CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205739Orig1s000

CHEMISTRY REVIEW(S)

M E M O R A N D U M

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

DATE: October 15, 2015

FROM: Kasturi Srinivasachar, Ph.D., ATL NDA 205739, OPQ / ONDP / DNDAPI / Branch I

SUBJECT: Final Quality Recommendations for NDA 205739

This is an addendum to the Integrated Quality Assessment of NDA 205739 which listed two issues to be resolved before the NDA could be approved:
1) A satisfactory response to the pending issue of elemental impurities in the drug substance and xanthan gum including acceptance criteria, analytical procedures and validation reports;
2) An overall "Acceptable" recommendation from the facilities reviewer.

Issue 1) has been satisfactorily addressed as documented below in the reviews by Raymond Frankewich, Ph.D. and Mohan Sapru, Ph.D. for drug substance and drug product respectively.
Issue 2) has been satisfactorily addressed by the Overall Manufacturing Inspection Recommendation of "Approve" issued on Aug. 10, 2015.

NDA 205739 is recommended for Approval from the Quality standpoint.

Kasturi Srinivasachar, Ph.D.
Application Technical Lead for NDA 205739

Kasturi Srinivasachar -A

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NDA 205739: Evaluation of Applicant's Responses to Pending Drug Substance Deficiencies

This is the second CMC Review of NDA 205739 for Drug Substance. It includes an evaluation of responses to the applicant to the following issues, which are addressed as heading topics in the review below:

- Question no. 3 in MidCycle Information Request Letter (MCIR);
- CMC Information Requests no. 1. And 2 in Late Cycle Communication.

In this review the Integrated Quality Assessment of NDA 205739, which includes the initial review of the NDA for Drug Substance, is referred to as the IQA.

Question no. 3 in Mid-Cycle Information Request Letter (MCIR)

This question was worded as follows in the MCIR dated April 15, 2015:

Establish separate acceptance criteria in the Release Specification for RLY5016S drug substance for each of the Class (b) (4) *metals determined in the test for Elemental Impurities. These individual acceptance criteria should be consistent with the recommendations of ICH Q3D.*

The applicant provided responses to this question in their amendments dated May 5, May 19, June 19, and June 25. A summary of the responses and the applicant's resolution to the original question is provided below.

Amendment dated May 5

- It was demonstrated that the combined levels of As, (b) (4) in the daily dose of RLY5016S drug substance and xanthan gum (the only excipient) was less than (b) (4)% the daily PDE of these elements listed in Q3D. Therefore no limits were proposed for these elements in accordance with Q3D (see Q3D, pp. 8-9). This was documented in the Integrated Quality Assessment of NDA 205739. The calculation used to justify this decision is discussed further in the response to the amendment dated June 19 below.

- The applicant (Relypsa) committed to further examine the determination of (b) (4) Pb, (b) (4) as described in Option 2b in Q3D. The applicant stated that it would take action to improve the quantitation limit (LOQ) for analysis of (b) (4) Pb content in xanthan gum, and will validate the analytical methods and generate the data for (b) (4) content in xanthan gum and for (b) (4) content in RLY5016S. Relypsa stated that it will provide the Agency for a timeline for this work within two weeks.

Amendment dated May 19

- The applicant committed to the following timelines:

- Provide individual acceptance criteria in RLY5016S drug substance and the xanthan gum excipient, for [redacted] lead and [redacted] that are within the established PDEs by 19 June 2015. The acceptance criteria will be set based on analytical method development data and not data generated using validated methods; the results will be confirmed once the methods are validated.

- Provide established test procedures and final method validation reports for analysis of [redacted] content in RLY5016S and the content of Class [redacted] elemental impurities in xanthan gum, including [redacted] lead [redacted] by 04 September 2015. In addition, data for representative lots of RLY5016S and xanthan gum will be provided.

Amendment dated June 19

- Specification for RLY5016S drug substance was revised to include acceptance criteria for elemental impurities, specifically for [redacted] Pb, based on available data (provided further below). Revised sec. 3.2.S.4.1 is provided.

- Specification for xanthan gum was revised to include acceptance criteria for elemental impurities (provided further below). Revised sec. 3.2.P.4.1 is provided.

- Data supporting the acceptance criteria for elemental impurities in RLY5016S and xanthan gum was provided in this amendment.

- Calculation of Maximum Daily Exposure for [redacted] Pb, [redacted] from RLY5016 for Oral Suspension (drug product). Results of these calculations support the proposed acceptance criteria in RLY5016S and xanthan gum.

- Commitment to provide by 25 June 2015 a revised analytical procedure for determination of elemental impurities (content of arsenic, [redacted] lead, [redacted]) in RLY5016S provided in Section 3.2.S.4.2 Analytical Procedures [RLY5016S, [redacted]] to include additional details of the [redacted] that were part of the method as validated.

- Commitment to provide by 10 July 2015 revised sections 3.2.P.4.2 Analytical Procedures and 3.2.P.4.3 Validation of Analytical Procedures containing the analytical procedure and validation report for the determination of elemental impurities (content of arsenic, [redacted] lead, [redacted]) in the drug product [RLY5016, for Oral Suspension, [redacted]].

- Commitment to provide by 4 September 2015 revised sections 3.2.S.3.2 Impurities and 3.2.S.4.5 Justification of Specifications [RLY5016S, [redacted]] for the drug substance. For sec. S.3.2, the revision will include include elemental impurity data for representative lots of RLY5016S and xanthan gum generated with the validated methods that support the acceptance criteria proposed. For sec. S.4.5, the revision will include the new method for analysis of [redacted] content in

RLY5016S, new validation report with English translation, and method validation summary will as part of the justification for the elemental impurities specification. The method for analysis of (b) (4) content is not intended as a routine regulatory release method. Elemental impurities data from representative lots of drug substance obtained using validated methods will be included to support the specification justification.

- Commitment to provide by 4 September 2015 revised sections 3.2.P.4.4 Justification of Specifications, 3.2.P.5.5 Characterization of Impurities, and 3.2.P.5.6 Justification of Specifications [RLY5016, for Oral Suspension, (b) (4)] for the drug product. The revision will contain a revised description of the rationale for control of elemental impurities in xanthan gum (sec. P.4.4) and also elemental impurity data for representative lots of xanthan gum obtained using the validated method. It will also include (P.5.5 and P.5.6) a description and discussion of control of elemental impurities in RLY5016 for Oral Suspension.

- Statement that implementation of the revised elemental impurity specifications for drug substance and xanthan gum has been initiated. It is indicated that implementation will be complete before 04 September 2015. All commercial lots of RLY5016S and xanthan gum will be tested and must pass the implemented acceptance criteria prior to commercialization of RLY5016 for Oral Suspension.

Revisions to sections of this NDA describing the drug product (3.2.P sections) are evaluated in the CMC assessment of the drug product for NDA 205739.

Discussion of revised specification of RLY5016S drug substance in June 19, 2015 amendment

The rationale for the proposed specifications is based on ICH Q3D Option (b) (4) For RLY5016S, the proposed acceptance criteria are based on development data (provided in this amendment) for (b) (4) in three registration lots and three process validation lots (six lots total) of drug substance and data for (b) (4) Pb, (b) (4) included in the original response to FDA Question 3 (in the May 5, 2015 amendment). For xanthan gum, the proposed acceptance criteria are based on new development data obtained using an analytical procedure employing an ICP-MS for analysis of the content of all four elements in eight lots of xanthan gum.

The following table exhibits the exposure to (b) (4) Pb (b) (4) contributed by RLY5016S and xanthan gum in the maximum daily dose of RLY5016 for Oral Suspension based on the highest levels observed in the representative lots of xanthan gum and RLY5016S tested. Where the highest level observed is below the limit of quantitation, the limit of quantitation value is used in the calculation. Note: the maximum dose of RLY5016S is currently the equivalent of 25.2 g patiromer, the maximum dose of drug product having been changed during labeling negotiations (see discussion below).

Calculated Maximum Exposure to (b) (4) Lead, (b) (4) from RLY5016 for Oral Suspension

Element	RLY5016S (max. dose = (b) (4) day)		Xanthan Gum (max. dose = (b) (4) day)		Total Content of Elemental Impurity in Drug Product (micrograms/day[a])	PDE per ICH Q3D, December 2014 (micrograms/day)	% of PDE
	Max. Content Observed (micrograms/g)	Contribution (micrograms/day)	Max. Content Observed (micrograms/g)	Contribution (micrograms/day)			
Pb							(b) (4)

(b) (4) Pb = lead; PDE = permitted daily exposure

[a] Sum of contribution from maximum daily dose of RLY5016S and xanthan gum.

[b] Limit of quantitation of the test method. Maximum result obtained was below this value.

Since the levels of (b) (4) are below (b) (4)% of their PDE values (like As, (b) (4)) no limit is proposed for these metals.

The proposed acceptance criteria for (b) (4) Pb in RLY5016S are (b) (4) gram, respectively. Additionally, proposed acceptance criteria for (b) (4) Pb in xanthan gum are (b) (4) gram, respectively. Revised specification for RLY5016S drug substance is provided below. Revised specification for xanthan gum is discussed in the CMC assessment of the drug product for NDA 205739.

The maximum daily dose (MDD) of RLY5016S drug substance of (b) (4)/day is the result of a theoretical calculation of the weight of RLY5016S that results from a dose of patriomer (polymer) (b) (4) patiromer was the maximum dose used during development. However, the maximum daily dose of patiromer provided for in the labeling is 25.2 grams. This is relevant in the discussion of how the amount of (b) (4) Pb in each batch of RLY5016S will be calculated (see discussion below following the specification). The theoretical calculation of the MDD of RLY5016S as (b) (4) is provided as follows in the amendment dated May 5, 2015:

$$maximum\ daily\ dose = \text{(b) (4)}$$

Where:

- Dose of patiromer = (b) (4)
- (b) (4)
- (b) (4)
- (b) (4) upper specification limit for (b) (4) expressed as a percentage ((b) (4)%)

Revised Specification for Release of RLY5016S Drug Substance

The specification provided below is for release. It is referred to in the NDA as the "(b) (4) Specification" after the name of the drug substance manufacturer. The acceptance specification for

RLY5016S drug substance used by the drug product manufacturer (referred to as the "(b) (4) Specification") is (b) (4) Specification. It is noted in this amendment that the analytical procedures used by (b) (4) are different in the following ways:

- Regarding the test for (b) (4) and unspecified impurities, drug product manufacturer (b) (4) while drug substance manufacturer (b) (4) uses a (b) (4) curve (same procedure otherwise);
- (b) (4) use different instruments for the test for Particle Size.

(b) (4) Specification for RLY5016S

Test Attribute	Method Type	Acceptance Criteria
Appearance	Visual	Off-white to light brown powder
ID method 1: IR	FTIR	Conforms with reference spectrum of reference standard
ID method 2: Fluorine Content[a]	(b) (4)	
ID method 3: (b) (4)	IC	Retention time of the main peak in the sample chromatogram matches the retention time of the (b) (4) peak in the standard
(b) (4) Content[a]	IC	(b) (4)
Patiromer Anion Content	Calculation	
(b) (4) Content[a]	LC-RI	
Total Potassium Exchange Capacity[b]	IC	
Particle Size Distribution	Laser Diffraction	
(b) (4)	(b) (4)	
(b) (4)[a]	HS-GC-FID	NMT (b) (4) ppm
Largest Single Unspecified Impurity[a]	HS-GC-FID	NMT wt%
Total Unspecified Impurities[a]		NMT wt%
Extractable Polymeric Impurities[a]	SEC-RI	NMT ppm
(b) (4)[a]	IC	NMT ppm
Elemental Impurities[c]	ICP-MS	
(b) (4)		NMT (b) (4) ppm
Lead (Pb)		NMT ppm
Fluoride[a]	F-ISE	NMT (b) (4) ppm
Microbial Enumeration Tests:		
Total Aerobic Microbial Count	USP <61> or Ph. Eur. 2.6.12	NMT (b) (4)
Total Combined Yeasts and Molds Count		NMT
Specified Microorganisms:		
Escherichia coli	USP <62> or Ph. Eur. 2.6.13	Absent

F-ISE = fluoride ion selective electrode; FTIR = Fourier transform infrared spectroscopy; HS-GC-FID = head space gas chromatography flame ionization detector; IC = ion chromatography; ICP-MS = induction coupled plasma-mass spectroscopy; ID = identity; IR = infrared spectroscopy; LC-RI = liquid chromatography refractive index; NLT = not less than; NMT = not more than; Ph. Eur. = European Pharmacopoeia; SEC-RI = size exclusion chromatography refractive index; USP = United States Pharmacopeia

[a] Calculated on (b) (4) weight basis

[b] Calculated on patiromer anion weight basis

[c] Calculated on "as is" basis (b) (4)

It is noted that Elemental Impurities are calculated on an "as is" basis meaning (b) (4) of the drug substance is not taken into account when performing the calculation. This is not the case with the

other impurity tests in the specification (Single / Total Unspecified Impurities, [redacted]) which are all calculated on [redacted] weight basis. Calculating Elemental Impurities on a "as is" basis will result in a lower number being reported for Elemental Impurities level in a batch. The limit for [redacted] Pb is calculated on [redacted] basis for a batch of RLY5016S for which [redacted] was at the upper limit ([redacted]%) is as follows:

Limit of [redacted] Pb on [redacted] basis = [redacted] ppm

It is important to understand whether or not this [redacted] limit will comply with the PDE for [redacted] Pb in Q3D. The maximum exposure to [redacted] Pb can be calculated for the MDD of RLY5016S based on the label (25.2 g) as it was above for the development MDD of [redacted]:

MDD = [(25.2 g patiromer) [redacted] day

Total daily dose of [redacted] Pb [redacted] basis = [redacted] day RLY5016S = [redacted] day

This limit complies with the oral PDE for both [redacted] Pb in Q3D, which is [redacted]. **However, it should be noted that any changes in this NDA (e. g. post-approval) intended to increase the dosage should be evaluated to make sure the limits for elemental impurities [redacted] Pb comply with the limits in Q3D**.

Amendment dated June 25, 2015

The revised Section 3.2.S.4.2 Analytical Procedures [RLY5016S, [redacted]], including the revised analytical procedure for Elemental Impurities in RLY5016S drug substance was submitted to the NDA. There are no changes to the analytical procedure. The revised procedure includes additional details of the digestion step that were part of the method as validated, but were inadvertently left out of the original method submitted with the NDA. In addition, some details were modified for clarity and reporting requirements for individual elements were added. Instructions for summing of individual elemental impurity data were removed.

Amendment dated July 10, 2015

The applicant provided the analytical procedure, validation summary, and validation report for determination of elemental impurities in xanthan gum. In addition, the applicant provided administrative documentation that they had committed to submitting by September 4, 2015. The administrative documentation consisted of revisions to sections 3.2.P.4.2, P.4.3, P.4.4, P.5.5, and P.5.6. **Evaluation of this information is performed in the CMC assessment of the drug product for NDA 205739**.

Revision to section 3.2.S.4.5 Justification of Specifications [RLY5016S, [redacted]] was provided in this amendment. An extensive discussion of the determination of the acceptance criteria for [redacted] Pb was provided, as was the justification for no acceptance criteria for As, [redacted]. These have been evaluated above.

sections 3.2.S.3.2 Impurities and 3.2.S.4.5 Justification of Specifications [RLY5016S, (b) (4)]

Amendment dated July 15, 2015

This amendment was submitted to revise the acceptance specifications of (b) (4) used in the manufacture of drug substance RLY5016S. Brief discussions of each specific material are provided below.

In this amendment the applicant also provided an updated section 3.2.P.2.2 to include information supporting the use of the (b) (4) preparation of the suspension for the selected commercial dosage strengths / packet sizes of 8.4 g, 16.8 g and 25.2 g patiromer as discussed at the 29 June 2015 Late Cycle Review Meeting. **This material is evaluated in the CMC assessment of the drug product for NDA 205739**.

Finally in this amendment the revision to section 3.2.S.3.2 Impurities [RLY5016S, (b) (4)] was provided. It contained a description of the control strategy for elemental impurities.

Revision of acceptance specification of (b) (4) used in RLY5016S manufacture

The specifications for the following materials have been revised as described.

(b) The specification has been revised to eliminate the test for Special Pathogens (b) (4)) which was in the specification which was submitted with the original NDA. The original specification was erroneous because this test was never performed as part of the evaluation of (b) (4).

It is important to note that (b) (4), which is also used in the manufacturing process. (b) (4)

(b) (4)

(b) (4)

Amendment dated July 20, 2015

In this amendment, the analytical procedure, validation summary, and validation report was submitted for the analytical procedure used to determine (b) (4) in RLY5016S drug substance.

The analytical procedure used is the same as the Elemental Impurities procedure described in sec. 2.3.S.4 of the IQA. The range of concentrations (ng/mL) of the (b) (4) calibration standard solutions is (b) (4) For (b) (4) the procedure is validated for the following parameters:

(b) (4)

It is reiterated that (b) (4) is not measured in RLY5016S drug substance because amounts measured in three registration lots and three process validation lots (six lots total) were (b) (4) % of the PDE for (b) (4) established in Q3D. The data is provided to establish the validity of those experiments.

CMC Information Requests no. 1 and 2 in Late Cycle Review Letter

Two comments were generated in the drug substance section of the IQR for NDA 205739 and were listed as Information Requests in the Late Cycle Communication Letter dated June 17, 2015. The applicant provided responses in an amendment dated June 26. The two drug substance comments and the applicant responses are provided below.

CMC IR #1. In your amendment dated May 5, 2015, you indicated that the following tests, which were used to generate data provided in the primary stability study, will not be used to generate stability data for future batches: Impurities in RLY5016S by GC-FID Method ; Impurities in RLY5016S by LC-UV Method 1; and Potassium Binding Capacity. Please update your stability protocol and specification in your NDA with regard to these tests.

Response. Relypsa is providing a revised (b) (4) Section 3.2.S.7.2 to describe the current status of the registration stability study as complete and to summarize the test attributes, method type, analytical procedures and acceptance criteria to be applied at each time point for the stability studies performed on the first three production lots of RLY5016S and the subsequent annual commitment lots (future studies).

Testing of the registration stability lots described in the NDA is complete for samples stored at the long-term refrigerated condition through 36 months and for samples stored at 25 °C / 60% RH (accelerated condition) through 6 months. The data from the study are under review; the final report for this study will be submitted to the NDA in the first NDA annual report.

Evaluation. A revised sec. 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment [RLY5016S, (b) (4)] is provided in the amendment. The Testing Schedules for the First Three Production Scale and Annual Commitment Lots are provided. These are the same as those in the original NDA.

RLY5016S Post-Approval Stability Testing Schedule for First Three Production Scale Lots

Storage Condition	Time (months)							
	0	3	6	9	12	18	(24)	(36)
2 – 8°C	Y	X	X	X	Y	Y	(Y)	(Y)

RLY5016S Post-Approval Stability Testing Schedule for Annual Commitment Lot

Storage Condition	Time (months)						
	0	6	12	18	(24)	(30)	(36)
2 – 8°C	Y	X	Y	Y	(Y)	(X)	(Y)

X = Test attributes = appearance, total potassium exchange capacity, [redacted] (b) (4) and largest single and total unspecified impurities

Y = X testing + microbiological testing

( ) = Optional time point

The stability specification is revised and is included in the amendment. It is reproduced below.

Stability Specification for RLY5016S

Test Attribute	Method Type	Analytical Procedure	Acceptance Criteria
Appearance	Visual	Appearance of RLY5016S by Visual Inspection with Color Cards	Off-white to light brown powder
Total Potassium Exchange Capacity[a]	IC	Total Potassium Exchange Capacity of RLY5016S by IC	[redacted] (b) (4)
[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4) of RLY5016S by [redacted] (b) (4)	
Largest Single Unspecified Impurity[b] Total Unspecified Impurities[b]	HS-GC-FID	Determination of [redacted] (b) (4) and Unspecified Impurities in RLY5016S by HS-GC-FID	NMT [redacted] (b) (4) wt% NMT [redacted] wt%
Fluoride[b]	F-ISE	Determination of Fluoride in RLY5016S by ISE	NMT [redacted] (b) (4) ppm
Microbial Enumeration Tests: Total Aerobic Microbial Count Total Combined Yeasts and Molds Count Specified Microorganisms: *Escherichia coli*	 USP <61> or Ph. Eur. 2.6.12 USP <62> or Ph. Eur. 2.6.13	 Microbial Enumeration Tests and Tests for Specified Microorganisms in RLY5016S	 NMT [redacted] (b) (4) NMT Absent

cfu = colony forming unit; F-ISE = fluoride ion selective electrode; HS-GC-FID = head space gas chromatography flame ionization detector; IC = ion chromatography; NMT = not more than; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

[a] Calculated on patiromer anion basis. Use lot release value.

[b] Calculated [redacted] (b) (4) weight basis

Other than the stability specification, it appears that no aspect of the stability commitment is changed with respect to what was provided in the original NDA.

It is noted that The NDA registration stability studies for RLY5016S drug substance to support storage at long-term (refrigerated) conditions are complete through 36 months. Data supporting storage at long-term conditions through (b) (4) months (proposed expiration period) were provided in the original NDA. Data supporting storage through 6 months at accelerated conditions (25°C/60%RH) were also provided in the original NDA.

The response to CMC IR#1 provides adequate clarity and is acceptable.

(b) (4)

Reviewer's Final Assessment and Signature: All the drug substance deficiencies have been satisfactorily resolved. From the perspective of drug substance, the application is recommended for approval.

Raymond P. Frankewich, Ph.D.
Review Chemist
OPQ/ONDP/DNDAPI/Branch I

NDA 205739: Evaluation of Applicant's Responses to Pending Drug Product Deficiencies

Background: The main pending issue concerns the control of elemental impurities by appropriate drug substance and excipient specifications. The ICH Q3D Option (b) (4) recommends taking into consideration the contribution of impurities from the proportion of each component of the drug product i.e., the drug substance and the excipient (s). Regarding the drug product, xanthan gum is the only excipient used in the formulation of RLY5016 for oral suspension (patiromer). Per recommendations of ICH Q3D Guideline for Elemental Impurities, December 2014 (ICH Q3D), the applicant was asked to set up individual acceptance criteria for Class (b) (4) elements per Option (b) (4), as appropriate, for the drug substance and the excipient xanthine gum (the identified deficiency was communicated to the applicant on April 15, 2015).

1. Summary of Applicant's Response, Dated May 5, 2015: The applicant demonstrated that the combined levels of arsenic (As), (b) (4) based on the daily dose of RLY5016S (drug substance) and xanthan gum was less than (b) (4)% the daily permissible daily exposure (PDE) limits for these elements, as listed in ICH Q3D. Based on these data from representative lots of both RLY5016S and xanthan gum, the applicant in compliance with with ICH Q3D provided valid justification for not proposing acceptance limits for these elements. Furthermore, the applicant committed to: a) lower the limit of quantitation (LOQ) for (b) (4) lead (Pb) in xanthan gum in order to improve estimation of the daily exposure to these elements from drug product, and b) implement validated test methods for (b) (4) testing for xanthan gum and RLY5016S, respectively, in order to comply with ICH Q3D.

2. Summary of Applicant's Response, Dated May 19, 2015: The applicant committed to submit individual acceptance criteria for (b) (4) Pb (b) (4) in the release specifications for RLY5016S and xanthan gum, and provide established and final methods with validation reports for analysis of (b) (4) content in RLY5016S and the content of Class (b) (4) elemental impurities in xanthan gum.

3. Summary of Applicant's Response, Dated June 19, 2015: The applicant (Relypsa) complied with the Agency request to establish acceptance criteria in the release specification for RLY5016S (drug substance) for each of the Class (b) (4) metals. The revised specification for RLY5016S (Section 3.2.S.4.1) has been reviewed by the drug substance reviewer. In addition, Relypsa provided an updated specification for xanthan gum that reflects addition of acceptance criteria for elemental impurities. Specifically, Relypsa proposed individual acceptance criteria for (b) (4) (b) (4) Pb in RLY5016S and xanthan gum based upon available data for the content of (b) (4) Pb, (b) (4) in representative lots of RLY5016S and xanthan gum.

Table 1: Content of Class (b) (4) Elemental Impurities in Representative Lots of Xanthan Gum, NF

Xanthan Gum Lot Number	Elemental Impurities in Representative Lots of Xanthan Gum (microgram/g)[a, b, c]											
	As	(b) (4)						Pb				(b) (4)
1L4290K												
1L4363K												
2B4674K												
2B4678K												
2B4685K												
415406K												
415490K												
4D2346K												

As = arsenic; (b) (4) NF = National Formulary; (b) (4) Pb = lead; (b) (4)

[a] Bulk excipient weight. (b) (4)
[b] Results obtained by induction coupled plasma-mass spectroscopy (ICP-MS)
[c] Developmental data generated using the analytical procedure that has subsequently been validated is reported. There may be minor difference in the reported LOQ's that do not affect the conclusions of these experiments.

The calculated maximum exposure to (b) (4) lead, (b) (4) from RLY5016 for oral suspension, and proposed acceptance limits for lead (b) (4) are tabulated below.

Calculated Maximum Exposure to (b) (4) Lead, (b) (4) from RLY5016 for Oral Suspension

Element	RLY5016S (max. dose = (b) (4) day)		Xanthan Gum (max. dose = (b) (4) day)		Total Content of Elemental Impurity in Drug Product (micrograms/day[a])	PDE per ICH Q3D, December 2014 (micrograms/day)	% of PDE
	Max. Content Observed (micrograms/g)	Contribution (micrograms/day)	Max. Content Observed (micrograms/g)	Contribution (micrograms/day)			
(b) (4)							(b) (4)
Pb							
(b) (4)							

(b) (4) Pb = lead; PDE = permitted daily exposure

[a] Sum of contribution from maximum daily dose of RLY5016S and xanthan gum.
[b] Limit of quantitation of the test method. Maximum result obtained was below this value.

Proposed Acceptance Limits for (b) (4) Lead in RLY5016S and Xanthan Gum

Element	RLY5016S (max. dose = (b) (4) day)		Xanthan Gum (max. dose = (b) (4) day)		Total Content of Elemental Impurity in Drug Product (micrograms/day[b])	PDE per ICH Q3D, December 2014 (micrograms/day)	% of PDE
	Proposed Specification (micrograms/g)	Contribution at Proposed Specification (micrograms/day)	Proposed Specification (micrograms/g[a])	Contribution at Proposed Specification (micrograms /day)			
(b) (4)							(b) (4)
Pb							
(b) (4)							

ICP-MS = induction coupled plasma-mass spectroscopy; Pb = lead; PDE = permitted daily exposure
[a] Limit was assigned based on an ICP-MS method range; limit could be (b) (4) ppm based on PDE
[b] Sum of contribution from maximum daily dose of RLY5016S and xanthan gum.

Revised specification limits for (b) (4) lead in xanthan gum (Section 3.2.P.4.1) are tabulated below.

Test Attribute	Method Type	Acceptance Criteria[a]
(b) (4)	ICP-MS	NMT (b) (4) ppm
Lead (Pb)		NMT ppm

ICP-MS = induction coupled plasma-mass spectroscopy; NMT = not more than
[a] Calculated on "as is" basis (b) (4)

Reviewer's Evaluation: Adequate. *The data concerning the levels of class (b) (4) elemental impurities in representative lots of xanthan gum indicate that the xanthan gum, NF complies with the requirements for Class (b) (4) elemental impurities specified in (b) (4) ICH Q3D Impurities: Guideline for Elemental Impurities, December 2014. Specifically, only (b) (4) lead are present at or above the control threshold of less than or equal to (b) (4)% of the permissible daily exposure (PDE) level in drug product as defined in the guidance. Hence, the applicant has not proposed acceptance limits for arsenic, (b) (4) because the observed maximum levels of these elemental impurities in representative lots of RLY5016S and xanthan gum amount to less than (b) (4)% of the PDE based on the relative contribution from each drug product component. It is important to note that the only excipient used in the drug product i.e., xanthan gum is a National Formulary (NF) compendial excipient that is tested to and must meet the NF specifications current at the time of testing. The individual acceptance limits for the content of (b) (4) lead elemental impurities have been established to supersede the NF requirements for these elements. As indicated in above-specified tabulated data, the applicant has adequately justified the proposed acceptance limits for these elemental impurities.*

4. Summary of Applicant's Response, Dated July 10, 2015: Relypsa provided the analytical procedure, validation summary, and validation report for determination of elemental impurities in xanthan gum.

Analytical Procedure (Section 3.2.P.4.2): In addition to the National Formulary methods and associated specifications, the applicant has developed an inductively-coupled plasma mass spectroscopy (ICP-MS) method ((b) (4)) for testing for the content of (b) (4) lead in xanthan gum.

Validation Summary (Section 3.2.P.4.3): The applicant provided the validation data and validation report for the determination of elemental impurities in xanthan gum by ICP-MS for determination of lead (b) (4) in xanthan gum. The parameters of precision accuracy, linearity, specificity, range, limit of quantitation and solution stability have been evaluated.

Justification (Section 3.2.P.4.4): The applicant provided justification for the proposed specification for elemental impurities in xanthan gum.

Justification for Specification for Elemental Impurities in the Drug Product (Section 3.2.P.4.5): In accordance with ICH Q3B (b) (4), only degradation products are controlled in the drug product. The specified degradation product is (b) (4); in addition, individual unspecified and total unspecified extractable impurities are also controlled in the drug product. The rationale for omitting tests for certain elemental impurities (b) (4), as part of the drug product specifications, has also been discussed in this section.

5. Summary of Applicant's Response, Dated July 15, 2015: The Section 3.2.P.2.2 has been updated to include a new (b) (4) suspension preparation procedure, based on studies designed to minimize (b) (4). This includes revised information regarding the amount of (b) (4) to be used to suspend RLY5016 for oral suspension prior to oral administration.

Reviewer's Evaluation: Adequate. *The applicant has provided details about inductively-coupled plasma mass spectroscopy (ICP-MS) method. Essentially, the elemental impurities analysis of xanthan gum by ICP-MS involves digestion of xanthan gum in (b) (4) under pressure in a (b) (4) digestion system. The arsenic (As), (b) (4) lead (Pb), (b) (4) in the (b) (4) sample are measured by ICP-MS using (b) (4) as internal standards. Since only (b) (4) lead are present at or above the control threshold of less than or equal to (b) (4) % of the permissible daily exposure level in drug product, the applicant will test only for the presence of (b) (4) lead in incoming lots of xanthan gum to be used in the drug product. The applicant's validation studies, aimed to examine the critical analytical parameters, demonstrate that ICP-MS method employed for determination of elemental impurities in xanthan gum is validated for precision, accuracy, linearity, specificity, range, limit of quantitation and solution stability. The limits of quantitation (LOQ) for (b) (4) lead have been determined at (b) (4) ppb. Based on validation studies, the ICP-MS method is suitable for its intended application.*

At the Type C CMC meeting with FDA on 27 March 2013, Relypsa included in the Meeting Package the rationale for not including a test for heavy metals or elemental impurities in the drug product specification. Relypsa proposed to test drug substance and the only excipient, xanthan gum, in accordance with USP <232> and <233>. The Agency agreed with the applicant's proposal. Considering that the drug product is composed of (b) (4) % RLY5016S and (b) (4) % xanthan gum, representing the maximum level of total elemental impurities present in the drug product for which contributions of elemental impurities from other sources are negligible, the limits set for elemental impurities in drug substance and xanthan gum ensure that the drug product will meet ICH Q3D

limits for Class (b) (4) *elemental impurities. Therefore, further control of elemental impurities in the drug product is not performed.* (b) (4) *are not controlled in the drug product because adequate controls are in place to control* (b) (4) *in the drug substance and xanthan gum. No* (b) (4) *are used in the drug product manufacturing process. Xanthan gum is certified by the vendor to comply with the requirements of USP <467>. Given that the content of* (b) (4) *is controlled in the drug substance and that xanthan gum meets USP <467> requirements, Relypsa has appropriately concluded that* (b) (4) *are adequately controlled in the individual components of the drug product. Therefore, monitoring of* (b) (4) *in the drug product as part of release specification has not been proposed.*

To minimize (b) (4) *procedure has been appropriately proposed. The patiromer powder is added to an initial amount of* (b) (4) (b) (4)

Reviewer's Final Assessment and Signature: All the drug product deficiencies have been satisfactorily resolved. The Office of Compliance has issued 'acceptable' recommendation for all the listed manufacturing and testing facilities. From Drug product perspective, the application is recommended for approval.
Mohan Sapru, Ph.D.
CMC Lead for Cardiovascular and Renal Products (Acting)
ONDP/OPQ/CDER

NDA 205739
Review 1

Drug Name/Dosage Form	Veltassa (patiromer) Powder for Oral Suspension
Strength	(b) (4) 8.4, (b) (4) 16.8, (b) (4) & 25.2 grams
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Relypsa, Inc.
US agent, if applicable	N/A

SUBMISSIONS REVIEWED	eCTD SEQUENCE NUMBER	DOCUMENT RECEIVED DATE
New/NDA	0000	10/21/2014
Quality/Response To Information Request	0003	12/22/2014
Quality/Quality Information	0005	2/4/2015
Quality/Quality Information	0009	4/1/2015
Quality/Response To Information Request	0010	5/5/2015
Quality/Quality Information	0014	5/15/2015
Labeling/Container-Carton Draft	0013	5/15/2015
Quality/Response To Information Request	0015	5/19/2015
Labeling/Package Insert Draft	0012	5/20/2015
Quality/Quality Information	0017	5/28/2015
Quality/Quality Information	0019	6/15/2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Raymond Frankewich	ONDP/DNDAPI/NDBI
Drug Product	Mohan Sapru	ONDP/DNDPI/NDPBI
Process	Vipul Dholakia	OPF/DIA/IABIII
Microbiology	Erika Pfeiler	OPF/DMA/MABI
Facility	Vipul Dholakia	OPF/DIA/IABIII
Biopharmaceutics	Elsbeth Chikhale/Angelica Dorantes	ONDP/DB/BBI
Regulatory Business Process Manager	Michael Folkendt	OPRO
Application Technical Lead	Kasturi Srinivasachar	ONDP/DNDAPI/NDBI
Laboratory (OTR)	Michael Trehy Ilan Geerlof-Vidavsky Cindy Diem Ngo Xiaofei Liu	OTR/DPA/PABI
Environmental Assessment (EA)	Raanan Bloom	ONDP

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

1. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPL-ETED	COMMENTS
(b) (4)	Type III					The DMF was not reviewed because all the needed details concerning the container closure system, including the details concerning web stock have been adequately provided in the submitted application

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	75615	Previously reviewed IND

3. CONSULTS: *N/A*

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

Executive Summary

1. Recommendations

1. Recommendation and Conclusion on Approvability

The NDA cannot be approved until 1) a satisfactory response is received to the pending issue of elemental impurities in the drug substance and xanthan gum including acceptance criteria, analytical procedures and validation reports; 2) an overall "Acceptable" recommendation is received from the facilities reviewer.

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

N/A

3. Summary of Quality Assessments

The proposed drug, Veltassa (patiromer) is a non-absorbed, cation-exchange polymer that binds potassium in the lumen of the colon and increases fecal potassium excretion. Patiromer is indicated for use in the treatment of hyperkalemia. Clinical development of this drug was carried out under IND 75,615. Patiromer refers to the USAN for the (b) (4) however, the drug is manufactured as the anion, the active moiety, with calcium-sorbitol as the counterion. It is an NME which is supplied as a powder for oral suspension in water in a number of strengths. Clinically, the drug was found to be effective in meaningful reductions in serum potassium; however, because it is non-absorbed and needs to be administered in large doses, drug-drug interactions can be a major issue in the intended patient population who will generally be on multiple medications. The Clinical Pharmacology reviewers are currently in discussions with the Applicant on the optimum time and frequency of dosing of Veltassa to circumvent this problem and the final outcome will be reflected in the labeling. From a Quality perspective, a significant drawback to this drug which affects patient use is its propensity to degrade upon storage to (b) (4) which can potentially have toxic effects at the doses proposed. The Applicant has mitigated this problem by recommending (b) (4) Additional details are in the Drug Product section below.

Drug Substance

The drug substance is a free flowing powder composed of individual spherical beads of a high molecular weight polymer (b) (4) (b) (4)

(b) (4)

Drug Product

(b) (4) strengths are proposed for marketing: (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g. The first (b) (4) strengths will be packaged in (b) (4) The Applicant was queried about this and their response was that there were no drop-outs or patient complaints for this issue during the clinical trials. An actual taste test with a sample provided by the Applicant confirmed that the powder was bland with no bitterness or other objectionable taste. The original NDA described a suspension (b) (4)

(b) (4)

However, late in the review cycle, the Applicant found that the original procedure for the preparation of the suspension resulted (b) (4) xanthan gum particles. (b) (4)

The drug product specification includes standard test attributes for a solid oral product for suspension, e.g. assay, uniformity of dosage units, (b) (4), appearance, identification, suspendability and bioburden. Some of the tests are unique given the polymeric nature of the product, e.g. total potassium exchange capacity in lieu of dissolution and extractable impurities. The only degradation product identified is (b) (4) and is quantitated using an (b) (4) method. The proposed limit of NMT (b) (4) ppm is acceptable to the pharmacology/toxicology team from a safety stand point.

Stability data have been submitted to show that the drug product is stable at the long term storage condition of 2-8°C for 18 months and at accelerated conditions of 25° C/60% RH for 6 months. No trends were observed except for (b) (4) levels which showed a marked increase at accelerated conditions similar to that observed in the drug substance. Based on the long term data and statistical analysis, an expiration dating period of 24 months has been proposed and found acceptable. In–use stability studies have also been carried out to qualify room temperature storage for up to 3 months. The in-use period is within the total 24 month dating period and the labeling reflects this.

Manufacturing Process

(b) (4)

Facilities

The inspection of the drug substance manufacturing facility, (b) (4), is pending at this time. This is a critical facility for this NME. Drug Product facilities are deemed acceptable.

Microbiology

This is a non-sterile drug product manufactured (b) (4) process. The microbiological quality of the drug product is controlled by a suitable testing protocol in accordance with USP <61> and <62>. The microbial limits proposed are consistent with

USP <1111>. In addition to release testing, the drug product will be tested for microbial limits annually as part of the post-approval stability protocol.

Biopharmaceutics

The drug product is a non-absorbed, insoluble polymer and hence a dissolution test is not included in the specification. Instead an in-vitro Total Potassium Exchange Capacity Test is proposed. Since this is a critical test for batch release, the analytical method was consulted to the FDA Laboratories in St. Louis for verification. They confirmed that the test sample provided met the specification but had a comment about sample preparation since the specified (b) (4) (b) (4) The Applicant was informed to address this issue and a satisfactory response was received. This method is considered suitable for batch release as well as stability testing.

No bridging studies are needed between the formulations used in early clinical studies. Formulation C with a single excipient (xanthan gum) was used in the pivotal Phase 3 trials and is the proposed commercial formulation. To support major post-approval manufacturing changes, the Applicant has developed two assays, an equilibrium and a kinetic potassium binding assay. This approach is consistent with FDA's in vitro bioequivalence requirements for other polymeric drugs such as sevelamer and cholestyramine.

Methods Validation

This application is for an NME and additionally, some unique analytical methods are employed in the specification of this polymeric drug substance and product. The following methods were identified for verification by the FDA Laboratories in St. Louis:

Drug Substance: Sorbitol Content, determination of fluoride by ISE, identity of the drug substance by fluoride content, calcium identity and calcium content by IC, particle size distribution by laser diffraction

Drug product: Total potassium exchange capacity by IC

The FDA Laboratory was unable to perform the identity test by fluoride content using oxygen combustion with ISE due to instrumentation limitations. The total potassium exchange capacity was performed on the drug substance and not on the drug product (b) (4) .

All methods were found to be acceptable for control and regulatory purposes. A comment was noted for the total potassium exchange capacity test (b) (4) his issue was conveyed to the Applicant and a satisfactory response received as noted in the biopharmaceutics assessment.

(b) (4)

Environmental Assessment

An Environmental Assessment was submitted by the Applicant and reviewed. The EA is considered adequate for approval of the NDA. A finding of no significant impact (FONSI) is recommended based on the available information.

Labeling

The proprietary name "Veltassa" was found acceptable by DMEPA
The established name (USAN) for the active moiety is (b) (4) and for the drug substance is "patiromer sorbitex calcium"
The strengths are based on the active moiety in accordance with the USP salt nomenclature policy and the equivalency statement for the salt is present on the back panel of the carton.
The long term and "in-use" storage conditions are supported by stability studies.
The revised dose preparation information (b) (4) is acceptable from the CMC perspective
The information in the Description and How Supplied Sections of the Package Insert are accurate.

Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Veltassa
Non Proprietary Name of the Drug Product	Patiromer
Non Proprietary Name of the Drug Substance	Patiromer Sorbitex Calcium
Proposed Indication(s) including Intended Patient Population	Hyperkalemia in patients (b) (4)
Duration of Treatment	Until serum potassium levels are in the normal range and stable
Maximum Daily Dose	(b) (4) of active
Alternative Methods of Administration	N/A

Biopharmaceutics Considerations

1. BCS Designation: N/A
   i) Drug Substance:
   ii) Drug Product:

2. Biowaivers/Biostudies: N/A
   i) Biowaiver Requests
   ii) PK studies
   iii) IVIVC

Novel Approaches: N/A

Any Special Product Quality Labeling Recommendations: N/A

Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: Kasturi Srinivasachar

Kasturi Srinivasachar -A

Digitally signed by Kasturi Srinivasachar -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300080217, cn=Kasturi Srinivasachar -A
Date: 2015.07.28 14:41:33 -04'00'

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

Note: The abbreviation MCIR refers to the Mid-Cycle Information Request, which was a communication dated April 15, 2015, that was sent to the applicant. The abbreviation MCR (mid-cycle response) refers to the applicant's response to the MCIR, which was provided in an amendment dated May 5, 2015.

2.3.S.1 General Information

In section 2.2.1 of the NDA submission (Introduction to the CTD / Pharmacological Class/Mode of Action) the drug substance and its clinical function is briefly described as follows:

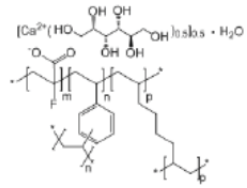
RLY5016 for Oral Suspension contains the drug substance, patiromer sorbitex calcium (referred to as RLY5016S), a new chemical entity that belongs to the pharmacologic class of Potassium Binders. Patiromer, the (b) (4) *of the drug substance, is a nonabsorbed, cation-exchange polymer that binds potassium in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels.*

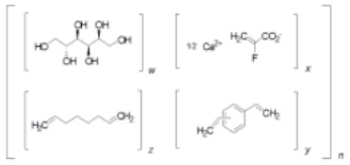
RLY5016, which is patiromer anion, is considered the active moiety since it is the molecular species that binds the potassium ion. RLY5016 is not (b) (4) during manufacturing. Therefore RLY5016S, which is referred to as a complex of RLY5016 with calcium and sorbitol, is proposed as the drug substance, (b) (4)

Nomenclature

A USAN Adopted Name (USAN Name) and a USAN Chemical Name have been established for (b) (4) of active moiety RLY5016, which is an anion. A USAN Name and a USAN Chemical Name for RLY5016S, the proposed drug substance, was pending when this NDA was filed (meaning that application for these names has been filed but final action by USAN has not been taken as of the date of this review). In an amendment dated March 31, 2015 (received April 1), the USAN names for RLY5016S were submitted to the NDA. Complete information regarding the nomenclature of (b) (4) RLY5016S is provided in a table in sec. S.1.1 of the NDA submission which is reproduced below.

Summary of Nomenclature for (b) (4) RLY5016S

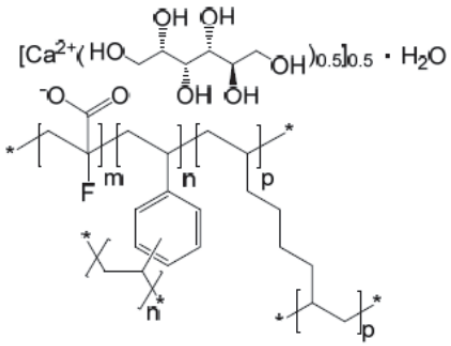
Company or Laboratory Code	**RLY5016S**
Chemical Abstract Service (CAS) Registry Number	1415477-49-4
Chemical Abstract Service (CAS) Name	Calcium, hydrolyzed divinylbenzene-Me 2-fluoro-2-propenoate-1,7-octadiene polymer sorbitol complexes
Structural Formula	 m = number of 2-fluoro-2-propenoate groups m = 0.91 n, p = number of crosslinking groups n + p = 0.09 * H_2O = associated water * = indicates an extended polymeric network

Company or Laboratory Code	**RLY5016S**
USAN Structural Formula	 Structure as assigned by USAN
International Union of Pure and Applied Chemistry (IUPAC) Name	(b) (4)
USAN Chemical Name	
United States Adopted Name (USAN)	Patiromer sorbitex calcium
Other Names	(b) (4) (b) (4) (Code name for RLY5016S at (b) (4)

Structure

A representation of the structural formula of both RLY5016S (the proposed drug substance) [redacted] (b) (4) are provided in the submission and reproduced below.

Structure of RLY5016S



m = number of 2-fluoro-2-propenoate groups m = 0.91

n, p = number of crosslinking groups n + p = 0.09

$^{\cdot}H_2O$ = associated water

* = indicates an extended polymeric network

[redacted] (b) (4)

The chemical structure of the RLY5016S polymer includes [redacted] (b) (4). The applicant indicates that based on its synthesis from these [redacted] (b) (4) starting materials, RLY5016S is a polymer that contains [redacted] (b) (4) A calcium-sorbitol complex is the counterion to the negatively charged, crosslinked polymer anion. RLY5016S contains approximately [redacted] (b) (4)% water.

It is noted in sec. S.1.2 of the NDA submission that no regular order of the monomers is implied by the structure, and that crosslinking is expected to occur randomly along the polymer chains. Given the preponderance of (b) (4) in the polymer, it is reasonable to expect that a significant portion of the molecular structure of the polymer includes 2-fluoro (b) (4) groups linking in series.

(b) (4)

From a macro perspective, RLY5016S is a free flowing powder composed of individual spherical beads. The applicant indicates that each RLY5016S crosslinked (b) (4) bead represents (b) (4).

Similar representations are provided for (b) (4) form of RLY5016S. The alternative representation is reproduced below.

(b) (4)

The molecular and empirical formulae of RLY5016S are based on (b) (4) the target calcium and sorbitol contents used in the synthesis of the drug substance. The formulae provided in the NDA and reproduced below do not include (b) (4).

- **Molecular formula of RLY5016S**: $(Ca_2C_6H_{14}O_6)_m(C_3H_2FO_2)_{4m}(C_{10}H_{10})_{4n}(C_8H_{14})_{4p}$, where (b) (4)

- **Empirical formula of RLY5016S**: $C_{613}H_{765}F_{114}O_{399}Ca_{57}$.

It is stated that each (b) (4) bead is (b) (4) and therefore the mass of an individual bead is equal to the mass of the (b) (4). The mass of a bead is dependent on its size and RLY5016S exhibits a distribution in particle size. **The molecular weight of a (b) (4) RLY5016S bead**, calculated

using an experimentally derived value for density and the theoretical calculated value for volume, is estimated to be [redacted].

Pharmacological Class

The pharmacological class of the drug is Potassium Binders. RLY5016 [redacted] is described as a nonabsorbed, cation-exchange polymer that binds potassium in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels.

Physical, chemical, biological and, if applicable, mechanical properties

This drug substance is defined as a cation-exchange polymer and a potassium binder. Its most important physical properties are those associated with potassium binding:

- **Total Potassium Exchange Capacity**: [redacted] (mean value from release and stability data)
- **Equilibrium Potassium Binding Capacity**: [redacted] (measured by incubating a sample of RLY5016S [redacted] potassium chloride solution)
- **Average Polymer Anion Content**: [redacted]% weight

Other important properties as a polymer:

- **Molecular weight**: [redacted]. This is calculated from experimentally derived value for density and the theoretical calculated value for volume for [redacted] bead. Each [redacted] bead is considered [redacted], since the polymer chains are highly crosslinked. The MW calculation is repeated below in an attempt to confirm this MW value.

  Density of bead: [redacted] (value is provided in sec. S.3.1; it is derived from bulk density ([redacted] for [redacted] spherical beads [redacted].

  Volume: [redacted] bead

  MW calculation: [redacted] bead

  [redacted]

- **Particle Size Target / Distribution**. It appears that the applicant intends to control the molecular weight distribution of RLY5016S drug substance by controlling the particle size distribution. The following values are provided

as physical properties of RLY5016S. The PSD values are acceptance criteria in the drug substance specification.

Target Average Particle Size: Approximately [redacted]
Particle Size Distribution: D ([redacted]): NLT [redacted]
D ([redacted]): [redacted]
D ([redacted]): NMT [redacted]

[redacted]

- **Appearance**: off-white to light brown powder.
- **Physical Form**: amorphous, free–flowing powder composed of individual spherical beads.
- **Solubility**: Insoluble in water, 0.1 M HCl, [redacted].

[redacted]

BCS Classification
There does not appear to be a discussion of the BCS classification of the drug substance, since RLY5016S is not absorbed or retained in the body and is insoluble in water.

Reviewer's Assessment: Adequate.

2.3.S.2 Manufacture

S.2.2 Description of the Manufacturing Process and Controls

1. **Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?**

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Although each attribute is dependent on particular manufacturing process parameters, each of the CQA is ensured by the drug substance specification. For each of the CQA, there is a test and acceptance criterion in the DS specification that controls it.

Reviewer's Assessment: Adequate.

Process Validation and/or Evaluation

5. **Is the proposed process validated adequately?**

No process validation information is provided. The following commitment is provided in sec. S.2.5 of the NDA submission:

Relypsa commits to validating the manufacturing process in accordance with the current FDA process validation guidelines in advance of commercial distribution.

In lieu of process validation information, this commitment will be accepted.

Manufacturing Process Development

6. **What process development and scale up information supports the commercial process and proposed control strategy?**

There appeared to be three main areas of focus for sec. S.2.6 of the NDA submission, Manufacturing Process Development. They were: development of RLY5016S drug substance as a potassium binder; development of the manufacturing process through the process used for the Phase 3 clinical / registration stability batches; development of critical process parameters. Each of these three areas is discussed in this review.

Development of RLY5016S drug substance as a potassium binder

In sec. S.2.6, justification is provided for the following decisions regarding development of RLY5016S as a drug substance:

- **Selection of a polymer with key functionality that binds potassium**. The RLY5016 polymer has a high potassium binding capacity because it is (b) (4) conditions of the colon, and possesses a low molecular weight. Other available polymers were either (b) (4)

24 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment: Adequate.

2.3.S.4 Control of Drug Substance

9. **Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?**

Specifications are provided for both the release of the drug product by its manufacturer ((b) (4) specification) and for acceptance of the drug substance by the drug product manufacturer ((b) (4) specification). The two specifications appear (b) (4). It is noted that (b) (4) testing may be performed "once the supplier is qualified". The specification reproduced below is the one that is presented as the (b) (4) specification used for release of the drug substance.

[redacted] Specification for RLY5016S

Test Attribute	Method Type	Acceptance Criteria
Appearance	Visual	Off-white to light brown powder
ID method 1: IR	FTIR	Conforms with reference spectrum of reference standard
ID method 2: Fluorine Content[a]	[redacted]	
ID method 3: [redacted]	IC	Retention time of the main peak in the sample chromatogram matches the retention time of the [redacted] peak in the standard
[redacted] Content[a]	IC	[redacted]
Patiromer Anion Content	Calculation	
[redacted] Content[a]	LC-RI	
Total Potassium Exchange Capacity[b]	IC	
Particle Size Distribution	Laser Diffraction	D [redacted] NLT D [redacted] 70 - D [redacted] NMT
[redacted]		
[redacted]	HS-GC-FID	NMT [redacted] ppm
Largest Single Unspecified Impurity[a]	HS-GC-FID	NMT [redacted] wt%
Total Unspecified Impurities[a]		NMT [redacted] wt%
Extractable Polymeric Impurities[a]	SEC-RI	NMT [redacted] ppm
[redacted]	IC	NMT [redacted] ppm
Elemental Impurities	ICP-MS	NMT [redacted] ppm
Fluoride[a]	[redacted]	NMT [redacted] ppm
Microbial Enumeration Tests: Total Aerobic Microbial Count Total Combined Yeasts and Molds Count	USP <61> or Ph. Eur. 2.6.12	 NMT [redacted] NMT [redacted]
Specified Microorganisms: *Escherichia coli*	USP <62> or Ph. Eur. 2.6.13	 Absent

F-ISE = fluoride ion selective electrode; FTIR = Fourier transform infrared spectroscopy; HS-GC-FID = head space gas chromatography flame ionization detector; IC = ion chromatography; ICP-MS = induction coupled plasma-mass spectroscopy; ID = identity; IR = infrared spectroscopy; LC-RI = liquid chromatography refractive index; NLT = not less than; NMT = not more than; Ph. Eur. = European Pharmacopoeia; SEC-RI = size exclusion chromatography refractive index; USP = United States Pharmacopeia

[a] Calculated on [redacted] weight basis

[b] Calculated on patiromer anion weight basis

The specification is adequate to assure the identity, strength, purity, and quality of the drug substance for the following reasons:

- ID is tested by three analytical procedures which focus on specific and important attributes of the drug substance (IR signals, presence of calcium, presence of fluorine as a degradant).
- Strength is measured by the capacity of the drug substance to exchange / absorb potassium, which is its intended function.
- Purity is determined by measuring the amounts of major process impurities in the drug substance, including polymeric impurities, [redacted] elemental

impurities, and the major [(b) (4)] used in the manufacturing process [(b) (4)], as well as unspecified impurities. In addition, fluoride is measured as fluoride ion (from CaF_2), which is an impurity and is believed to be the only degradation product. Justification for measurement of these species as impurities in the drug substance (and the exclusion of others) is discussed above in Question no. 8 (impurities / potential impurities).

- Quality is determined by establishing specific limits on the amount of species that are essential to the performance and stability of the drug substance including Patiromer Anion; Sorbitol; Calcium ion; moisture (tested by [(b) (4)]). In addition, the particle size of the drug substance is controlled, which aids its quality but also establishes a standard for the molecular weight of the polymer, since each [(b) (4)] bead is considered by the applicant to be [(b) (4)].

Batch Analysis Data

Batch analysis data are provided in section S.4.4 of the NDA submission for a total of 37 batches of RLY5016S and seven (7) batches of RLY5016.

In the response to the following question (no. 10 below), discussions of justification of acceptance criteria in the above specification are provided for each analytical procedure which is summarized. In these discussions, reference is often made to data from "24 representative lots of RLY5016S", which comes from the NDA submission sec. S.4.5. These references are the same as those in sec. S.4.5 of the NDA submission. They include lots which were used for registration stability studies and for the production of drug product for use in the RLY5016-205 and RLY5016-301 clinical studies, and lots manufactured subsequently. Analysis data for these lots was provided in sec. S.4.4 of the NDA submission, Tables 3 – 8.

In fact, data from tables 3 – 8 cover only 17 batches. Tables 3 – 11 cover 25 batches, all of which were manufactured at [(b) (4)], the intended manufacturer of the drug substance. Results are provided for RLY5016S manufactured as far back as 2008. The rest of the data was for batches manufactured at [(b) (4)].

The release data for all the batches in Tables 3 – 11 was reviewed. There were no failures of acceptance criteria. For many of these batches different tests (e. g. [(b) (4)]), and different acceptance criteria relative to those in the proposed Release Specification were used. For the most part, the early [(b) (4)] batches conform with the current proposed Release Specification.

10. **Are all the analytical procedures appropriately described and validated for their intended use?**

Brief summaries are provided for the following analytical procedures and of the efforts to validate them. In addition, a brief summary of the justification of the acceptance criteria is also provided.

- Calcium Content

- Patiromer Anion Content
- Sorbitol Content
- Total Potassium Exchange Capacity
- Particle Size Distribution
- (b) (4) and Largest Single / Total Unspecified Impurit(y/ies)
- Extractable Polymeric Impurities
- (b) (4)
- Elemental Impurities
- Fluoride

The other analytical procedures referenced in the Specification are not discussed because they either use the same procedures as those listed above (ID tests), use simple methodology that does not require explanation (b) (4) or are described in compendia (Microbial Enumeration Tests / *E. Coli*)

(b) (4)

29 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4)

<u>Reviewer's Assessment</u>: Pending. The following comment will be expressed to the applicant in the Late Cycle communication process:

In your amendment dated May 5, 2015, you indicated that the following tests, which were used to generate data provided in the primary stability study, will not be used to generate stability data for future batches: Impurities in RLY5016S by GC-FID Method 1; Impurities in RLY5016S by LC-UV Method 1; and Potassium Binding Capacity. Please update your stability protocol and specification in your NDA with regards to these tests.

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

<u>Reviewer's Assessment and Signature</u>:
Raymond P. Frankewich, Ph.D.
Review Chemist, OPQ/ONDP/DNDAPI/Branch I
7/5/2015

<u>Secondary Review Comments and Concurrence</u>:
Concur. Kasturi Srinivasachar, 7/9/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3. P DRUG PRODUCT

The drug product, RLY5016 for oral suspension (Veltassa), a potassium binder, has been developed for the treatment of hyperkalemia. RLY5016 for oral suspension consist of the drug substance (referred to as RLY5016S), and xanthan gum, an excipient. The drug substance consists of the active moiety, patiromer that contains calcium-sorbitol counterion. Specifically, patiromer is a non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon and increases fecal potassium excretion, leading to removal of potassium from the body and lowering of serum potassium levels. The recommended starting dose of RLY5016 for oral suspension is (b) (4) 8.4 grams patiromer (b) (4) with meals, based on serum potassium level.

2.3. P.1 Description and Composition of the Drug Product

The qualitative and quantitative compositions of the RLY5016 for oral suspension, (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g strengths, are tabulated below.

Qualitative and Quantitative Composition of RLY5016 for Oral Suspension

			RLY5016 for Oral Suspension (grams Patiromer)			
			Configuration A		Configuration B	
			(b) (4)			(b) (4)
			(b) (4) 8.4	(b) (4) 16.8	(b) (4)	25.2
Component	Function	Composition (wt%)	Qua	acket (gra		
RLY5016S[a]	Active Ingredient	(b) (4)	16.80	33.60		50.40
Xanthan gum, NF						(b) (4)
Total Weight[b]:		100.0	(b) (4) 16.92	(b) (4) 33.84	(b) (4)	50.76

NF = National Formulary

[a] Nominal amounts of RLY5016S

[b] Fill weight may vary; the composition (wt%) does not vary. Total fill weight is adjusted to deliver the target amount of patiromer using patiromer anion content of the RLY5016S lot(s) used to produce the RLY5016 Powder Blend. For the example in this table, the fill weight for (b) (4) was calculated as follows: (b) (4) = patiromer anion content taken from the RLY5016S certificate of analysis]

RLY5016 for oral suspension is available in (b) (4) packets made from (b) (4) laminate web stock that is heat-sealed (b) (4).

Configuration A**:** [redacted] packet size is the container closure system for the following [redacted] strengths i.e., [redacted] 8.4 g [redacted] patiromer.

Configuration B**:** [redacted] packet size is the container closure system for the [redacted] strengths i.e., 16.8 g, [redacted] and 25.2 g patiromer.

Reviewer's Assessment*: *In adequate. *RLY5016 for oral suspension is intended to be administered orally after suspending in water. Each packet contains the drug substance, RLY5016S (the active ingredient), formulated with* [redacted] *% xanthan gum* [redacted]*. The proportion (weight %) of each component added to the powder blend is kept constant. The only excipients used i.e., xanthan gum is compendial grade,* [redacted]*. Though* [redacted] *for oral suspensions is regarded as a critical quality attribute (CQA) and the proposed dosage strengths range from* [redacted] *25.2 grams, it is not clear why the proposed high drug load formulation does not involve the use of suitable* [redacted] *of the drug substance.*

Deficiency (Communicated to the Applicant on April 14, 2015): Regarding the composition of RLY5016 for oral suspension, the formulation does not involve the use of any [redacted], and it is it is not clear whether the calcium sorbitol counterion [redacted]. To address the [redacted] concerns, provide justification, with supporting data, [redacted] in RLY5016 for oral suspension.

Summary of Applicant's Response (May 5, 2015): Addition of [redacted] was evaluated early in development of the product. Relypsa decided to keep the formulation "simple" due to the high doses of drug substance/drug product needed for administration; therefore, [redacted] formulation. In early clinical studies, [redacted] used [redacted] water for administration. [redacted] The overall experience in study participants in the clinical development program (734 adult subjects, including 149 subjects taking the product daily for at least 1 year) have indicated a high degree of acceptability [redacted] of RLY5016 for oral suspension. In the future, Relypsa may choose to provide options to patients that include [redacted].

Reviewer's Revised Assessment*: *Adequate. *Though* [redacted] *is generally considered a CQA for oral solutions, however, the applicant has pointed to several risk mitigation factors to support avoidance of the* [redacted] *proposed formulation. The applicant contends that because high doses of drug*

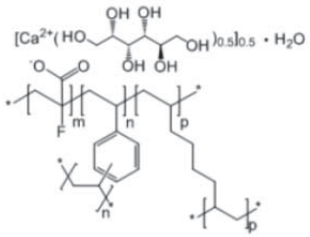
product are needed for administration, (b) (4). More importantly, given that the drug product (b) (4) patients (b) (4) have not discontinued participation in the clinical studies (b) (4). The (b) (4) issue was also discussed with the clinical reviewer and the Director, Division of Cardiovascular and Renal products who together determined that based on clinical trials, the (b) (4) of this formulation does not raise any concerns from patient safety and therapeutic efficacy point-of-view. (b) (4) Using a risk-based review approach, involving overall risk-and-benefit analysis, the proposed drug formulation (b) (4) is deemed acceptable.

2.3. P.2 Pharmaceutical Development

a) Drug Substance: RLY5016S is the Relypsa code for patiromer calcium-sorbitol counterion, the drug substance. The drug substance is an amorphous, free flowing powder that is composed of individual spherical beads. Each RLY5016S cross-linked (b) (4) bead represents (b) (4)

(b) (4)

RLY5016S



m = number of 2-fluoro-2-propenoate groups m = 0.91

n, p = number of crosslinking groups n + p = 0.09

* H_2O = associated water

* = indicates an extended polymeric network

b) Physicochemical Properties and Particle Size Distribution: RLY5016S is manufactured as free-flowing spherical beads of approximately (b) (4) diameter using a (b) (4) process. Published literature suggest that particles greater than approximately (b) (4)

c) Dissolution Testing: RLY5016S is a cross-linked polymer that does not require systemic absorption for its therapeutic or pharmacologic effect. The polymer remains intact in the gastrointestinal tract where it exerts its potassium binding effect. Dissolution

testing of the drug product is not proposed as a routine commercial release test because of the lack of a solubility of the polymer.

d) Formulation for Clinical Studies: Throughout development, three different formulations were used in clinical studies. The initial formulation (Formulation A) consisted of drug substance supplied in a high density polyethylene (HDPE) bottle that was used in Phase 1 and early Phase 2 clinical studies. Formulation development activities resulted in a (b) (4) formulation (Formulation B) that was used in some Phase 2 clinical studies. The formulation was simplified to include a single excipient (xanthan gum) resulting in Formulation C, which was used in a Phase 1 clinical study, late Phase 2 clinical studies, the Phase 3 clinical study and was used to produce the primary stability lots. Formulation C is the intended commercial formulation. The three formulations evaluated during development provide a suspension upon mixing with water.

e) Excipient Compatibility Study: A compatibility study was performed that evaluated various excipients mixed with RLY5016S. The compatibility of each excipient with RLY5016S was determined by (b) (4)

f) Phase 1, Phase 2, Phase 3, and Commercial Formulation (Formulation C): Formulation development work was performed to simplify the formulation to contain a single excipient (xanthan gum). Different technical grades of xanthan gum were also evaluated and the optimal quantity of xanthan gum in the formulation was determined. The suitability of each formulation evaluated was determined by monitoring viscosity results and visual inspection.

g) Evaluation of Xanthan Gum Technical Grade: An initial study was performed to evaluate (b) (4) xanthan gum (b) (4). The formulations prepared with each grade of xanthan gum showed comparable (b) (4)

Lot	Xanthan Gum	Quantity (wt %)	Viscosity Results
(b) (4)			

(b) (4)

j) Changes to Drug Product Name and Expression of Packet Strength During Development: While the nomenclature and expression of drug product content is different for the primary stability/Phase 3 clinical trial lots versus the lots of drug product used in Clinical Study RLY5016-205, (b) (4) Formulation C is the intended commercial formulation. Over the course of development, the components and composition of Formulation C did not change. Activities during development that drove the changes in drug product nomenclature include the following: (b) (4) The commercial label will express content in terms of patiromer.

k) Optimization of Water Quantity for Suspension of the Drug Product:

A study was performed to identify a range of drug product to water (diluent) ratios that result in adequate suspendability and a suspension that is pourable. The results of this study demonstrate that the drug product is adequately suspended (b) (4) in water. The applicant claims that the volume of water used to suspend the drug product (i.e., the contents of a packet) has been selected to ensure that a satisfactory suspension is achieved that allows for administration of the full contents of each packet.

l) Newly Proposed (b) (4) **Suspension Preparation (May 20, 2015 submission):** Because the preparation of the drug product suspension has been found to be associated with (b) (4) A (b) (4) suspension preparation procedure has been selected (b) (4) In the (b) (4) method, the drug product is added to a portion of the total amount of water and the mixture is stirred to form a slurry. The remaining water is added and the suspension stirred a second time before consuming the suspension. The recommended pre-dilution volume for Step 1 and the additional volume of water for Step 2 to prepare the suspension for each patiromer dose are tabulated below.

Recommended Pre-dilution Volume and Additional Volume of Water Used to Suspend Each Patiromer Dose

Patiromer Dose (g)	Weight of DP Blend (g)[a]	Step 1: Pre-dilution Volume[b]			Step 2: Additional Volume[b]		
		mL	Tablespoons (tbsp.)	Fluid Ounces	mL	Tablespoons (tbsp.)	Fluid Ounces
(b) (4)							

***Reviewer's Assessment*: Adequate.** *Pharmaceutical development studies have aimed to achieve the optimal particle size distribution for the drug substance, excipient selection and excipient compatibility to ensure consistent drug product quality with the desired quality attributes. Specifically, the studies focused on characterization of drug substance properties, optimization of drug substance specification, and drug product formulation, including excipient selection, study of excipient-drug substance compatibility and development of suitable analytical procedures for measuring potassium binding capacity of the drug substance. Per the original submission, the applicant stated that the drug substance in RLY5016 for oral suspension is 'patiromer calcium-sorbitol counterion* (b) (4) *'. Based on structural characterization data concerning the drug substance, the Agency recommended that phrases such as "* (b) (4) *" be removed from the original submission. In compliance with the Agency recommendation, the applicant revised the description of the drug substance and stated that "the active ingredient is patiromer sorbitex calcium which consists of the active moiety, patiromer, a non-absorbed potassium binding polymer with a calcium-sorbitol counterion". Calcium comprises*

about (b) (4)% of the (b) (4) weight of RLY5016 (b) (4) the anion represents (b) (4)% of RLY5016. (b) (4)

The target drug product profile, defined by the applicant, is a safe and efficacious powder for suspension formulation that requires a minimum quantity of diluent for suspension. The formulation was designed to contain a minimal number and amount of excipients to keep the total amount of powder per dose and volume of diluent necessary for suspension of the polymer as low as possible. A (b) (4) is the only excipient included in the formulation. RLY5016 for oral suspension is composed of RLY5016S (b) (4)%) and xanthan gum ((b) (4)%). As the drug product is primarily composed of the drug substance and the drug product does not require systemic absorption for pharmacological activity, there are limited physicochemical properties that influence drug product performance. The proposed particle size is large enough to prevent absorption (b) (4) The applicant appropriately contends that presence of xanthan gum in Formulation C (intended commercial formulation) is not expected to alter the permeation or absorption of the drug substance. Regarding different xanthan gum technical grades (b) (4), since Xantural (b) (4) and the (b) (4) different technical grades of xanthan gum all provided comparable solution viscosity results, Xantural (b) (4) has been selected as the xanthan gum technical grade for intended commercial formulation. The applicant has not listed (b) (4) as a critical quality attribute, presumably, in light of experience with use of intended commercial formulation (b) (4) in clinical trials (for details, refer to reviewer assessment for the Description and Composition of the Drug Product). Regarding microbiological attributes, testing of drug product lots according to USP <61> and <62> has been part of the development program.

The results from product development studies suggest that the drug product can be suspended in the volumes of water indicated in the product label without adversely impacting the quality of the suspension achieved or the binding capacity and stability of patiromer. For the commercial product, the label claim for content of active ingredient per packet will be expressed as patiromer content. The suspendability study results demonstrate that the drug product is adequately (b) (4) xanthan gum concentrations of (b) (4) in water. However, the optimization of water quantity for suspension of the drug product studies don't seem to have adequately addressed the issue of possible effect of (b) (4) xanthan gum particles on drug product suspension. Per May 20, 2015 submission, the applicant has revealed that the preparation of the drug product suspension is associated with occasional formation of (b) (4) xanthan gum particles. Based on studies conducted to identify a suspension preparation method designed (b) (4), the applicant has proposed a two-step suspension process. In the two-step method, the drug product is added to a portion of the total amount of water and the mixture is stirred to form a slurry. The remaining water is added and the suspension stirred a second time before consuming the suspension. The Veltassa dose preparation

instructions in the draft label text and in the 'Instructions for Use' have been updated accordingly. The preparation instructions, the 'Directions for Use' on the container labels and carton labels have also been similarly revised.

2.3.P.4 Control of Excipients

Xanthan gum, the only excipient used in the formulation, is a National Formulary (NF) compendial excipient. The compendial analytical procedures used are performed as described in the National Formulary (NF) monograph and do not require validation.

***Reviewer's Assessment*: Pending.** *RLY5016 for oral suspension does not contain any excipients of human or animal origin. Xanthan gum is the only excipient used in the formulation of RLY5016 for oral suspension. It is tested using the current compendial methods listed in the National Formulary (NF) monograph. Per recommendations of ICH Q3D Guideline for Elemental Impurities, December 2014 (ICH Q3D), individual acceptance criteria need to be set for Class (b) (4) elements (b) (4) as appropriate, for the drug substance. ICH Q3D (b) (4) recommends taking into consideration the contribution of impurities from the proportion of each component of the drug product (excipient and drug substance). The applicant contends that acceptance criteria for As, (b) (4) are not required to be added to the drug substance specification because the estimated maximum daily exposure for each element from drug product is (b) (4) % of the respective PDE for each of the elements. Xanthan gum is tested for heavy metals, lead and arsenic per the NF monograph for xanthan gum. However, per applicant's response (May 5, 2015), the applicant acknowledges that method development and method validation are required to improve the limit of quantitation (LOQ) in the assays for (b) (4) and lead (Pb) in xanthan gum. In addition, the applicant does not have data or a validated method for analysis of (b) (4) content in xanthan gum. The applicant has acknowledged that data has not been generated for (b) (4) content of RLY5016S, because a method for (b) (4) analysis is (b) (4) at the drug substance manufacturing site.*

Per applicant's response (May 5, 2015), the applicant has committed to establish the appropriate methods, and generate the required additional elemental impurities data, for determination of (b) (4) Pb, and (b) (4) content in representative lots of of xanthan gum. Furthermore, the applicant will validate the analytical methods and generate the data for (b) (4) content in xanthan gum and for (b) (4) content in RLY5016S. The applicant intends to submit this CMC information in the month of September, 2015. Given that the drug product is to be made available in (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g strengths, it is important to reliably monitor the levels of elemental impurities in the drug substance and the excipient xanthan gum.

2.3. P.5 Control of Drug Product

a) Specification: As a part of control strategy, the drug product attributes are controlled via release specification. The levels of degradant impurity i.e., fluoride are determined in RLY5016 for oral suspension by potentiometry using a fluoride ion-selective electrode (ISE). The applicant has appropriately provided detailed validation reports for the analytical procedures used for testing the drug product attributes.

Specifications for RLY5016 for Oral Suspension

Test Attribute	Method Type	(b) (4) Method Number	Acceptance Criteria
Appearance	Visual	CTMLP-2657	Off-white to light-brown powder; occasional white particles may be present
Suspendability of Drug Product	Visual	CTMLP-3271	The volume of suspended material is ≥ 50% at 3 minutes. The product is readily re-dispersible on shaking.
Identification Method 1: FTIR	FTIR	CTMLP-2681	IR spectrum of sample matches reference spectrum of RLY5016S
Method 2: Presence of (b) (4)	IC	CTMLP-2863	Retention time of the main peak in the sample chromatogram matches the retention time of the (b) (4) peak in the standard
Patiromer Anion Content	Gravimetry	CTMLP-2704	(b) (4) % of label claim
Uniformity of Dosage Units Weight Variation	USP <905>	NA	Meets the requirements in USP <905>
Total Potassium Exchange Capacity[a]	IC	CTMLP-2891	(b) (4) (b) (4)
Extractable Impurities[b] Individual unspecified Total unspecified	HPLC-UV	CTMLP-2707	NMT (b) (4) NMT
Microbiological Examination of Nonsterile Products Total Aerobic Microbial Count Total Combined Yeasts and Molds Count Specified Organism *E. coli*	USP <61> and <62>	MM-1386	NMT (b) (4) NMT Absent

cfu = colony forming unit; (b) (4) ion-selective electrode; FTIR = Fourier transform infrared spectroscopy; HPLC-UV = high performance liquid chromatography with ultraviolet detector; IC = ion chromatography; NA = not applicable; NMT = not more than; USP = United States Pharmacopeia

[a] calculated on patiromer anion basis

[b] calculated on RLY5016 for Oral Suspension (b) (4) weight basis

b) Batch Analysis: The applicant has provided batch analysis data for : a) drug product lots produced at (b) (4) (commercial production facility) that were used in clinical studies, and primary or supportive stability studies, and b) for drug product lots produced at (b) (4) that were used in clinical studies.

c) Validation of Analytical Methods: The method validation reports for drug product methods in use at (b) (4) have been adequately described in the submission, and are acceptable.

***Reviewer's Assessment*: Adequate.** *The proposed drug product specification has been set up to test product critical quality attributes (CQAs) on release. The acceptance criterion for TKEC is based on the acceptance criterion for drug substance and is supported by data obtained from the primary and supportive stability drug product lots. Batch analysis data provided for drug product lots produced at (b) (4) (commercial production facility) and for drug product produced at (b) (4) (used in clinical studies) show that the tested product attributes conform to the proposed specification criteria. At the Type C CMC meeting with FDA on 27 March 2013, the applicant provided rationale for not including a test for heavy metals or elemental impurities in the drug product specification. For elemental impurities, Relypsa proposed to test drug substance and the only excipient, xanthan gum, in accordance with USP <232> and <233>. The Agency has previously agreed with this proposal from the applicant. However, as indicated above, the applicant will need to develop and validate methods to determine levels of (b) (4) lead (Pb) and (b) (4) in xanthan gum. Consistent with ICH Q3B (b) (4) Impurities in New Drug Products, July 2006 , only degradation products are controlled in the drug product. The specified degradation product is calcium fluoride (controlled as fluoride); in addition, individual unspecified and total unspecified extractable impurities are also appropriately controlled in the drug product. Regarding toxicity assessment of fluoride content in the drug product, the applicant has provided animal toxicity data and concluded that there is no acute or chronic safety risk of fluorosis to patients taking the highest proposed dose of RLY5016 for oral suspension ((b) (4) day), even if all of the drug product ingested over the course of their treatment contains fluoride degradant at the limit of NMT (b) (4) ppm. The applicant contends that based on toxicology assessment, the level of fluoride in drug substance and the available batch analysis data for the drug product, manufactured at (b) (4) the commercial acceptance criterion for fluoride is considered justified. Based on input from the concerned reviewer, the pharmacology and toxicology review team does not have any safety concerns about the applicant's proposed acceptance limit (NMT (b) (4) ppm) for the fluoride content in the drug product. The forced degradation studies demonstrate that up to (b) (4) ppm fluoride in the drug product does not impact potassium binding or the total potassium exchange capacity.*

The analytical procedures are appropriately described and validated for their intended use. Importantly, the following methods have been verified and found acceptable for quality control and regulatory purposes by the Division of

Pharmaceutical Analysis, St. Louis, MO 63110:
a) Sorbitol Content in RLY5016S by LC-RI
b) Particle Size Distribution of RLY5016S by Laser Diffraction
c) Determination of Fluoride in RLY5016S by ISE
d) Calcium Identity and Calcium Content of RLY5016S by IC
e) Total Potassium Exchange Capacity of RLY5016S for by IC

(b) (4) *are not controlled in the drug product because adequate controls are in place to control* (b) (4) *in the drug substance and xanthan gum. No* (b) (4) *are used in the drug product manufacturing process. A dissolution test attribute is not applicable to the drug product because of the insolubility of the polymer in most aqueous and organic solutions.* (b) (4) *content is controlled in the drug substance. The level of calcium does not change with long-term storage in the drug substance or the drug product. Therefore, calcium content is not controlled in the drug product. The applicant contends that potassium binding capacity will not be determined for each drug product lot because the total potassium exchange capacity (TKEC) adequately measures the capacity of RLY5016S to bind potassium while minimizing lot to lot variability in the data set for the drug product.*

2.3.P.6 Reference Standards or Materials

The three types of standards used for release and/or stability testing of RLY5016 for oral suspension presented are:

a) In-house manufactured and qualified RLY5016S standard,
(b) Certified National Institute of Standards and Technology (NIST) traceable standards,
(c) Reference material purchased from a commercial source and used as obtained.

Certified standards used to analyze the drug product are tabulated below.

Certified NIST Traceable Reference Standards Used to Test RLY5016 for Oral Suspension

Material Name	Method Type
Fluoride standard (b) (4)	Fluoride content
Calcium standard (b) (4)	Calcium identification
Potassium standard for IC, (b) (4)	Total potassium exchange capacity

IC = ion chromatography

Reference Material: (b) (4) reference material is obtained from a commercial source and the material is used as obtained to test unspecified impurities in RLY5016 for oral suspension by liquid chromatography with ultraviolet detection (LC-UV).

***Reviewer's Assessment*: Adequate.** *The in-house manufactured and qualified standard is the RLY5016S primary reference standard. The RLY5016S primary reference standard is used to generate a reference spectrum for identification of RLY5016 for oral suspension by Fourier transform infrared spectroscopy (FTIR). The details concerning method of preparation, analytical characterization and qualification of the RLY5016S primary reference standard are adequately described under Section 3.2.S.3.1. The certified standards used for quantitative ion analysis are NIST traceable, and are obtained from commercial suppliers.*

2.3.P.7 Container Closure System

i) Primary Packaging: RLY5016 for Oral Suspension (Veltassa) will be made available in (b) (4) packets made from (b) (4) laminate web stock that is (b) (4) . Two packet sizes are used to package drug product.

Configuration A: (b) (4) packet size is the container closure system for the (b) (4) drug product strengths i.e., (b) (4) 8.4 g patiromer (b) (4).

Configuration B: (b) (4) packet size is the container closure system for the for the (b) (4) drug product strengths i.e., 16.8 g patiromer, (b) (4) and 25.2 g patiromer.

Description of (b) (4) Laminate Web Stock for Each Packet Configuration

(b) (4)

Reviewer's Assessment: *Adequate. Though the applicant has referred to Type III DMF* (b) (4) *for web stock information, however all the needed details concerning the container closure system, including the details concerning web stock have been adequately provided in the submitted application. The web stock used to form the packet Configurations A and B is composed of* (b) (4) *The applicant has provided schematic representations of the two packet configurations. The representative technical data sheet, specifications, and representative certificates of analysis for the web stock are acceptable.*

2.3.P.8 Stability

2.3.P.8.1 Stability Studies and Data Analysis: The applicant has provided:

- Primary stability data from 12 lots of drug product (b) (4) 16.8 and 25.2 g strengths) manufactured from (b) (4) drug substance lots.
- Four (4) of the 12 primary stability lots were also evaluated for in-use stability. Additional supportive stability data are provided for 12 drug product lots manufactured from drug substance produced at (b) (4).
- Four (4) of the 12 supportive stability lots have also been evaluated for in-use stability.
- Data from a controlled room temperature (CRT) feasibility study, forced degradation studies, photostability, and thermal cycling have been provided in the submission.
- Detailed Statistical analysis of primary stability data in support of proposed drug product expiration dating period.

Methods and Acceptance Criteria for Stability Studies

Attribute	Method Description	(b) (4) Method Number	Acceptance Criteria
Appearance	Visual	CTMLP-2657	Off-white to light-brown powder; occasional white particles may be present
Total % (b) (4)	IC	CTMLP-2863	(b) (4)
Patiromer Anion Content	Gravimetry	CTMLP-2704	
Potassium Binding Capacity (K-binding)[b]	IC	CTMLP-2901	
Total Potassium Exchange Capacity (TKEC)[b]	IC	CTMLP-2891	
(b) (4)			
Extractable Impurities[a] Individual unspecified Total unspecified	HPLC-UV	CTMLP-2707	(b) (4) NMT NMT
Microbiological Examination of Nonsterile Products[g] Total Aerobic Microbial Count Total Combined Yeasts and Molds Count Specific Organism: *E. coli*	USP <61> USP <62>	MM-1386	(b) (4) NMT NMT Absent
Sedimentation[i]	Visual	CTMLP-2682	Report Results

Proposed Expiration Dating Period: A statistical analysis has been performed on the long-term data from the primary stability study. Analyses follow the methods described in ICH Q1E *Evaluation of Stability Data*, June 2004. The applicant has proposed 24-month

expiration dating period for the drug product using the proposed commercial container closure system.

In-Use Stability Studies: To support a label storage statement that permits drug product storage at room temperature after long-term storage at 2-8°C, the applicant has provided data concerning in-use stability study that has been conducted over a 2- to 4-month period for samples held at 25°C/60% RH after up to 12-month storage at 2-8°C. Appearance, total % (b) (4), patiromer anion content, potassium binding capacity, total potassium exchange capacity, (b) (4) extractable impurities, and sedimentation showed no discernible trend.

Forced Degradation and ICH Photostability Studies: The forced degradation study of the drug product has been conducted using a single lot of drug product to assess the effect of stress conditions on the drug product as well as determine the degradation pathways and confirmed the methods are stability-indicating. The drug product has been exposed to acid, base, thermal and oxidative stress conditions. With the exception of thermal stress, the results of the forced degradation study demonstrate that the drug product is stable to the stress conditions applied. The rate of increase in fluoride levels across the 4-month test interval is temperature-dependent and consistent with Arrhenius kinetics. The results of the thermal cycling study support the conclusion that the drug product can withstand (b) (4); however, drug product should not be exposed to excessive heat during thawing.

***Reviewer's Assessment*: Adequate.** *The primary and supportive stability studies have been designed to bracket the stability of the* (b) (4) *drug product strengths packaged in two packet configurations to support an expiration dating period for all potential commercial strengths. The bracketing design meets ICH Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products. The manufacturing process used for production of the primary stability lots simulated the process that is to be applied to production lots, and used production equipment of the same class per the FDA Draft Guidance for Industry, SUPAC: Manufacturing Equipment Addendum, April 2013. The primary stability lots have been packaged in the same primary container closure system as proposed for marketing. The drug product lots placed on formal ICH stability studies are of the same quality and meet the specifications for commercial drug product.*

This stability data demonstrate that the drug product is stable at long-term storage condition of 2-8°C and at accelerated conditions of 25°C ± 2°C /60%RH for a period of 18 months and 6 months, respectively. No significant trend of change over time has been observed for tested product attributes i.e., appearance, total % (b) (4)*, patiromer anion content, potassium binding capacity, total potassium exchange capacity,* (b) (4) *extractable impurities, sedimentation and microbiological aspects. All these product attributes have remained within acceptance criteria However, fluoride, designated as a degradant shows an increasing trend (range: from* (b) (4) *ppm) at long-term storage condition and a more pronounced increasing trend at accelerated storage condition (range: from* (b) (4) *ppm). A statistical analysis has been performed on the long-term primary stability data. For all attributes and lots evaluated, an expiration dating period has statistically been determined to be* (b) (4) *months. Hence, the applicant has appropriately proposed 24-month expiration dating period based on statistical analysis of the primary stability data. The results from the in-use stability study demonstrate that the drug product remains within specification after storage at 25°C ± 2°C /* (b) (4) *%RH RH for up to* (b) (4) *months and following refrigeration at 2-8°C for up to* (b) (4) *months. The* (b) (4) *results for all lots tested over the in-use periods meet the stability protocol and commercial acceptance criterion of NMT* (b) (4) *ppm. Fluoride for all lots evaluated in the in-use stability study ranged from* (b) (4) *ppm. The in-use stability data shows an increase in fluoride at the rate of approximately* (b) (4) *ppm per month. These results support proposed labeling that allows RLY5016 for oral suspension to be stored for up to 3 months at room temperature conditions. This in-use period will be within the total proposed expiration dating period of 24 months. The results from stress studies support the following added labeling statement: "Avoid exposure to excessive heat above 104°F (40°C)".*

2.3.P.8.2 Post-Approval Stability Commitment

2.3.P.8.2.1 Registration Stability Studies: The applicant commits to continue the ongoing primary and supportive ICH registration stability programs through the end of the proposed drug product shelf-life. Results of the stability studies will be reported in the NDA annual report in accordance with 21 CFR 314.81(b)(2).

2.3.P.8.2.2 First Production Lots: The first three production lots of the lowest and highest marketed strengths of drug product per packet configuration will be entered into stability studies. Samples will be stored at 2 –8°C for 24 months and at 25°C/60% RH for 6 months in accordance with ICH guidelines. In-use stability studies will also be conducted as part of the stability program on at least three lots per packet configuration from the lots selected for the long-term and accelerated stability program. The in-use samples will be transferred from the 2 - 8ºC chamber to a 25ºC/60% RH chamber at the 9-, 15- and 21-month time points. The transferred in-use samples will then be tested at the 1- and 3-month time points.

Reviewer's Assessment: Adequate. *The post-approval stability protocols and commitments are acceptable. As required by 21 CFR 314.81(b)(1)(ii), the applicant commits to report to the FDA any failure of a distributed drug product lot that fails to comply with established specifications. If the applicant confirms that the deviation is a single occurrence that does not affect the safety or efficacy of the drug product, Relypsa will discuss the failure with the Agency and provide justification for the continued distribution of the lot. Otherwise, if confirmed, the applicant will withdraw from the market any lot of the drug product found to fall outside the drug product stability specifications.*

(b) (4)

(b) (4)

Reviewer's Assessment: Not acceptable. Currently, a manufacturing site change is filed as at least a CBE-30, according to the Changes guidance.

(b) (4)

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: From Drug product perspective, the application is not recommended for approval until the pending deficiencies are satisfactorily addressed by the applicant, and an "overall acceptable" recommendation is made by the Office of Compliance for all the listed drug product manufacturing and testing facilities. (b) (4)

Mohan Sapru, Ph.D.
CMC Lead for Cardiovascular and Renal Products (Acting)
ONDP/OPQ/CDER
7/2/2015

Supervisor Comments and Concurrence:
Concur. Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting)
7/6/2015

ASSESSMENT OF THE PROCESS

2.3.P.3 Manufacture

P.3.2 Batch Formula

(b) (4)

(b) (4)

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ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

The Biopharmaceutics assessment is being focused on the evaluation of the information for the in vitro *Total Potassium Exchange Capacity assay* and the in vitro bioequivalence information (*Equilibrium Binding and Kinetic Binding assays)* supporting the approval of the NDA.

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

The proposed drug product is a non-absorbed cation-exchange polymer which binds potassium in the lumen of the colon. Due to the lack of solubility of the polymer, the dissolution test is not included in the specifications controlling the quality of the proposed product. Instead the Applicant is proposing to include an in vitro *Total Potassium Exchange Capacity (TKEC) Test* (CTMLP-2891) as part of the Drug Product Specifications.

- ***Proposed in vitro total potassium exchange capacity test and acceptance criteria:***

The proposed in vitro *Total Potassium Exchange Capacity (TKEC) Test* and acceptance criteria are shown in the following table:

Test Attribute	Method Type	Patheon Method Number	Acceptance Criteria
Total Potassium Exchange Capacity[a]	IC	CTMLP-2891	(b) (4)

[a] calculated on patiromer anion basis

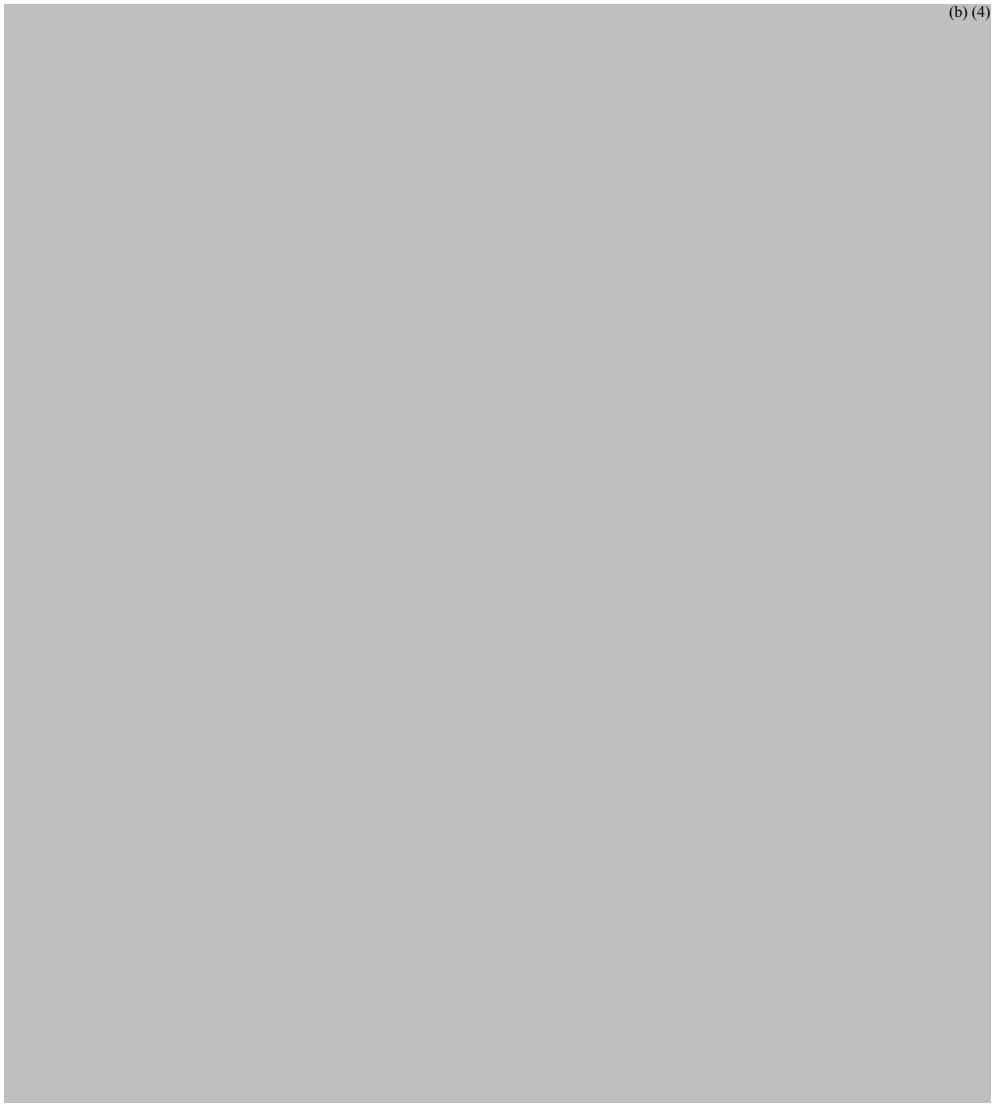
- ***CTMLP-2891 Method description summary (3.2.P.5.2):***

A sample of RLY5016 for Oral Suspension (b) (4)

The method validation report is submitted in section 3.2.P.5.3 of the NDA.

- ***In Vitro Total Potassium Exchange Capacity (TKEC) Acceptance criterion:***

The batch release results obtained from the total potassium exchange capacity test for the primary and supportive stability lots of RLY5016 for oral suspension are shown in the following Table:



Reviewer's Assessment:

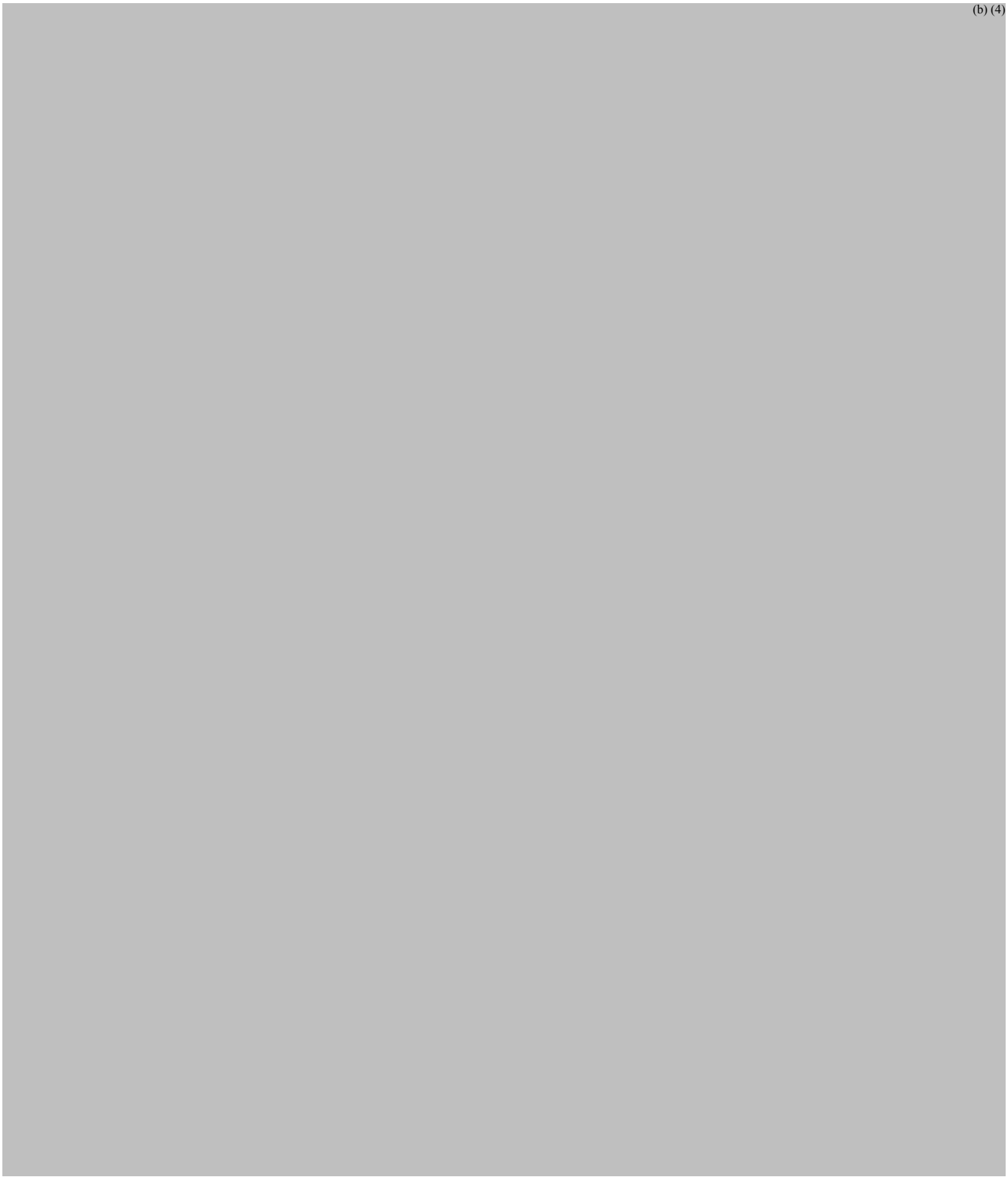
In vitro Total Potassium Exchange Capacity Test:

A consult request for the method validation of this test was sent to the FDA Laboratories in St. Louis, Missouri. The report for this consult was entered in DARRTS on 5/29/15. The report concludes the following:

1. *Total potassium exchange capacity of the RLY5016S based on* (b) (4) *weight is* (b) (4) *meeting specification of* (b) (4)
2. (b) (4)

Based on the above comments, the following information request was sent to the Applicant on 6/9/2015.

> ***"During our methods validation analysis, we noticed that for the proposed Total Potassium Exchange Capacity Test, the*** (b) (4)



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

- ***Formulation Bridging:***

Throughout development, three different formulations were used in the clinical studies. The initial formulation (Formulation A) consisted of drug substance supplied in a high density polyethylene (HDPE) bottle that was used in Phase 1 and early Phase 2 clinical studies. The formulation development activities resulted in a (b) (4) formulation (Formulation B) that was used in some Phase 2 clinical studies. The formulation was simplified to include a single excipient (xanthan gum) resulting in Formulation C, which was used in a Phase 1 clinical study, late Phase 2 clinical studies, the Phase 3 clinical study, and was also used to produce the primary stability lots. **Formulation C is the intended commercial formulation**. The three formulations evaluated during development provide a suspension upon mixing with water. Over the course of development, the components and composition of Formulation C did not change. Therefore, formulation bridging is not needed because Formulation C was used in all Phase 3 pivotal studies.

- ***In vitro Bioequivalence Testing:***

To support major post-approval manufacturing changes that require bioequivalence, the Applicant developed two assays to evaluate the functionality of RLY5016 for Oral Suspension to bind potassium. The approach taken by the Applicant with these assays is consistent with the FDA's in vitro bioequivalence requirements used for other polymeric drugs such as cholestyramine, colesevelam, and sevelamer.

The Applicant developed both, the equilibrium binding and the kinetic binding (supportive) assays. The equilibrium and kinetic binding assays for RLY5016 for Oral Suspension are unique as the polymer binding site is anionic compared to the cationic binding sites in other polymeric drug products. The equilibrium binding and kinetic binding assay development and critical assay parameters are summarized in Section 3.2.P.2.2.3.6.2 and Section 3.2.P.2.2.3.6.3 of the NDA, respectively.

(b) (4)

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(b) (4)

Reviewer's Assessment:

- ***Formulation Bridging:***

Formulation bridging is not required to support this NDA because there were no major manufacturing changes made during or between Phase 2 and Phase 3 clinical development and commercialization.

(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Recommendation and Signature:

The Division of Biopharmaceutics recommends **APPROVAL** of NDA 205739 for Veltassa (partiomer) Powder for Oral Suspension.

June 19, 2015

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, OPQ

Secondary Review Comments and Concurrence:

I concur with Dr. Elsbeth Chikhale's Biopharmaceutics assessment and recommendation.

June 19, 2015

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Branch Chief
Division of Biopharmaceutics, OPQ

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:

RLY5016 is a powder that is intended for reconstitution with water immediately prior to oral administration. Three presentations of the drug product are available, containing (b) (4) 8.4 g, (b) (4) of the active pharmaceutical ingredient.

The drug product is manufactured by (b) (4) The drug product is tested for microbial limits at release using methods consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use) which state that nonaqueous preparations for oral use should contain TAMC of NMT (b) (4) and TYMC of NMT (b) (4) and that *Escherichia coli* should be absent. The microbial limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>.

The drug product will also be tested for microbial limits annually as part of the post-approval stability protocol.

Reviewer's Assessment:

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol.

2.3.P.7 Container/Closure System

23. 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:

Reviewer's Assessment: N/A, product is nonsterile.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

24. 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:

Reviewer's Assessment: N/A

25. 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:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
Erika Pfeiler
3/19/2015

Secondary Review Comments and Concurrence:
Stephen Langille, Ph.D.
Senior Review Microbiologist
3/19/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

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

Applicant's Response: NA

Review of Environmental Assessment

A. Background

Relypsa, Inc. is filing a New Drug Application (NDA) for RLY5016 for Oral Suspension pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. The applicant has submitted an environmental assessment (EA; dated July 28, 2014) pursuant to 21 CFR part.

RLY5016 for Oral Suspension is a non-absorbed polymeric new drug intended for the treatment of hyperkalemia. RLY5016 acts by binding and removing potassium and thus reducing the concentration of free potassium in the gastrointestinal lumen and establishing a gradient by further potassium secretion, resulting in a reduction of total

body potassium. The drug product is available in (b) (4) strengths: (b) (4) 8.4, (b) (4) 16.8, (b) (4) and 25.2 grams.

In an August 12, 2013, letter, Relypsa submitted a Request for Type C Meeting and an EA proposed testing program and questions. Due to the insoluble nature of RLY5016 polymer, Relypsa submitted the request to obtain agreement on the proposed testing plan. The FDA responded in an August 30, 2013 'Meeting Granted letter' wherein FDA stated that written responses to the questions would be provided in lieu of a meeting. Written responses were provided in a November 23, 2013 letter. The FDA was in general agreement with Relypsa's proposed testing plan. The provided EA follows the agreed upon plan. To note the testing plan follows similar recommendations provided for other insoluble drug products (sevelamer carbonate, colesevelam hydrochloride).

B. Discussion

Executive Summary

This EA supports an NDA for RLY5016 for Oral Suspension. The EA was prepared in accordance with 21 CFR Part 25 by Relypsa, Inc. and in accordance with FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998, with modifications as discussed November 23, 2013, FDA letter.

The EA was be performed on the basis of fate and effect data for the drug substance; RLY5016S (i.e., without the xanthan gum). RLY5016S is expected to enter the environment from patient use and disposal. Due to its chemical nature, RLY5016S is expected to partition to sewage biosolid and enter the terrestrial environment by application to soils. Aquatic exposures are expected to be minimal. The sponsor used ecotoxicology data to estimate toxicity parameters. A screening-level environmental risk analysis was performed for fluoride, a degradation product, using information available from publicly available scientific literature. Specifically, based on ecotoxicity effects data for terrestrial invertebrates and plants and for aquatic receptors, comparison of terrestrial and aquatic environmental concentrations (EIC, EEC) to toxicity values allows the conclusion that RLY5016S residues in the environment are not expected to present a significant environmental impact.

C. Environmental Assessment

1. ***EA Date:*** July 28, 2014
2. ***Applicant***: Relypsa, Inc.((b) (4)
3. ***Address:*** (b) (4)
4. ***Proposed Action:*** Relypsa, Inc.is requesting approval of RLY5016 for Oral Suspension intended for the treatment of hyperkalemia.
5. ***Identification of Chemicals:***

Active moiety: (b) (4) ***Drug Substance: RLY5016S***

The drug substance, RLY5016S, consists of a negatively-charged, cross-linked polymer anion, (b) (4) (i.e., the active moiety), with a calcium-sorbitol (b) (4) as the

counter-ion (RLY5016S). For this EA, laboratory testing was conducted on the drug substance, RLY5016S (i.e., without the xanthan gum). The drug product, RLY5016, contains (b) (4) %t by weight (wt%) of the drug substance, RLY5016S, and (b) (4) wt% of an excipient, xanthan gum

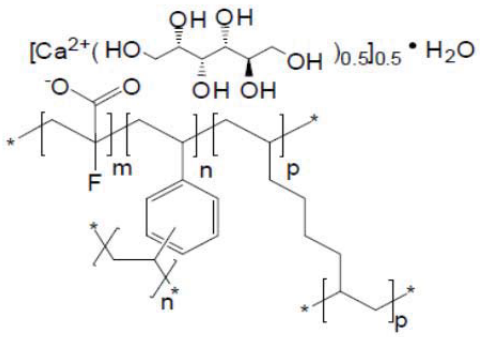
RLY5016S Nomenclature:

Name	***RLY5016S***
Established Name (U.S. Adopted Name-USAN)	Applied for
Brand/Proprietary Name /Tradename	Veltassa: To be approved
Chemical Abstracts Index Name (inverted form)	(b) (4)
Systematic Chemical Name (uninverted form)	Not available
IUPAC Name	(b) (4)

Chemical Abstracts Service (CAS) Registration Number: *1415477-49-4*
Molecular Formula: $C_{613}H_{765}F_{114}O_{399}Ca_{57}$.
Molecular Weight: "The molecular weight of a (b) (4) RLY5015S bead is estimated as (b) (4) The estimate is calculated using an experimentally-derived value for density and the theoretical calculated value for volume.
Structural Formula:

(a) Structure of RLY5016S; (b) Alternative representation of RLY5016S

(a)



(b) (4)

m = number of 2-fluoro-2-propenoate groups (m=0.91)
n, p = number of crosslinking groups n + p = 0.09

•H_2O = associated water
* = indicates an extended polymeric network

6. Environmental Characterization

Environmental Fate and Effects

RLY5016S

Environmental depletion mechanisms (i.e., biodegradation, hydrolysis) were not investigated due to analytical limitations. Polymeric degradation products of RLY5016 for Oral Suspension have not been observed. Fluoride, as calcium fluoride, is the only observed degradation product of RLY5016 for Oral Suspension.

Review Comments: The assessment assumes no degradation for purposes of estimating exposure concentrations. Environmental concentrations are based on worst case scenarios (this includes production estimates for the 5th year post approval and therefore includes drug product disposed of post-production from home environments). According to the applicant, the biodegradation test is not feasible. Although mineralization could be measured, any other degradation cannot be characterized due to analytical limitations. If no significant risk is indicated for the worst-case situation, then additional information on biodegradation would not be required for this specific application. A fuller explanation of why such a study is not feasible would assist in the assessment.

Environmental Fate/Exposure Concentrations

The sponsor estimates a projected annual production of the RLY5016S for use in the U.S. after 5 years at (b) (4) /year. This equates to (b) (4) yr as the polymer anion (i.e., active moiety).

Terrestrial Exposure Concentrations

Due to its insolubility and partitioning characteristics, the environmental fate of RLY5016S for Oral Suspension is predicted to be primarily terrestrial. After entering publicly owned treatment works (POTWs) in human wastes, RLY5016S is expected to partition into sludge, rather than effluent. The application of sludge as biosolids to soils is the primary pathway by which RLY5016S is expected to enter the environment.

This terrestrial exposure calculation ($EIC_{biosolids}$) assumes: (1) all of the annual active moiety production is used throughout the United States and enters the POTW system in proportion to the population;(2) the active moiety is not degraded within the POTW system; and (3) the active moiety partitions entirely to biosolids. The $EEC_{amended\ soil}$ uses the highest estimate of biosolid application rates. The modelled exposure concentrations are used to evaluate ecological effects in aquatic systems assuming 100% loading to wastewater effluent following treatment by POTWs.

Conservative estimates of terrestrial exposure to the active moiety (polymer anion) and its degradation product, fluoride, are summarized below:

Terrestrial Exposure Summary

Chemical	EIC (mg/kg biosolids)	EEC (mg/kg amended soil)
Active Moiety Fluoride	(b) (4)	

*assumes biosolids application rate of (b) (4) tons per acre

Aquatic Exposure Concentrations

Hypothetical, worst-case estimates of aquatic exposure to the polymer anion and its degradation product, fluoride, are summarized.

Aquatic Exposure Summary

Chemical	EIC (µg/L effluent)	EEC (µg/L surface water)
Active Moiety Fluoride	(b) (4)	

Review Comments: The applicant uses worst-case estimates as recommended in the FDA response to the sponsor's request for the Type C Meeting noted above. In addition, the applicant uses a value of (b) (4) tons per acre for biosolid application rates. The EPA provides a range of values between (b) (4) tons per acre, so the provided estimate is highly conservative. A more typical agricultural soil application rate is (b) (4) tons per acre. A more typical EEC $_{\text{amended soil}}$ for agricultural soils would therefore be (b) (4).

Environmental Effects

Testing was conducted to determine the toxicity of RLY5016S to microorganisms present in activated sludge. RLY5016S has no significant adverse effects on activated sludge no adverse effects on wastewater treatment processes are expected due to the usage of RLY5016S.

Terrestrial

Estimated margins of safety between toxicity parameters and expected concentrations are provided below for *Eisenia fetida.*

Estimated Margin of Safety for RLY5016S on Terrestrial Invertebrates

Toxicity Value	RLY5016S (mg/kg)	Active Moiety (mg/kg)	EIC (mg/kg biosolids)	EIC-based Margin of Safety	EEC (mg/kg amended soil)	EEC-based Margin of Safety
LC_{50}	(b) (4)					

*****assumes biosolids application rate of (b) (4) tons per acre

Testing was conducted to determine the acute toxicity of RLY5016S to oat (*Avena ativa*), radish (*Raphanus sativus*), and lettuce (*Lactuca sativa*) seeds and seedlings. Estimated margins of safety are provided below:

14-day Acute Toxicity to Terrestrial Plants

	NOEC (mg/kg)	EC_{25} (mg/kg)	EC_{50} (mg/kg)

Percent Emergence Oats (*A. sativa*) Radish (*R. sativus*) Lettuce (*L. sativa*) Fresh Shoot Weight Oats (*A. sativa*) Radish (*R. sativus*) Lettuce (*L. sativa*)	(b) (4)

Estimated Margin of Safety for RLY5016S on Terrestrial Plants

Toxicity Value	RLY5016S (mg/kg)	Active Moiety (mg/kg)	EIC (mg/kg biosolids)	EIC-based Margin of Safety	EEC (mg/kg amended soil)	EEC-based Margin of Safety
EC_{50}	(b) (4)					
NOEC						

*****assumes biosolids application rate of (b) (4) tons per acre

Review Comments: Testing was conducted to determine the acute toxicity of RLY5016S to earthworms (*Eisenia fetida)* at nominal RLY5016S concentrations of (b) (4) . Earthworms exhibited no significant adverse effects due to RLY5016S at any concentration tested. The NOEC was therefore set at (b) (4) No effects were seen at the highest test concentration for oats and lettuce. An effect was observed for fresh shoot weight for radish with an EC_{50} > (b) (4) the highest concentration tested. The EEC is based on a conservative biosolids estimate . USEPA (United States Environmental Protection Agency (USEPA). 2000a. Biosolids Technology Fact Sheet. Land Application of Biosolids. USEPA Office of Water. EPA-832-F-00-064) presents a range of (b) (4) tons per acre for multiple biosolid application scenarios including agricultural land, forest land, range land, and reclamation land, with the highest typical application rate for agricultural soils of (b) (4) tons per acre. For this EA, the applicant chose to use a rate of (b) (4) tons per acre ((b) (4)), a conservative estimate. Therefore, the margins of safety would be expected to be > (b) (4) in the vast majority of agricultural scenarios.

Aquatic

Testing was conducted to determine acute toxicity of RLY5016S to the freshwater green alga, *Pseudokirchneriella subcapitata*. Estimated margins of safety are provided below :

Estimated Margin of Safety for RLY5016S on Freshwater Algae

Effect Level	RLY5016S (mg/L)	Active Moiety (mg/L)	EIC (µg/L POTW effluent)	EIC-based Margin of Safety	EEC (µg/L surface water)	EEC-based Margin of Safety
EC_{50}	(b) (4)					

Based on the non-soluble nature of the drug substance and high margin of safety for freshwater green algae was calculated (> (b) (4) based on EIC), no further GLP aquatic toxicity testing (i.e., fish and invertebrates) was conducted. However, pilot testing was conducted with water fleas (*Daphnia magna*) and rainbow trout (*Oncorhynchusmykiss*). The 48-hour EC50 for daphnia was empirically estimated to be> (b) (4). The NOEC was reported as < (b) (4). The 96-hour LC50 for rainbow trout was empirically estimated to be > (b) (4) and the NOEC was empirically estimated to be (b) (4)

Review Comments: RLY5016S is not expected to be present in treated POTW effluent and thus exposures to aquatic organisms is expected to be minimal. Nevertheless, as a conservative screening analysis, the applicant included an aquatic risk assessment. A high margin of safety was noted for water fleas (*Daphnia magna*) and rainbow trout (*Oncorhynchus mykiss*), even when considering a worst-case scenario EEC of (b) (4).

(b) (4)

Risk Characterization

Reviewer's comments: RLY5016S is insoluble and is therefore expected to partition primarily to sewage biosolids (sewage sludge). Terrestrial exposure will occur when biosolids are applied to soils. Worst-case scenarios are used to estimate environmental concentrations and margins of safety between concentrations and effect values. Risk estimates were based on this approach for both terrestrial and aquatic organisms for RLY5016S and fluoride. No significant ecological impacts are expected to occur due to patient use and post-production disposal by patient of the drug product.

7. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

8. Submitted Study Reports

The following study reports were submitted in support of the EA. The studies were conducted in accordance with OECD guidelines and Good Laboratory Practice regulations

- Determination of the Water Solubility of RLY5016S Based on OECD Guideline 105
- Determination of the Solvent Solubility of RLY5016S Based on OECD Guideline 105 (Solvent Solubility Modification of the Water Solubility Method)
- RLY5016S - Activated Sludge Respiration Inhibition Test Following OECD Guideline 209
- RLY5016S - Acute Toxicity to Earthworms (*Eisenia fetida*) Following OECD Guideline #207
- RLY5016S – Seedling Emergence and Seedling Growth Test Following OECD Guideline #208
- RLY5016S − 72-Hour Toxicity Test with the Freshwater Green Alga, *Pseudokirchneriella subcapitata*, Following OECD Guideline 201

The following pilot study reports were preliminary and did not conform to data quality standards associated with GLP

- RLY5016S - Acute Toxicity to Water Fleas, (*Daphnia magna*) Under Static Conditions
- RLY5016S - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, Following OECD Guideline #203
- RLY5016S – 72-Hour Acute Toxicity Test with Freshwater Green Alga, *Pseudokirchneriella subcapitata* Following OECD Guideline 201

D. Literature Reviewed

No literature on RLY5016/RLY5016S/Patiromer as related to environmental occurrences, fate and ecotoxicity were found. Other polymeric drug products (sevelamer hydrochloride, colesevelam hydrochloride) appear to behave similarly in the environment. No literature in fate and effects was identified for these compounds.

E. Comments and Conclusions

The EA is adequate for approval of the NDA. It contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and supporting reports, and of the scientific validity of the "no significant effects" conclusions of the EA, no significant adverse environmental impacts are expected from approval of this NDA.

Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application

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Cumulative Impact
(not intended to support reviewer's conclusions for this proposed action)

NDA 205-739 (RLY5016) is an original submission. There are no U.S. marketed generic applications or other NDA applications and RLY5016 is not listed in the IMS National Sales data set. Environmental introductions are due solely to approval of this application.

Reviewer's Assessment:

The EA supports an NDA for RLY5016 for Oral Suspension. The EA was prepared in accordance with 21 CFR Part 25 and in accordance with FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998, with modifications as discussed November 23, 2013, FDA letter.

The EA was be performed on the basis of fate and effect data for the drug substance; RLY5016S (i.e., without the xanthan gum). RLY5016S is expected to enter the environment from patient use and disposal. Due to its chemical nature, RLY5016S is expected to partition to sewage biosolid and enter the terrestrial environment by application to soils. Aquatic exposures are expected to be minimal. The sponsor used ecotoxicology data to estimate toxicity parameters. A screening-level environmental risk analysis was also performed for fluoride, a degradation product, using information available from publicly available scientific literature. Based on ecotoxicity effects data for terrestrial invertebrates and plants and for aquatic receptors, comparison of terrestrial and aquatic environmental concentrations (EIC, EEC) to toxicity values allows the conclusion that RLY5016S residues in the environment are not expected to present a significant environmental impact.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

The EA is adequate for approval of the NDA. It contains sufficient information to enable

the agency to determine whether the proposed action may significantly affect the quality of the human environment. Based on an evaluation of the information provided in the EA and supporting reports, no significant environmental impacts are expected from approval of this NDA. Based on the information available to date, a finding of no significant impact (FONSI) is recommended for this application.

Raanan Bloom Ph.D.
Reviewer, ONDP/EA Team
7/6/2015

Secondary Review Comments and Concurrence:
Concur
Scott Furness, Ph.D.
Deputy Director
Office of New Drug Product/OPQ
7/6/2015

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

Labeling & Package Insert

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

Item	Information Provided in NDA
Proprietary name and established name	Proprietary: Veltassa Established Name: Patiromer
Dosage form, route of administration	Dosage: Veltassa for Oral Suspension Route: Oral
Controlled drug substance symbol (if applicable)	N/A
A concise summary of dosage forms and strengths	Veltassa for Oral Suspension (b) (4) 8.4 g, (b) (4) 16.8 g, (b) (4) and 25.2 g

Reviewer's Assessment: Adequate. Regarding draft label text, the information concerning proprietary name, established name, and dosage and route of administration is acceptable from the CMC perspective.

B. Section 2.2. Dose Preparation Instructions

Reviewer's Assessment: Adequate. The dose preparation instructions, involving (b) (4) suspension i.e., addition of water, (b) (4)

C. Section 11. Description

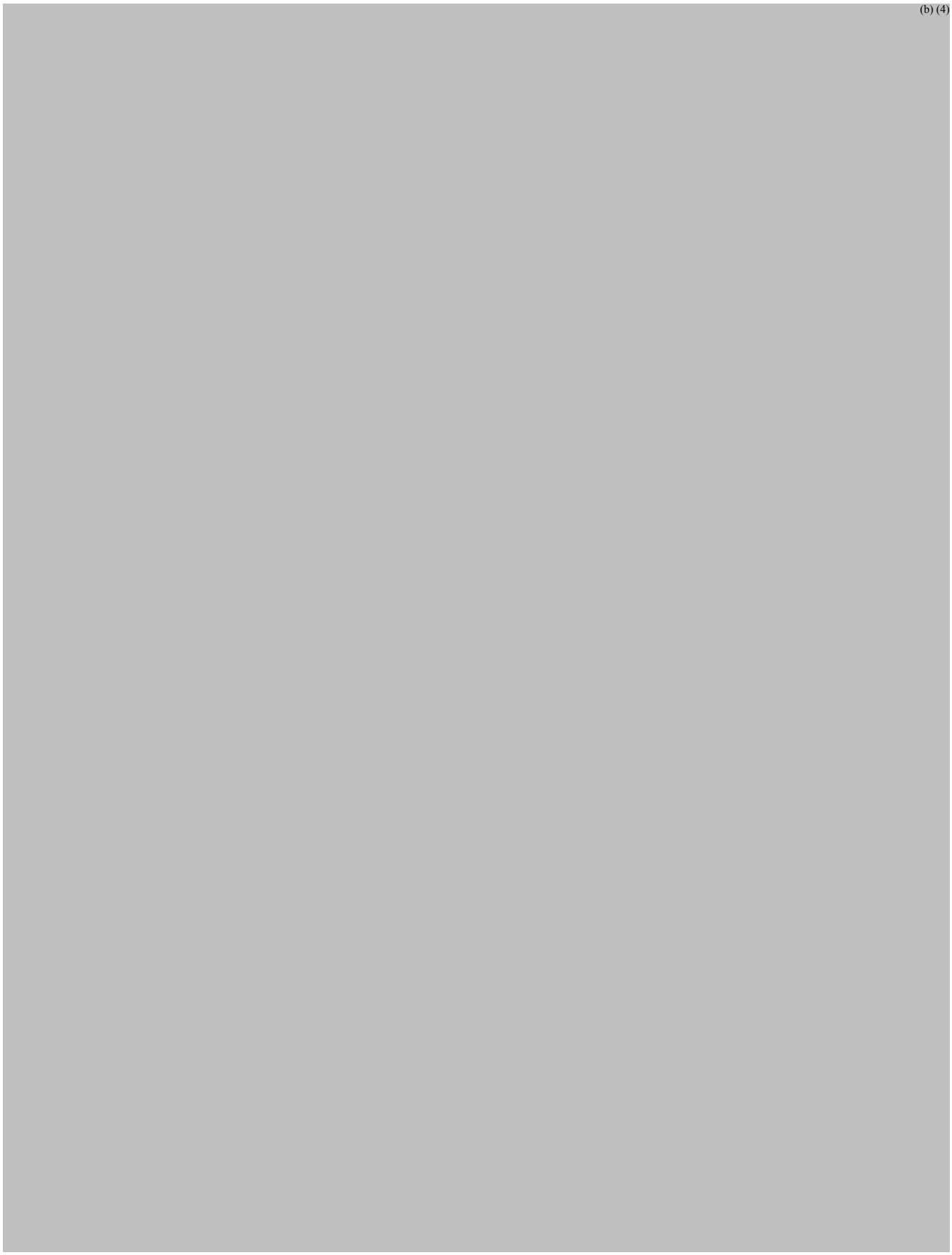
Reviewer's Assessment: Adequate. It is clearly indicated that the active ingredient is patiromer sorbitex calcium which consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium-sorbitol counterion. The chemical structure of patiromer sorbitex calcium has been included under 'Description'. The description of dosage form and strengths is acceptable.

D. Section 16.2. Stability and Storage

Reviewer's Assessment: Adequate. The specified storage conditions are supported by the drug product stability data, including results from in-use stability testing. The instructions for storage are acceptable from CMC perspective.

E. Representative Carton Label

(b) (4)



Reviewer's Assessment: Adequate. The carton adequately displays the proprietary, established names, dosage strength, package content, directions for use, and storage instructions. The specified information on the carton is acceptable from CMC perspective.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: The labelling is acceptable from CMC perspective.
Mohan Sapru, Ph.D.
CMC Lead for Cardiovascular and Renal Products (Acting)
ONDP/OPQ/CDER
7/2/2015

Secondary Review Comments and Concurrence:
Concur. Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting)
7/6/2015

II. List of Deficiencies To Be Communicated

1. In your amendment dated May 5, 2015, you indicated that the following tests, which were used to generate data provided in the primary stability study, will not be used to generate stability data for future batches: Impurities in RLY5016S by GC-FID Method 1; Impurities in RLY5016S by LC-UV Method 1; and Potassium Binding Capacity. Please update your stability protocol and specification in your NDA with regard to these tests.
2. (b) (4)

III. Attachments

1. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Impurity formation exceeds specification	L	Fluoride (as CaF_2) is the only degradant and its formation can be significantly retarded by storing both DS and DP under refrigeration	Acceptable	The combination of long-term and in-use storage can be confusing to patients and pharmacists
Physical stability (solid state)	Morphic form interconversion	L	Insoluble, non-absorbed amorphous powder -- inherent property of drug substance	Acceptable	
Content Uniformity	Segregation; particle size/shape	L	Formulation is (b) (4) % drug, (b) (4) excipient	Acceptable	Decrease in ratio of drug to excipient could increase risk
(b) (4)					
Microbial Limits	Moisture; equipment, process environment	L	No water in product manufacturing process; microbial limits test included in drug product specification	Acceptable	Change in manufacturing process and /or deletion of microbial limits test from the product specification could increase risk
In vitro Total Potassium Exchange Capacity (TKEC) Test	Total number of potassium binding sites on the polymer	L	Control of manufacturing process	Acceptable	Changes in the manufacturing process could affect the TKEC

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

METHODS VALIDATION REPORT SUMMARY

TO: Raymond P. Frankewich, Ph.D., CMC Reviewer
Kasturi Srinivasachar, Ph.D., CMC Lead

Office of New Drug Quality Assessment (ONDQA)
E-mail Address: raymond.frankewich@fda.hhs.gov
Phone: (301)-796-1354
Fax: (301)-796-9749

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

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

SUBJECT: Methods Validation Report Summary

Application Number: 205739

Name of Product: Veltassa (patiromer) Powder for Oral Suspension

Applicant: Relypsa, Inc.

Applicant's Contact Person: Sarah McNulty, Vice President, Regulatory Affairs

Address: 700 Saginaw Drive
Redwood City, CA 94063

Telephone: 650-421-9570 Fax: 650-421-9770
Email: smcnulty@relypsa.com

Date Methods Validation Consult Request Form Received by DPA: 11/26/2014

Date Methods Validation Package Received by DPA: 11/26/2014

Date Samples Received by DPA: 12/17/2014

Date Analytical Completed by DPA: 05/29/2015

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.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-2135
FAX (314) 539-2113

Date: May 29, 2015

To: Raymond P. Frankewich, Ph.D., CMC Reviewer, OPQ/ONDQA
Katsuri Srinivasachar, Ph.D., CMC Lead, OPQ/ONDQA

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

From: Ilan Geerlof-Vidavsky, Chemist, CDER/OPQ/OTR/DPA
Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Xiaofei Liu, Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification of NDA 205379: Patiromer powder for oral suspension

The following methods were verified and found acceptable for quality control and regulatory purposes.

1) Sorbitol Content in RLY5016S by LC-RI
2) Particle Size Distribution of RLY5016S by Laser Diffraction
3) Determination of Fluoride in RLY5016S by ISE
4) Calcium Identity and Calcium Content of RLY5016S by IC
5) Total Potassium Exchange Capacity of RLY5016S for by IC

The Division of Pharmaceutical Analysis was unable to perform the following method due to instrumentation limitations:

1) Identity of RLY5016S by Fluorine Content Using Oxygen Combustion with ISE

Additionally, the Total Potassium Exchange Capacity of RLY5016S by IC method is identical for the drug substance and drug product and was performed on the drug substance only.

Analyst worksheets can be viewed through the following link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880a43e47

Summary of Results:

1) Sorbitol Content in RLY5016S by LC-RI

Sorbitol content on a (b) (4) Weight basis is (b) (4) %, meeting specification of (b) (4) %.

2) Particle Size Distribution of RLY5016S by Laser Diffraction

	Average Value (µm)	Acceptance Criteria	
D (b) (4)	(b) (4)	NLT (b) (4)	pass
D		(b) (4)	pass
D		NMT (b) (4)	Pass

3) Determination of Fluoride in RLY5016S by ISE

Average inorganic F ion in RLY5016S is (b) (4) ppm, meeting specification of NMT (b) (4) ppm.

4) Calcium Identity and Calcium Content of RLY5016S by IC

- Calcium retention time is (b) (4) % of the reference standard, confirming positive identification of RLY5016S. The % Agreement specification is (b) (4) %.
- Calcium content of RLY5016S (b) (4) weight basis) is (b) (4) %, meeting specification of (b) (4) wt%.

5) Total Potassium Exchange Capacity of RLY5016S for by IC

- Total potassium exchange capacity of the RLY5016S based on (b) (4) weight is (b) (4), meeting specification of (b) (4)
- (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
05/29/2015

MICHAEL L TREHY
05/29/2015

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 205739	**Submission Type: 505(b)(1)**	**Established/Proper Name: Patiromer/Veltassa (proposed)**
Applicant: Relypsa, Inc.	**Letter Date: October 21, 2014**	**Dosage Form: Powder for Oral Suspension**
Chemical Type: 1 (NME)	**Stamp Date: October 21, 2014**	**Strength: (b) (4) 8.4, (b) (4) 16.8, (b) (4) 25.2 grams patiromer**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	x	☐	
2.	Botanical[1]	☐	x	
3.	Naturally-derived Product	☐	x	
4.	Narrow Therapeutic Index Drug	☐	x	
5.	PET Drug	☐	x	
6.	PEPFAR Drug	☐	x	
7.	Sterile Drug Product	☐	x	
8.	Transdermal[1]	☐	x	
9.	Pediatric form/dose[1]	☐	x	
10.	Locally acting drug[1]	x	☐	Non-absorbed cation-exchange polymer that binds potassium in the lumen of the colon
11.	Lyophilized product[1]	☐	x	
12.	First generic[1]	☐	x	
13.	Solid dispersion product[1]	☐	x	
14.	Oral disintegrating tablet[1]	☐	x	
15.	Modified release product[1]	☐	x	
16.	Liposome product[1]	☐	x	
17.	Biosimiliar product[1]	☐	x	

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FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
18.	Combination Product _____		☐	x	
19.	Other_____		☐	☐	
	Regulatory Considerations				
20.	USAN Name Assigned		x	☐	(b) (4)
21.	End of Phase II/Pre-NDA Agreements		x	☐	Designation of drug substance and starting materials
22.	SPOTS (Special Products On-line Tracking System)		☐	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	x	
24.	(b) (4)				
25.	Other_____		☐	☐	
	Quality Considerations				
26.	Drug Substance Overage		☐	x	
27.	Design Space	Formulation	☐	x	
28.		Process	☐	x	DS process parameter ranges (referred to as "design space" by Applicant) defined using systematic experimentation and DOE.
29.		Analytical Methods	☐	x	
30.		Other	☐	☐	
31.	Real Time Release Testing (RTRT)		☐	x	
32.	Parametric Release in lieu of Sterility Testing		☐	x	
33.	Alternative Microbiological Test Methods		☐	x	
34.	Process Analytical Technology[1]		☐	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	x	☐	Total potassium exchange capacity, fluoride content etc.
36.		Excipients	☐	☐	
37.		Microbial	☐	☐	
38.	Unique analytical methodology[1]		x	☐	Fluoride content by ion selective electrode
39.	Excipients of Human or Animal Origin		☐	x	
40.	Novel Excipients		☐	x	
41.	Nanomaterials[1]		☐	x	
42.	Hold Times Exceeding 30 Days		☐	x	
43.	Genotoxic Impurities or Structural Alerts		☐	x	
44.	Continuous Manufacturing		☐	x	
45.	Other unique manufacturing process[1]		x	☐	(b) (4)
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	x	
47.	New delivery system or dosage form[1]		☐	x	
48.	Novel BE study designs		☐	x	
49.	New product design[1]		☐	x	
50.	Other_____		☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	x	☐	☐	EA report submitted
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o (b) (4)	x	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	x	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x	☐	☐	
	DRUG SUBSTANCE INFORMATION				

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C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	x	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	x	☐	☐	
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used	x	☐	☐	

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FILING REVIEW

C. FILING CONSIDERATIONS					
	in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	x	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product?	x	☐	☐	Formulation bridging cannot be done via a BE study because the drug is not systemically absorbed. Instead, the Applicant has conducted equilibrium

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)				kinetic binding assay studies to support the bridging of the different formulations.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	x	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	x	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	x	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	x	☐	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	x	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	☐	☐	x	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be				

C. FILING CONSIDERATIONS					
	marketed with summaries of test results for those samples				

Kasturi Srinivasachar -S

Digitally signed by Kasturi Srinivasachar -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300080217, cn=Kasturi Srinivasachar -S
Date: 2014.11.25 11:51 58 -05'00'