APPLICATION NUMBER:

208984Orig1s000
022128Orig1s017

CHEMISTRY REVIEW(S)
### Submission Overall Manufacturing Facility Status

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### Submission Manufacturing Facilities

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

/s/

JONATHAN T DOW
11/15/2016
Review of Chemistry, Manufacturing, and Controls

Drugs Product Name
- Proprietary: SELZENTRY Tablets
- Nonproprietary/USAN: Maraviroc

Pharmacological Category/Indication: Treatment of HIV-1 infection

Dosage Form: Tablets

Strengths: 25mg, 75mg, 150mg and 300mg Maraviroc / tablet

Route of Administration: Oral

Dispensed: R

Special Products: ☐ Yes ☒ No

Chemical Name: 4,4-Difluoro-N-[(1S)-3-{exo-3-(3-isopropyl-5-methyl-4H1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide

Molecular Formula: C_{29}H_{41}F_{2}N_{5}O

Molecular Weight: 513.67

Supporting Documents: NA


Remarks/Comments:
This Efficacy supplement requests approval to manufacture two lower strength tablets (25mg and 75mg) of SELZENTRY (maraviroc) Tablets and to revise the Label accordingly. The two new strengths for pediatric use will be manufactured using a process similar to the manufacture of the current and approved commercial maraviroc tablets, 150 mg and 300mg. Consequently, the manufacturer, batch formulation, manufacturing process and equipment, packaging, and much of the testing remain unchanged and already approved. Nevertheless, considerable attention has been paid to ensuring the validity of using analogous methods and testing in the manufacture of lower strength tablets. For example, one manufacturing step, the pursuance, is based on successful studies with all tablet strengths. The lower strength tablets used in the clinical studies do differ from the commercial pediatric product, These minor modifications made to the clinical formulation are identical to the differences that existed between the clinical and commercial adult tablets and are unlikely to affect drug quality or efficacy.
Assessment was made on potential effects of [redacted]. 

The regulatory specifications for the maraviroc 25mg and 75mg tablets are essentially identical to those for the adult strength tablets. The only noted differences are the acceptance criteria for Appearance, [redacted]. Although testing is similar, revision has been made based on the lower tablet strengths. Four tests have undergone revision: ID, Content Uniformity, Assay, and Dissolution. These analytical procedures (as well as the entire testing monograph) have been presented, along with the results from their validation studies. The package is well-organized and is acceptable. Results from testing clinical and commercial batches of 25mg and 75mg tablet strength have been provided. All test results for the batches of maraviroc 25mg and 75mg tablets comply with the specifications; they not only agree with one another but also agree with the comparative results from a 150mg batch. The justification for the proposed acceptance criteria and the rationale for the selection of the test methods have been adequately discussed and are aligned with maraviroc adult strength tablets. Justification included the reason for excluding other test requirements.

The proposed commercial container closure system for maraviroc 25mg and 75mg tablets is the same as that in use with the 150mg and 300mg commercial formulations—namely, a high density polyethylene bottle and [redacted] closure with heat induction seal. The HDPE bottles have been tested in accordance with USP and have met all established acceptance criteria for “Tight Containers.”

Stability studies with maraviroc 25mg and 75mg tablets packaged in HDPE bottles were carried out using long-term, intermediate, and accelerated conditions. Only results from 12mo and 6mo of study are available at this time with three commercial batches of 25mg tablets. With the 75mg tablets, however, results from 60mo and 6mo are available from three batches manufactured as part of the original adult strength filing. These results can be considered as primary support in that batch size was [redacted] only tablet debossing (as proposed for commercial product) is missing and will have no impact on product stability, and the packaging used was the presently-proposed HDPE bottles. Supporting studies included stability testing with one clinical batch of 25mg tablets and photostability studies with one batch of each pediatric strength. Comparison with stability results with the adult strength tablets was provided.

The data from the long-term primary and supporting stability studies demonstrated that, after as many as 60 months, there were no significant trends in any of the measured parameters. All results complied with the specifications. The results of Dissolution testing further documented that the fast-dissolving nature of the tablets (Q= [redacted] at 30min) had not been affected. Biopharmaceutics review concluded that the dissolution method previously approved for the 150mg and 300mg SELZENTRY Tablets and used as the quality control method for release and stability testing of batches of the newly proposed pediatric strength tablets provided dissolution data that supported the bridging between the clinical and commercial formulations of the proposed tablets. During the course of this review, [redacted], the sponsor committed to [redacted] the acceptance criterion for dissolution testing to Q= [redacted] at 15 minutes.

The review concluded: “From a Biopharmaceutics perspective, NDA-022128-
SUPPL-17 for the proposed two new lower strength Selzentry® (maraviroc) tablets (25 mg and 75 mg) is recommended for Approval.”

The exceptional product stability was evident in the results using accelerated conditions, in which all batches tested during 6 months remained within specifications and showed no adverse stability trends. Further confirmation of a stable product was provided by the results of the photostability studies, which demonstrated that the tablets are stable to light and require no precautionary packaging or labeling. Finally, comparison with stability results reported for the 150mg and 300mg tablets reinforced this conclusion about exceptional product stability. The proposed expiration date of 60 months can be approved for maraviroc 25mg and 75mg tablets packaged in HDPE bottles. The storage conditions approved for the adult tablets is applicable to the label for the pediatric tablets: “Store at 25°C (77°F); excursion permitted between 15°C and 30°C (59°-86°F) [USP Controlled Room Temperature].”

The post-approval stability protocol and commitment are standard.

As noted by various FDA guidances: “Validated quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference.” In other words, “the stability-indicating test does not have to be the assay method used to determine product strength.” The validation studies on the HPLC method for monitoring degradation products established the linearity (to $\%$) and accuracy in measuring degradants and demonstrated that they are well-resolved from the active ingredient, which permits making a reliable estimate of the quantity of any degradant.

A categorical exclusion from environmental assessment requirements has been justified and is acceptable. The Package Insert includes under Dosage Forms and Strengths and Description adequate description of the two new tablet strengths. In How Supplied/Storage and Handling (Tablets only) the identification of the 4 tablet strengths is clear and satisfactory. The Container labels adequately provide the required information and differentiate the contents by label color: green for 25mg tablets and grey for 75mg tablets.

Because the lower strength tablets will be manufactured at the same sites that manufacture the approved higher strengths [censored] no site inspection appears needed. However, the Office of Process and Facilities has issued an Overall Manufacturing Inspection Recommendation of Approval for all facilities based on profile.

CONCLUSIONS & RECOMMENDATIONS: The CMC information presented in the submission is sufficient to recommend APPROVAL of this supplement.

cc: Orig. NDA 22-128
DMIIHP/Division File
DMIIHP/CSO/A.Patel

Allan Fenselau, Ph.D., Review Chemist

DRAFT SUPPLEMENT LETTER

There are no CMC–specific deficiencies.

Page 3 of 30
Biopharmaceutics Consult

The Biopharmaceutics Review dated 21-OCT-2016 by Dr. Y. Zhao (Biopharmaceutics reviewer) noted that the dissolution method previously approved for the 150 mg and 300 mg SELZENTRY (maraviroc) Tablets has been employed as the quality control method for release and stability testing of batches of the newly proposed SELZENTRY (Maraviroc) Tablets 25 mg and 75 mg. The provided dissolution data were found to support the bridging between the clinical and commercial formulations of the proposed 25 mg and 75 mg SELZENTRY Tablets. During the course of this review, the sponsor committed to the acceptance criterion for dissolution testing Q(≥93) % at 15 minutes. The appropriateness of a dissolution acceptance criterion of Q(≥90) % at 15 minutes was evaluated. The review concluded: “From a Biopharmaceutics perspective, NDA-022128-SUPPL-17 for the proposed two new lower strength Selzentry® (maraviroc) tablets (25 mg and 75 mg) is recommended for Approval.”

Post-Approval Stability Protocol and Commitment: The stability program for primary batches was completed through 60 months for the maraviroc 75mg tablets in accord with the accepted protocol. The stability program for maraviroc 25mg tablets registration batches was completed to only 12 months, but will run to 60 months per this protocol. The registration batches were manufactured at the proposed commercial site, by the proposed commercial process, of the proposed commercial scale. Maraviroc 25mg and 75mg tablets are manufactured from a consequently, no additional batches will be placed on stability to confirm the proposed shelf-life.

Annual production batches will be selected at a yearly rate of at least one lot of each strength (assuming adequate production) for stability testing per the approved protocol. The resulting data from these studies will be forwarded to the Agency in the recommended format at time intervals. Any batch found to fall outside the approved specifications will be investigated and the findings communicated to the Agency. The post-approval stability protocol will be:
Post-Approval Stability Protocol for Lots

The following tests will be applied to the protocol above:

5. Test Methods
“While 211.166 (a) (3) merely requires that test methods be reliable, meaningful, and specific, section 211.165 (e) gives more guidance by stating that the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Section 211.194 (a) (2) further requires that all testing methods used shall be verified under actual conditions of use. Testing procedures must include a stability indicating test which will distinguish the active ingredient from any degradation products and be able to make a reliable estimate of the quantity of any degradate. The stability indicating test does not have to be the assay method used to determine product strength.”

17. Environmental Assessment
As stated in 21 CFR Part 25.31(a), action on an NDA or NDA supplement is categorically excluded from environmental assessment requirements when the estimated concentration of drug substance at the point of entry into the aquatic environment will be below 1 part per billion. The sponsor claims that, to their knowledge, no extraordinary circumstances exist.
18. Establishment Inspection

Because the lower strength tablets will be manufactured by the same sites that manufacture the approved higher strengths using a [REDACTED] for tablet manufacture by the approved process, no site inspection appears needed. Nevertheless, a request was made by OPF for information on these facilities, which was subsequently met (see following Panorama exchanges).

On 16-AUG-2016, the Office of Process and Facilities issued an Overall Manufacturing Inspection Recommendation of Approval for all facilities based on profile. Confirmation of this can be seen in the Inspection Management Form that follows on the next page.
19. LABEL

A. Labeling & Package Insert

PI Evaluation (Tablets):

Dosage Forms and Strengths: Two new tablet strengths are included and adequately described.

Description: Tablet is adequately described. The IUPAC name and structural drawing are correct. The molecular formula and weight were verified, and the solubility statement is appropriate.

How Supplied/Storage and Handling (Tablets only): All 4 tablet strengths included and adequately described. Use of “XX-mg tablets: Bottle of Y tablets (NDC xxxxx-xxx-xx)” is clear and satisfactory.

Carton/Container Label Evaluation (Tablets):

Bottle Configuration: The HDPE bottles do not have cartons. A representative sample of the 120-tablet bottle label is shown below. Required information is provided and is adequate. Tablet strengths are differentiated by label color: green for 25mg tablets and grey for 75mg tablets.

Primary Signer: Allan Fenselau

Secondary Signer: David Lewis

(Branch Chief)
Comments: concur; recommended for approval from the standpoint of CMC.
BIOPHARMACEUTICS REVIEW
Division of Biopharmaceutics/OND/POQ

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<td>Acting Biopharmaceutics Lead: Elsbeth Chikhale, PhD</td>
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<td>Acting Branch Chief: Angelica Dorantes, PhD</td>
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BACKGROUND:

FDA approved New Drug Application (NDA) 022128 for Selzentry® (maraviroc) Tablets 150 mg and 300 mg, on August 6, 2007. FDA approved an expiration dating period of 24 months when stored at 25°C [USP Controlled Room Temperature] for Maraviroc Tablets 150 mg and 300 mg (see NDA-022128 CMC Review by Dr. Stephen Miller dated 06/18/2007 in DARRTS).

SUBMISSION:

The Applicant, Viiv Healthcare Co., submitted this efficacy supplement (S-017) to NDA 022128 seeking approval of two lower strength tablets (25 mg and 75 mg). Maraviroc immediate release tablets 25 mg and 75 mg, are intended for pediatric use. The Applicant states that Maraviroc 25
mg and 75 mg film-coated tablets are manufactured using the and film-coat system as the approved Maraviroc 150 mg and 300 mg film-coated tablet. The different tablet strengths have different tablet size, weight and debossing.

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This Biopharmaceutics review evaluates the dissolution method and acceptance criterion for the newly proposed Selzentry® (maraviroc) Tablets, 25 mg and 75 mg. In addition, this Biopharmaceutics review evaluates the dissolution data supporting the bridging between the clinical and commercial formulations of the newly proposed lower strength Selzentry® (maraviroc) Tablets, 25 mg and 75 mg.

REVIEW:

Approved dissolution method and dissolution acceptance criterion for Selzentry® (maraviroc) Tablets 150 mg and 300 mg:

The Applicant states that maraviroc is a Biopharmaceutics Classification System (BCS) Class III drug. The drug substance has high solubility across the physiological pH range and the drug product performance is not limited by solubility or dissolution (Page 6, Formulation Development, Module 3.2.P.2).

The FDA approved dissolution method and dissolution acceptance criterion for Maraviroc Tablets 150 mg and 300 mg is as follows (see NDA-022128 CMC Review by Dr. Stephen Miller dated 06/18/2007 in DARRTS):

Apparatus: USP I (Basket)
Rotation speed: 100 rpm
Dissolution medium: 0.01M HCl
Volume of dissolution medium: 900 mL
Dissolution medium temperature: 37 ± 0.5°C
Acceptance criterion: Q= 67% at 30 minutes

Reference ID: 4013632
Figure 1. Dissolution profiles of the research and commercial formulation tablets (150 mg and 300 mg maraviroc) using the approved dissolution method (Page 81, NDA-022128 CMC Review by Dr. Stephen Miller dated 06/18/2007 in DARRTS).

**Dissolution method for Selzentry® (maraviroc) Tablets 25 mg and 75 mg:**

The Applicant proposed to use the FDA approved dissolution method for Maraviroc Tablets 150 mg and 300 mg for the newly proposed Maraviroc Tablets 25 mg and 75 mg. The dissolution method is as follows:

- **Apparatus:** USP I (Basket)
- **Rotation speed:** 100 rpm
- **Dissolution medium:** 0.01M HCl
- **Volume of dissolution medium:** 900 mL
- **Dissolution medium temperature:** 37 ± 0.5°C

**Reviewer’s assessment of the proposed dissolution method for Selzentry® Tablets 25 mg and 75 mg:**

The Applicant used the appropriate dissolution method as the quality control method for the newly proposed Selzentry® (Maraviroc) Tablets 25 mg and 75 mg batch release (Module 3.2.P.5) and stability testing (Module 3.2.P.8).

**Dissolution acceptance criterion for Selzentry® (maraviroc) Tablets 25 mg and 75 mg:**

The Applicant originally proposed

The following dissolution data (Figure 2 and Tables 2 & 3) were submitted:
Reviewer's Assessment of the proposed dissolution acceptance criterion:

It is not clear that dissolution profile data for the proposed Maraviroc 25 mg (Figure 2) was obtained in 0.01M HCl medium or 0.1M HCl medium. Moreover, the proposed dissolution acceptance criterion of Q= (b) % at (b) minutes is not acceptable. Therefore, based on the provided dissolution profile data (Figure 2 and Tables 2 & 3), and information from the original NDA (Figure 1), the following Information Request (IR) was send on 10/05/2016:

1. Clarify whether you used 0.1 N HCl or 0.01 N HCl to obtain the dissolution data in Figure 3.2.P.2.2-1 (Dissolution Profile Comparison of Maraviroc 25 mg Commercial and Clinical Tablets in 0.1 M HCl), on page 7 in Formulation Development in Module 3.2.P.2.2.

2. Based on the provided dissolution data in this Supplement and in the original NDA, we recommend that you implement a dissolution acceptance criterion of Q= (b) % at 15 minutes (b) Please provide an updated drug product specification Table(s) accordingly.

Applicant's Response dated 10/13/16 to FDA's IR dated 10/5/16:

1. The data presented in Figure 3.2.P.2.2-1 was for the dissolution profile in 0.01M HCl. The applicant wishes to clarify that there was a typographical error in the title of the figure. A revised version of the section is provided which now includes the dissolution profile for both strengths in 0.1M HCl, pH 4.5 acetate buffer, 0.01M HCl and pH 6.8 phosphate buffer.

2. At present, dissolution data at 15 minutes are not available on batches from routine manufacture for any strength. Per Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997 which recommends a specification of Q=80% in 60 minutes or less,
Reviewer’s Assessment of the Applicant’s Response dated 10/13/16 to FDA’s IR dated 10/5/16:

Based on the provided dissolution data for the proposed Maraviroc Tablets 25 mg and 75 mg, a dissolution acceptance criterion of \( Q = \frac{b}{a} \% \) at \( n \) minutes is too permissive and not acceptable. Therefore, the following additional Information Request was sent on 10/17/2016:

(1) We acknowledge your Response dated 10/13/2016 to our IR dated 10/05/2016, including your commitment to

\[
Q = \frac{b}{a} \% \text{ at } 15 \text{ minutes dissolution acceptance criterion}
\]

(2) Regarding the newly proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets, the proposed dissolution acceptance criterion of \( Q = \frac{b}{a} \% \) at \( n \) minutes is not acceptable. Based on the provided dissolution data, we recommend that you implement a dissolution acceptance criterion of \( Q = \frac{b}{a} \% \) at 15 minutes for the proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets. Provide an updated drug product specification table accordingly.

Applicant’s Response dated 10/19/16 to FDA’s IR dated 10/17/16:

(1) We acknowledge your acceptance of our commitment to

\[
Q = \frac{b}{a} \% \text{ at } 15 \text{ minutes dissolution acceptance criterion}
\]

(2) Please find attached a revised section 3.2.P.5.1. Specification(s) for the 25 mg and 75 mg Selzentry® (maraviroc) tablets, incorporating the dissolution acceptance criteria \( Q = \frac{b}{a} \% \) at
Reviewer’s Assessment of the Applicant’s Response dated 10/19/16 to FDA’s IR dated 10/17/16:

In the Applicant’s Response dated 10/19/2016, the Applicant accepted the Agency’s recommendation of revising the dissolution acceptance criterion to Q= (b)(4)% at 15 minutes, for batch release and stability testing for the newly proposed 25 mg and 75 mg Maraviroc Tablets. Additionally, the Applicant submitted a revised drug product specification Table. The response is acceptable.

Bridging of clinical and commercial formulation:

In addition, the Applicant stated that minor modifications are made between the clinical and commercial tablet batches (Applicant’s Response dated 10/13/2016, Page 5, Formulation Development, Module 3.2.P.2). The Applicant stated that the changes for the proposed Maraviroc 25 mg included:

(1)

(2)

(3)

Table 4. Composition of Maraviroc 25 mg, 75 mg and 150 mg Tablets used in the paediatric clinical study A4001031 compared to the proposed commercial formulation (Applicant’s Response dated 10/13/2016, Page 2, Formulation Development, Module 3.2.P.2)

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Based on the dissolution profile data in Figures 2 and 3, multi-point dissolution profiles using the proposed dissolution method for the Maraviroc 25 mg and 150 mg clinical and commercial batches are similar. The similarity factor (f₂) values were not calculated because more than (b)(4)% drug is dissolved at 15 minutes. Since the 75 mg Tablets are bracketed between the 25 mg and 150 mg tablets, it is implied that the dissolution profiles for the commercial and clinical 75 mg Maraviroc Tablets are also similar. Therefore, the provided dissolution data support the bridging
between the commercial and clinical formulations of the proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets.

Reviewer's Overall Comments:

The Applicant used the dissolution method previously approved for the 150 mg and 300 mg Selzentry® (maraviroc) Tablets as the quality control method for the newly proposed Selzentry® (Maraviroc) Tablets 25 mg and 75 mg batch release (Module 3.2.P.5) and stability testing (Module 3.2.P.8).

The following dissolution method and revised dissolution acceptance criterion for the proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets are acceptable:

Apparatus: USP I (Basket)
Rotation speed: 100 rpm
Dissolution medium: 0.01M HCl
Volume of dissolution medium: 900 mL
Dissolution medium temperature: 37 ± 0.5°C
Acceptance criterion: Q = 83% at 15 minutes

The Applicant commits to Q = 83% at 15 minutes dissolution acceptance criterion

The provided dissolution data support the bridging between the clinical and commercial formulations of the proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets.

CONCLUSIONS AND RECOMMENDATION:

From a Biopharmaceutics perspective, NDA-022128-SUPPL-17 for the proposed two new lower strength Selzentry® (maraviroc) tablets (25 mg and 75 mg) is recommended for APPROVAL.

The additional CMC information provided to support the proposed new strengths for the drug product should be reviewed by the assigned CMC Reviewer(s).

Signature
Yang Zhao
(Affiliate)

Yang Zhao, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Signature
Elsbeth G.
Chikhale

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Reference ID: 4013632
Recommendation: Approval

NDA 208984
Review #1

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<tr>
<td>Drug Substance</td>
<td>Monica Cooper</td>
<td>Kasturi Srinivasachar</td>
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<td>Drug Product</td>
<td>Victor Zottig</td>
<td>Steve Miller</td>
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<td>Process</td>
<td>David Anderson</td>
<td>Edwin Jao</td>
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<td>Erika Pfeiler</td>
<td>John Arigo</td>
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<td>Rebecca Dombrowski</td>
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<td>Sarah Mollo</td>
<td>Alan Stevens</td>
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<td>Katelyn Bittleman</td>
<td>Matthew Krueger</td>
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<tr>
<td>Regulatory Business Process Manager</td>
<td>Bamidele (Florence) Aisida</td>
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<tr>
<td>Application Technical Lead</td>
<td>Stephen Miller</td>
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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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<th>Holder</th>
<th>Item Referenced</th>
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<td>0(b)(4)</td>
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<td>Type III</td>
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<td>Type III</td>
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<td>Type III</td>
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B. Other Documents: IND, RLD, or sister applications

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<td>Selzentry (maraviroc) Tablet</td>
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2. CONSULTS

OPQ-XOPQ-TEM-0001v03 Page 3 of 7 Effective Date: 18 Feb 2016
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<td>Clinical</td>
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<td>Other</td>
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Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 208984 for Selzentry (maraviroc) oral solution is recommended for Approval from the Product Quality perspective.

Selzentry (maraviroc) oral solution is supplied as a carton that includes a 10 mL oral dosing syringe, and a press-in bottle adapter, in addition to the bottle containing 230 mL of solution. It is therefore a drug-device combination, and the product quality and performance were evaluated from both the drug and device perspectives, and found to be acceptable. Additionally, the facilities involved with manufacture and control of the oral solution, plus the facilities responsible for quality assurance of the device components and final packaging of the drug-device combination, were found to be acceptable.

II. Summary of Quality Assessments

A. Product Overview

Selzentry (maraviroc) Oral Solution is a new dosage form developed in response to a pediatric Post-Marketing Requirement to extend dosing to include pediatric patients. Tablets (150 mg and 300 mg) were previously approved. New lower strength tablets (25 mg and 75 mg) have also been developed, and were submitted under the original tablet NDA (22128 S-017).

<table>
<thead>
<tr>
<th>Proposed Indication(s) including Intended Patient Population</th>
<th>Treatment of HIV infection in pediatric patients 2 years or older and weighing at least 4 kg. in combination with other antiretroviral</th>
<th>b(4)</th>
<th>b(4)</th>
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</thead>
<tbody>
<tr>
<td>Duration of Treatment</td>
<td>Chronic dosing until resistance develops</td>
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<tr>
<td>Maximum Daily Dose</td>
<td>Daily dose range: twice a day. There is sufficient solution to provide 46 days or 3.5 days dosing at the lowest and highest daily doses.</td>
<td>b(4)</td>
<td></td>
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<tr>
<td>Alternative Methods of Administration</td>
<td>None</td>
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B. Quality Assessment Overview

**Drug Substance:** Information on the maraviroc drug substance is generally referenced to NDA 22128.
**Drug Product:** The Selzentry (maraviroc) oral solution will be supplied as a bottle that will provide 230 mL of solution. The drug product formulation including the pH was chosen to maintain solubility, assay and prevent microbial growth in a palatable oral solution. The strawberry flavoring is described in DMF and is of acceptable quality. All other inactive ingredients are compendial, and have appropriate controls on quality. The safety of the oral solution after storage in the container-closure system is primarily based on the suitability of the materials of construction for use in contact with foods (per 21 CFR 174-186). These regulations are appropriate for aqueous solutions such as this product, and examination of the Drug Master Files (DMFs) for the [b](4) bottle, and the cap liner verified compliance with the 21 CFR 174-186. Additionally, the applicant provided data showing conformance of the bottle and cap liner with USP <661.2> including [b](4) in extraction studies. Additional data from the manufacturer (DMF [b](4)) will be provided in October, and this will be reviewed under that DMF. See Dr. Victor Zottig’s drug product review for further information supporting safety of the container-closure system. Long-term stability studies were conducted at the 30°C/35%RH and accelerated studies were conducted at 40°C/20%RH in order to measure water loss under worst-case conditions. Water loss by permeability from the HDPE bottle was less than [b](4) % per year at the long-term storage condition, which is far below the amount allowed by USP. There were no other significant trends on stability, and total impurities never exceeded [b](4)%. The 24 month expiration dating period is supported by the 12 month data on the primary NDA batches, supportive data (18 months on one batch), accelerated and stress studies, including a 60-day in-use study.

**Process:** The manufacturing process is relatively simple,
Device Performance and Safety: Sarah Mollo in CDRH’s Office of Device Evaluation performed a design review to support the functionality and safety of the device components (10 ml oral dosing syringe and press-in bottle adaptor). As amended, the information provided supports the acceptability of both the design requirements, and of the essential performance of the device components. Performance of the drug-device combination is supported by the dosing accuracy study, leak-testing, revised syringe markings, and instructions for use. Safety of the devices as used with the aqueous maraviroc oral solution is supported by biocompatibility studies on the syringe [b] along with knowledge of [b] used in manufacture, USP <87> and USP <661> studies on the syringe barrel and plunger, and biocompatibility studies including an extractable study /risk assessment on the adapter.

Facilities: The facilities involved in manufacture of maraviroc drug substance and oral solution were evaluated by Rebecca Dombrowski (CDER Office of Process and Facilities). These facilities were determined to be acceptable based on inspectional history and manufacturing experience. After evaluation of the facilities involved with oversight and manufacture of the device components, no Pre-Approval Inspections were determined to be necessary. Katelyn Bittleman (CDRH Office of Compliance reviewer) recommended that the next routine inspection of the Viiv Healthcare [b] covers compliance with all the requirements of 21 CFR part 4, and that those results be communicated to the CDRH OC. See Final Risk table and the [b] Facility reviews for additional details.

A biopharmaceutics review was not needed for this oral solution NDA.

C. Special Product Quality Labeling Recommendations

Please modify the bottle label and carton label with the following changes:

- Include “[see USP Controlled Room Temperature],” after storage temperatures.
- Include bar code per 21 CFR 201.25

D. Final Risk Assessment (see Attachment I)
41 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
LABELING

R Regional Information

1.14 Labeling

Review of Module 1 Labeling and Prescribing Information

Section 1 Prescribing Information (adequate)

(a) The “Highlights” section includes the product title, drug name (proprietary and established name), dosage form, and route of administration. A concise summary of the dosage forms and strengths is adequately described:

SELZENTRY® (maraviroc) tablets, for oral use
SELZENTRY® (maraviroc) oral solution

(b) The “Full Prescribing Information” Section is complete

Section 3 Dosage Forms and Strengths (adequate)

-Oral solution described as “20 mg per mL clear, colorless, strawberry-flavored oral solution.

Section 11 Description (adequate)

-The list of excipients, IUPAC name and structural drawing are correct, molecular formula and weight were verified, and the solubility statement is appropriate.

Section 16 How Supplied/Storage and Handling (adequate with change)

-The information is acceptable, except “Bottle of (b) (4)” should be changed to “Bottle of 230 mL” because this is more appropriate based on the filling target and the amount expected to remain in the bottle after use (see Process Review Chapter). Container labels have already been updated to show 230 mL.

End of the PI/After Section 17 Instructions (adequate)

-Manufacturer/distributor name provided.
MICROBIOLOGY

Product Background:

NDA/ANDA: 208984

Drug Product Name / Strength: Maraviroc Oral Solution/20 mg/mL

Route of Administration: Oral

Applicant Name: Viiv Healthcare Company

Manufacturing Site: (6)(4)

Method of Sterilization: N/A, product is nonsterile.

Review Summary:

List Submissions being reviewed (table):  
Submission: 06 May 2016
IR Response: 29 June 2016
IR Response: 30 September 2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

S Drug Substance

Reviewer’s Assessment: N/A

P.1 Description of the Composition of the Drug Product

Maraviroc oral solution (20 mg/mL) is a nonsterile aqueous solution for oral administration. The product is intended for multiple doses, and contains sodium benzoate.

Reviewer’s Assessment: The drug product is adequately described.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes
Container/Closure and Package Integrity

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

Antimicrobial Effectiveness Testing

Reviewer’s Assessment: Testing indicates that the product is adequately preserved.  
Acceptable

P.3 Manufacture

Reviewer’s Assessment: The manufacturing process and associated controls are acceptable.  
Acceptable

P.3.1 Manufacturers

(Manufacturing, packaging, testing, releasing)
P. 3.3 Description of the Manufacturing Process and Process Controls

The product is formulated using purified water. Maximum holding time is not stated.

**Reviewer’s Assessment:**

Acceptable

*Aseptic Fill Manufacturing Process*

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

*Buildings and Facilities*

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

*Overall Manufacturing Operation*

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

*Sterilization/Depyrogenation of containers, closures, equipment and Components – See P.3.5*

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

*Environmental Monitoring*

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

P. 3.5 Process Validation and/or Evaluation

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

*Aseptic Fill Manufacturing Process*

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

*Drug Product Solution Filtration*

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

*Product*
Reviewer’s Assessment: N/A, product is nonsterile.

Validation

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

Holding Periods

Maximum holding periods were not described.

<table>
<thead>
<tr>
<th>Reviewer’s Assessment:</th>
<th>Acceptable</th>
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</thead>
</table>

Sterilization/Depyrogenation of containers, closures, equipment and components

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

Bulk Drug Solution Components that are Sterilized Separately

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

Component/Equipment Sterilization

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

Component Depyrogenation

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

Media Fill Procedures and Specification

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

Actions Concerning Product When Media Fills Fail

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

P.5 Control of Drug Product

Reviewer’s Assessment: Product testing is adequately described and appropriately validated.

P. 5.1 Specification
The microbiological 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). Note that the acceptance criteria for aqueous preparations for oral use include a TACM of NMT \( b(4) \) and a TYMC NMT \( b(4) \).

**Reviewer's Assessment:** The specification is suitable for a nonsterile oral drug product.

**Acceptable**

**P.5.2 Analytical Procedures**

The drug product is tested for microbial limits at release using methods described in 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 acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). Note that the acceptance criteria for aqueous preparations for oral use include a TACM of NMT \( b(4) \) and a TYMC NMT \( b(4) \) and the absence of *Escherichia coli* and *Burkholderia cepacia* complex species (BCC) per mL.

**Reviewer's Assessment:** Analytical methods are adequately described and appropriate for the product.

**Acceptable**

**P.5.3 Validation of Analytical Procedures**

The applicant provided a summary of satisfactorily completed suitability studies for compendial methods.
Reviewer’s Assessment: Methods are appropriately validated.

Acceptable

**Endotoxins**

Reviewer’s Assessment: N/A, product is intended for oral administration.

**Sterility**

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

**P.7 Container Closure**

**Summary table of the container closure system proposed**

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

**P.8 Stability**

Reviewer’s Assessment: The stability program described is satisfactory.
P. 8.1 Stability Summary and Conclusion

Reviewer’s Assessment: The stability program described is satisfactory.

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Reviewer’s Assessment: The stability program described is satisfactory.

Acceptable

P.8.3 Stability Data

Reviewer’s Assessment: The stability data presented are satisfactory.

Acceptable

A Appendices

Reviewer’s Assessment: N/A

A.2 Adventitious Agents Safety Evaluation

Reviewer’s Assessment: N/A

A.2.1 Materials of Biological Origin

Reviewer’s Assessment: N/A

A.2.2 Testing at Appropriate Stages of Production

Reviewer’s Assessment: N/A

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer’s Assessment: N/A

A. 2.4 Viral Clearance Studies

Reviewer’s Assessment: N/A
Regional Information

Executed Batch Records

Reviewer’s Assessment:

Comparability Protocols

Reviewer’s Assessment: N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

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

Post-Approval Commitments:

Reviewer’s Assessment: N/A

Lifecycle Management Considerations

Reviewer’s Assessment: N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Erika Pfeiler, Ph.D.

Secondary Reviewer Name and Date: John Arigo, Ph.D.
## ATTACHMENT I: Final Risk Assessments

**Final Risk Table for Selzentry (maraviroc) Oral Solution, 20 mg/mL**

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<th>Attribute/ CQA</th>
<th>Factors that can impact the CQA</th>
<th>From Initial Risk Identification</th>
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<tr>
<td>Physical Stability (Phase Separation)</td>
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</tr>
<tr>
<td>Physical stability (solid state)</td>
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<td>Content uniformity</td>
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<td>Dosing Accuracy</td>
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<td>(b)(4)</td>
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<tr>
<td>Palatability</td>
<td>Is there any concern about palatability at end of shelf-life?</td>
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<td>(b)(4) Clinical study supports palatability;</td>
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<td>Microbial limits</td>
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<td>Leachables</td>
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<td>Amendments to NDA and DMFs provide sufficient assurance of safety of bottle and cap liner, syringe and bottle adapter.</td>
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<tr>
<td>Drug Facilities</td>
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<td>Assay (Preservative or Antioxidant)</td>
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<td>pH</td>
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</table>

CDRH recommends that the next routine inspection of ViiV Healthcare (FEI: 3008108109) or (b)(4) covers compliance with all the requirements of 21 CFR part 4, including the applicable Quality System (21 CFR 820) requirements – Management Controls (21 CFR 820.20), Design Controls (21 CFR 820.30), Purchasing Controls (21 CFR 820.50), and CAPA (21 CFR 820.100).

ATTACHMENT II: List of Deficiencies for Complete Response

Responses have been received to all Information Requests, and there are no remaining deficiencies from the Product Quality perspective.

OVERALL ASSESSMENT AND SIGNATURES:

From the Product Quality perspective NDA 208984 is recommended for Approval.

Stephen Miller, Ph.D.; CMC-Lead and ATL for NDA 208984
### Submission Overall Manufacturing Facility Status

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### Submission Manufacturing Facilities

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