CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210793Orig1s000
207318Orig1s003

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210793
Review 01

Drug Name/Dosage Form	Pimavanserin Capsules
Strength	34 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ACADIA Pharmaceuticals Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*31-AUG-2017*
Amendment	*03-OCT-2017*
Amendment	*25-OCT-2017*
Amendment	*31-JAN-2018*
Amendment	*09-MAR-2018*
Amendment	*14-MAR-2018*
Amendment	*20-MAR-2018*
Amendment	*10-APR-2018*

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Rao Kambhampati/Wendy Wilson-Lee	ONDP
Drug Product	Rao Kambhampati/Wendy Wilson-Lee	ONDP
Process	Tianhong Zhou/Nallaperumal Chidambaram	OPF
Microbiology	Tianhong Zhou/ Nallaperumal Chidambaram	OPF
Facility	Steve Hertz/Ruth Moore	OPF
Biopharmaceutics	Joan Zhao/Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Teshara Bouie	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP
Environmental Analysis	Rao Kambhampati/Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	III		(b) (4)	Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	III			Adequate	n/a	Sufficient information in NDA
	IV			Adequate	n/a	Sufficient information in NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	207318	Pimavanserin Tablets
IND	68384	Pimavanserin

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

*OPQ recommends **APPROVAL** of NDA 210793 for pimavanserin capsules, 34 mg.*

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Treatment of hallucinations and delusions associated with Parkinson's disease psychosis***
Duration of Treatment	***Chronic***
Maximum Daily Dose	***34 mg***
Alternative Methods of Administration	***None***

FDA approved pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis under NDA 210793 in April 2016. Pimavanserin received breakthrough therapy designation in 2014. The approved product is available as a 17 mg tablet and requires dosing of two tablets once daily. The current NDA is for a new 34 mg capsule that achieves the recommended daily dose in one capsule. This offers an improvement in ease of use for the indicated patient population – mainly elderly patients often with physical or mental impairments that may impact the ability to administer or swallow two tablets. The new dosage form is developed as a (b) (4) immediate release capsule based on the formulation and control strategy for the approved tablet. The Applicant requested priority review of the new dosage form.

Given prior experience with pimavanserin in a solid oral dosage form, this is considered low risk drug product. Pimavanserin is both highly soluble and highly permeable, the formulation is simple with a high drug load, and a similar control strategy and packaging compared to the approved product is proposed. Key product quality review issues included establishing an appropriate drug product expiry for the new dosage form and impact of manufacturing on drug product performance and stability, including solid state. The approved tablet product manufacturing process is based on (b) (4). The proposed capsule manufacturing process is based on (b) (4)

B. Quality Assessment Overview

The Applicant did not propose any changes to the drug substance compared to that used in the already approved tablet drug product. All CMC information for the drug substance is cross-referenced to the approved NDA (NDA 207318).

The components and composition include compendial excipients except capsule shell, which is made of compendial excipients or FDC act listed colorants. The drug product specifications including the analytical methods are acceptable. Batch analysis data demonstrated that the drug product can be manufactured with consistent quality and purity. The non-compendial analytical method validation reports are adequate. The proposed container and closure system is commonly used in the packaging of solid oral dosage forms. **Adequate drug product stability data were provided for three registration batches to support 24 months expiration dating period at the recommended storage conditions.**

The manufacturing process of pimavanserin 34 mg capsules involves (b) (4)

(b) (4)

(b) (4)

(b) (4)

All facilities in NDA 210793 are acceptable for the listed responsibilities. The claim of categorical exclusion based on 21 CFR 25.31(b) and 25.15(d) is acceptable.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criterion, as well as formulation bridging in product development. The Applicant did not submit an official BCS designation request with supporting information/data in the NDA for the FDA's review. However, the Applicant notes that pimavanserin tartrate behaves like a BCS Class (b) (4) compound based on its (b) (4) solubility and permeability characteristics.

Based on the provided, the proposed dissolution method is accepted for the QC dissolution testing of the proposed drug product. The selections of the dissolution conditions (e.g., apparatus, medium, rotation speed) were adequately justified. The discriminating ability of the dissolution method could not be demonstrated due to the fast dissolution of the drug product. This is acceptable, considering the product is for immediate release and is designed to dissolve rapidly. The Applicant proposed the dissolution acceptance criterion of Q (b) (4) % at (b) (4) minutes; however, we recommended a dissolution acceptance criterion of Q= (b) (4) % (Q) at 20 minutes for the proposed drug product. The recommended acceptance criterion was conveyed to the Applicant during the review cycle and was agreed upon and adopted by the Applicant.

No bridging is needed as the proposed commercial formulation was used in the BE study ACP-103-043. The proposed commercial scale up (from (b) (4) capsules per batch) is not expected to impact drug release. The Applicant is seeking approval for only one dosage strength (34 mg) and thus biowaiver request is not applicable for the application.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment I)

ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 210793 Pimavanserin Capsules, 34 mg

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Assay	Formulation Raw materials Container closure Process/Scale/Equipment Site	Low	(b) (4)	**Acceptable**	
Solid State		Low		**Acceptable**	Changes to manufacturing should be evaluated for impact on polymorphism
Content Uniformity		Low		**Acceptable**	(b) (4)
Microbial Limits		Low		**Acceptable**	
Dissolution		Low		**Acceptable**	
Water Content		Low		**Acceptable**	
Particle Size		Low		**Acceptable**	

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LABELING Review of NDA 210793

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

Note: The package insert includes information for 34 mg capsule and 10 mg tablet. Since the NDA 210793 involves capsules only, therefore, information related to capsules only is included in this review.

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	Nuplazid® (pimavanserin)
Dosage form, route of administration	Capsule, for oral use
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: 34 mg

2. *Section 2 Dosage and Administration*

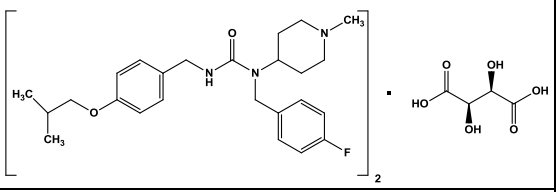
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Not applicable

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	Capsule
Strengths: in metric system	34 mg
Active moiety expression of strength with equivalence statement (if applicable)	34 mg strength capsules. Note: Usually the equivalency statement is not included in this section
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	• 34 mg strength capsules. The capsules are opaque white and light green with "PIMA" and "34" printed in black.

4. *Section 11 Description*

APPEARS THIS WAY ON ORIGINAL

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	Nuplazid® (pimavanserin)
Dosage form and route of administration	Capsule, oral
Active moiety expression of strength with equivalence statement (if applicable)	Each capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base.
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>)	Not applicable
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Atypical antipsychotic
Chemical name, structural formula, molecular weight	Urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N*'-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). 
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Not applicable

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	34 mg Capsule
Available units (e.g., bottles of 100 tablets)	Bottle of 30
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	34 mg Capsule: Opaque white and light green capsule with "PIMA" and "34" printed in black.
Special handling (e.g., protect from light)	Not applicable
Storage conditions	34 mg Capsule: Store at 20°C to 25°C (68ºF to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. To prevent potential capsule color fading, protect from light.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Acadia Pharmaceuticals Inc., San Diego, CA 92130 USA

Reviewer's Assessment of Package Insert: ***Adequate***
The latest version contained all the required information and it complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***
   Commercial Bottle Label:

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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))	Yes	Yes
Dosage strength	Yes	Yes
Net contents		
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)		Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)		
Name of manufacturer/distributor	Yes	Yes
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate***
The latest versions of the bottle label, Tri-fold sample label of the blister pack, and the carton label (of the Tri-fold blister pack) contained all the required CMC related information.

List of Deficiencies: None

Overall Assessment and Recommendation: Acceptable. Recommended for approval.

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 5/3/2018

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

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: 210793-ORIG-1 [505(b)(1)]

Drug Product Name / Strength: Pimavanserin (NUPLAZID) Capsules, 34 mg

Route of Administration: Oral

Applicant Name: ACADIA Pharmaceuticals Inc.

Review Summary:
NUPLAZID (pimavanserin) Capsules, 34 mg is proposed for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. The application crosses-references NDA 207318 for NUPLAZID® (pimavanserin) tablets, 17 mg, which was approved on April 29, 2016. The recommended daily dose for NUPLAZID® tablets is 34 mg, i.e., two 17 mg tablets once daily, and the proposed Pimavanserin Capsules 34 mg will allow patients to take a single capsule once daily.

The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting proposed dissolution method and acceptance criterion, as well as formulation bridging in product development.

In Vitro Dissolution Method and Acceptance Criterion:
The Applicant adopted the approved dissolution method for NUPLAZI® Pimavanserin Tablets 17 mg for the proposed Pimavanserin Capsules, 34 mg. Based on the provided dissolution data, the following dissolution methods and revised acceptance criterion are acceptable and agreed upon for release and on stability:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP I (Basket)	100 RPM	0.1 N HCl	900 mL	NLT (b)(4)% (Q) at 20 minutes

Formulation Bridging:
Formulation bridging is not needed because the proposed commercial Pimavanserin Capsules have the same formulation, image, and manufacturing site as the Biobatch 16JM-294 used in BE study (ACP-103-043).

RECOMMENDATION:
Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 210793 for Pimavanserin Capsules, 34 mg, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Joan Zhao, PhD 04/16/2018
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Ta-Chen Wu, PhD 05/08/2018
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	08/31/2017
12 Month Stability Results	10/3/2017
IR Response	4/10/2018

I. BCS Designation

The Applicant did not submit an official BCS designation request with supporting information/data in the NDA for the FDA's review. However, the Applicant notes that Pimavanserin tartrate behaves like a BCS Class (b) (4) compound based on its (b) (4) solubility and permeability characteristics.

Drug Substance Solubility:

The drug substance, Pimavanserin Tartrate, has a pKa of 8.6±0.1. Pimavanserin is freely soluble in the pH range (b) (4) as summarized in table below:

Table 1. Solubility of Pimavanserin Tartrate

Media	Solubility[a]
Water	Freely soluble
(b) (4)	

a Solubility description follows the current USP.

b (b) (4)

c

Permeability:

The Applicant reported (b) (4) permeability of pimavanserin tartrate based on results of Human Mass Balance Study ACP-103-016 (pimavanserin is (b) (4) absorbed from the gastrointestinal tract) and *In Vitro* Permeability Studies 7ACADP9R3 and 8ACADP3R2((b) (4) permeability across the Caco-2 cell monolayers).

II. Formulation:

Table 2 summarizes the qualitative and quantitative composition of the proposed immediate-release oral Pimavanserin 34-mg capsules.

Table 2. Composition of Pimavanserin 34 mg Capsules

Component	Function	Quality Standard	Quantity Per Capsule	
			mg/Capsule	% w/w
Pimavanserin tartrate	Active ingredient	In-house	40.0[a]	40.0%
Microcrystalline cellulose	(b) (4)	NF		(b) (4)
Magnesium stearate		NF		
(b) (4)				
HPMC capsule shell	(b) (4)	In-house		
Total				

NF = National Formulary; NA = Not applicable

[a] 40 mg of pimavanserin tartrate salt is equivalent to 34 mg of pimavanserin free base.

[b] Typical average weight of an empty capsule shell is indicated. HPMC capsule shells are composed of hypromellose (HPMC), titanium dioxide, yellow iron oxide, FD&C blue #1, and black iron oxide.

(b) (4)

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(b) (4)

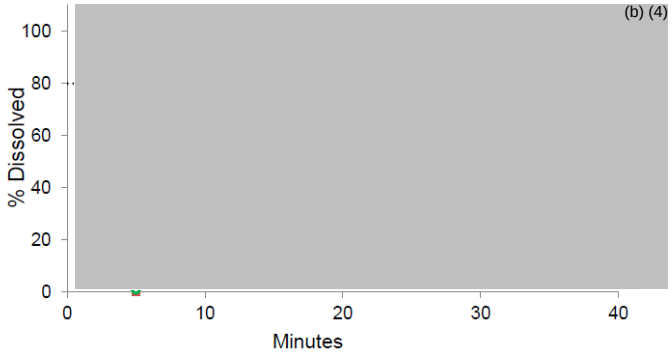
Reviewer's Comment:
Based on the provided, the proposed dissolution method is accepted for the QC dissolution testing of the proposed drug product. The selections of the dissolution conditions (e.g., apparatus, medium, rotation speed) were adequately justified.

The discriminating ability of the dissolution method could not be demonstrated due to the fast dissolution of the drug product. This is acceptable, considering the product is for immediate release and is designed to dissolve rapidly.

Dissolution Acceptance Criteria:
The Applicant proposed the dissolution acceptance criterion of Q=(b) (4)% at (b) (4)minutes for the current proposed dissolution method. Based on the dissolution data of the Biobatch 16JM-294 (Appendix I) as well as the registration batches (16JM-292 and 16JM-293)[2,3], also as illustrated in Figure 6, this Reviewer recommended a dissolution acceptance criterion of Q (b) (4)% (Q) at 20 minutes for the proposed drug product. The recommended acceptance criterion was conveyed to the Applicant during the review cycle and was agreed upon (see Appendix III).

[2] Appendix II
[3] \\cdsesub1\evsprod\nda210793\0001\m3\32-body-data\32p-drug-prod\pimavanserin-capsule\32p2-pharm-dev\pdr-17-061-02.pdf

Figure 6. Pimavanserin Capsules, 34 mg, Registration Batches Dissolution Profiles in 900 mL 0.1 N HCl (n=12)



IV. Bridging of Formulations:

No bridging is needed as the proposed commercial formulation was used in the BE study ACP-103-043. The proposed commercial scale up (from (b) (4) capsules per batch) is not expected to impact drug release.

V. Biowaiver Request:

The Applicant is seeking approval for only one dosage strength (34 mg) and thus biowaiver request is not applicable for the application.

R Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

APPENDIX I: Dissolution Profiles of Biobatch 16JM-294 Using the Proposed Dissolution Method

Table A-1 Dissolution of Pimavanserin 34 mg Capsules Lot 16JM-294 in 0.1N HCl, 900 mL 100 RPM

% Dissolved							
Run #1							
Vessel ID	5 min	10 min	15 min	20 min	25 min	30 min	40 min
A1	0	23	67	94	94	94	92
A2	0	37	82	88	89	85	88
A3	0	32	86	88	87	86	83
A4	0	40	84	84	82	83	79
A5	0	37	85	92	92	93	90
A6	0	51	86	92	92	92	89
Run #2							
B1	0	14	95	96	96	96	96
B2	0	30	102	103	103	103	102
B3	0	44	67	91	87	93	91
B4	0	34	70	98	99	99	99
B5	2	63	92	95	95	95	94
B6	0	31	70	86	94	94	93
Mean	0	36	82	92	93	93	91
St. Dev.	0.6	12.7	11.5	5.4	5.7	5.8	6.4

3 month (long term)

Table A-9 Dissolution of Pimavanserin 34 mg Capsules Lot 16JM-294 in (b) (4) Blisters in 0.1N HCl, 900 mL 100 RPM Stability Sample 3 month at 25°C/60%RH

% Dissolved				
Vessel ID	10 min	15 min	30 min	40 min
V1	0	85	101	101
V2	70	98	101	101
V3	75	98	101	101
V4	54	97	104	104
V5	62	88	100	100
V6	55	78	100	100
Mean	53	91	101	101
St. Dev	27.1	8.3	1.5	1.5

9 month (long term)

Table A-6 Dissolution of Pimavanserin 34 mg Capsules Lot 16JM-294 in 30 count HDPE Bottles in 0.1N HCl, 900 mL 100 RPM Stability Sample 9 month at 25°C/60%RH

% Dissolved				
Vessel ID	10 min	15 min	30 min	40 min
V1	61	89	97	97
V2	25	96	99	100
V3	8	55	101	101
V4	81	94	99	99
V5	49	92	101	101
V6	65	95	98	98
Mean	48	87	99	99
St. Dev	27.1	15.8	1.6	1.6

APPENDIX II: Pimavanserin Capsules 34 mg Registration Batches

Manufacturing				Packaging		Use
Bulk Batch No.	Mfg. Date	Batch Size (units/batch)	Drug Substance Batch No.	Package Configuration	Pkg. Batch No.	
16JM-292	Aug 2016	(b) (4)	14460694	30ct Bottle	3068068-SB	Registration Stability
				(b) (4) Blisters	3068978	
16JM-293	Aug 2016		14460694	30ct Bottle	3068510-SB	Registration Stability
				(b) (4) Blisters	3069056	
16JM-294	Aug 2016		14460694	30ct Bottle	3068527-SB	Registration Stability, Bioequivalence Study ACP-103-043
				(b) (4) Blisters	3069057	
16JM-403	Dec 2016		14460694	30ct Bottle	3108951-SB	Scale-up
				(b) (4) Blisters	3109439-SB	

APPENDIX III: *Biopharmaceutics Information Request dated April 3, 2018 and the Applicant's Response on April 10, 2018*

Biopharmaceutics Information Request Comments:

1. *Based on the dissolution data provided for your proposed Pimavanserin Capsules, 34 mg, FDA recommends the dissolution acceptance criterion of NLT (b)(4)% (Q) at 20 minutes.*

2. *Be aware that setting of the dissolution acceptance criterion are based on stage 2 testing (n=12) and therefore sometimes stage 2 testing and occasional stage 3 testing maybe needed.*

3. *Revise the finished product QC specifications and other pertinent NDA documents accordingly.*

Applicant's Response to Biopharmaceutics-IR Comment 1:
ACADIA agrees to the FDA recommendation to change the dissolution acceptance criterion to NLT (b)(4)% (Q) at 20 minutes.

Applicant's Response to Biopharmaceutics-IR Comment 2:
ACADIA acknowledges that Stage 2, and potentially Stage 3 testing, may be required.

Applicant's Response to Biopharmaceutics-IR Comment 3:
ACADIA is providing the following sections with the revised dissolution acceptance criterion.

- Section 3.2.P.5.1 Specifications.
- Section 3.2.P.5.2 Analytical Procedures.
- Section 3.2.P.5.6 Justification of Specification.

Reviewer Comment:
The Applicant's responses to all IR comments are satisfactory.

Zhuojun Zhao

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Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 5/08/2018 05:33:11PM
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Wendy
Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/21/2018 07:59:39PM
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