptic partial agonist and dopamine D1 receptor-dependent modulator of glutamate, and a serotonin reuptake inhibitor.

Claim of Categorical Exclusion: In the 6/22/2018 and 5/9/2019 submissions, under section 1.12.14, the applicant has revised it's EIC calculations and claim of categorical exclusion in response to IRs from the EA Team. The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of no extraordinary circumstances under 21 CFR 25.21. Minimal supporting information is provided. An estimated environmental concentration is calculated (see below). No environmental effects data are provided.

Environmental Exposure: Using the (b) (4) (42 mg) as a worst-case scenario, the trade and total dosage unit projections for year five correspond to (b) (4) kg per year, respectively, of the active moiety, ITI-007 free base.

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: Adequate

Modeled and available information indicates a low potential for lumateperone tosylate interaction with estrogen and androgen receptors. Modeled aquatic toxicity results show a large margin between exposure and effects. The Fish Plasma Model output indicates that additional studies may be required. However based on the expected low exposure concentrations, model results indicate a low environmental risk is expected due to approval of this application.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.

Primary Environmental Reviewer Name and Date: Raanan A. Bloom, Ph.D.

Secondary Reviewer Name and Date: Scott Furness, Ph.D.

Raanan Bloom

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Date: 5/21/2019 11:02:36AM
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Michael Furness

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David Claffey

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