EXCLUSIVITY SUMMARY

NDA # 22128 SUPPL # 17 HFD #
NDA  208984
Trade Name  SELZENTRY
Generic Name  maraviroc
Applicant Name  Viiv Healthcare
Approval Date, If Known

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
      YES ☒  NO ☐

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

      505(b)(1) SE5

   b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety?  (If it required review only of bioavailability or bioequivalence data, answer "no.")
      YES ☒  NO ☐

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
c) Did the applicant request exclusivity?

NDA 22128/S-17  YES ☐  NO ☒
NDA 208984  YES ☒  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

NDA 208984  3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐  NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐  NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA # (s).

NDA# maraviroc 22128

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO  

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA # (s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES ☒  NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES ☒  NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

   YES ☐  NO ☒

   (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

   YES ☐  NO ☒

   If yes, explain:
(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☑

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study A4001031, An Open-Label, Multicenter, Multiple-Dose Pharmacokinetic, Safety, and Efficacy Trial of Maraviroc in Combination with Optimized Background Therapy for the Tx of Antiretroviral-Experienced CCR5-Tropic HIV-1 Infected Pts 2 to < 18 yrs old

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☑

Investigation #2 YES ☐ NO ☑

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:
b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1  YES ☐  NO ☒

Investigation #2  YES ☐  NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Trial A4001031: An Open-Label, Multicenter, Multiple-Dose Pharmacokinetic, Safety and Efficacy Trial of Maraviroc in Combination with Optimized Background Therapy for the Treatment of Antiretroviral-Experienced CCR5-Tropic HIV-1 Infected Children 2-<18 Years of Age

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 65229  YES ☒  ! NO ☐
! Explain:

Investigation #2

IND #  YES ☐  ! NO ☐
! Explain:
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ NO ☐

Explain:

YES ☐ NO ☐

Explain:

Investigation #2

YES ☐ NO ☐

Explain:

YES ☐ NO ☐

Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☑

If yes, explain:

Name of person completing form:  Andrew Gentles, PharmD
Title:  Regulatory Project Manager, Division of Antiviral Products
Date:  10/31/16

Name of Division Director signing form:  Jeff Murray, MD, MPH
Title:  Deputy Director, DAVP
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW A GENTLES
11/04/2016

JEFFREY S MURRAY
11/04/2016
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>208984</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
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<tr>
<th>Proprietary Name: SELZENTRY</th>
<th>Applicant: ViiV Healthcare Company</th>
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<tr>
<td>Established/Proper Name: maraviroc</td>
<td>Agent for Applicant (if applicable): Mark Baumgartner</td>
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<td>Dosage Form: oral solution</td>
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<td>351(k)</td>
<td>351(a)</td>
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### For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)

<table>
<thead>
<tr>
<th>No changes</th>
<th>New patent/exclusivity (notify CDER OND IO)</th>
</tr>
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<tbody>
<tr>
<td>Date of check:</td>
<td></td>
</tr>
</tbody>
</table>

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- Proposed action: 11/04/2016
- User Fee Goal Date is 11/06/2016

Previous actions (specify type and date for each action taken)

| None |

### If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain:

| Received |

### Application Characteristics³

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¹ The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.
Review priority:  □ Standard  ☒ Priority  
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)  
☐ Fast Track  ☐ Rx-to-OTC full switch  
☐ Rolling Review  ☐ Rx-to-OTC partial switch  
☐ Orphan drug designation  ☐ Direct-to-OTC  
☐ Breakthrough Therapy designation  
(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

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<td>☒ Submitted in response to a Pediatric Written Request</td>
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<td>☐ REMS not required</td>
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Comments:
- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)  
  □ Yes  ☒ No
- Public communications (approvals only)  
  - Office of Executive Programs (OEP) liaison has been notified of action  
    □ Yes  ☒ No
  - Indicate what types (if any) of information were issued  
    □ None  ☐ FDA Press Release  ☐ FDA Talk Paper  ☐ CDER Q&As  ☐ Other
- Exclusivity  
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  
    ☒ No  □ Yes
  - If so, specify the type
- Patent Information (NDAs only)
  - Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.  
    ☒ Yes

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**  
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  
  ☒ Included
- Documentation of consent/non-consent by officers/employees  
  ☒ Included
## Action Letters
- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s) - 11/4/16

## Labeling

### Package Insert *(write submission/communication date at upper right of first page of PI)*
- Most recent draft labeling *(if it is division-proposed labeling, it should be in `track-changes` format)*
  - Included – 11/1/2016
- Original applicant-proposed labeling
  - Included – 5/06/2016

### Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*
- Most recent draft labeling *(if it is division-proposed labeling, it should be in `track-changes` format)*
  - Included
- Original applicant-proposed labeling
  - Included – 5/06/2016

### Labels *(full color* carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*
- Most recent draft labeling
  - Included – 10/27/16

### Proprietary Name
- Acceptability/non-acceptability letter(s) *(indicate date(s))*
- Review(s) *(indicate date(s))*
  - N/A

### Labeling reviews *(indicate dates of reviews)*
- RPM:
  - PLR Review 07/01/2016
  - CSO Review - 11/4/16
- DMEPA: None 08/10/2016
- DMPP/PLT (DRISK): None 10/07/2016
- OPDP: None 10/07/2016
- SEALD: None
- CSS: None
- Product Quality: None
- Other: None

## Administrative / Regulatory Documents

### RPM Filing Review^4/Memo of Filing Meeting *(indicate date of each review)*
- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
  - 07/01/2016
  - Not a (b)(2)

### NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Included

### Application Integrity Policy (AIP) Status and Related Documents
[http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
- Applicant is on the AIP
  - Yes ☒  No ☐

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^4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
- This application is on the AIP
  - If yes, Center Director’s Exception for Review memo (indicate date)
  - If yes, OC clearance for approval (indicate date of clearance communication)

- Pediatrics (approvals only)
  - Date reviewed by PeRC 10/12/2016
  - If PeRC review not necessary, explain:______

- Breakthrough Therapy Designation
  - Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)

- CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)

- CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)

  (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

- Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)

  - 10/31/16; 10/25/16; 10/12/16; 09/27/16; 09/21/16; 09/08/16; 08/19/16; 08/10/16; 08/08/16; 07/25/16; 07/22/16; 07/19/16; 07/14/16; 07/05/16; 06/21/16; 06/15/16; 06/06/16; 05/31/16; 05/18/16;

- Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)

- Minutes of Meetings
  - If not the first review cycle, any end-of-review meeting (indicate date of mtg)
  - Pre-NDA/BLA meeting (indicate date of mtg)
  - EOP2 meeting (indicate date of mtg)
  - Mid-cycle Communication (indicate date of mtg)
  - Late-cycle Meeting (indicate date of mtg)
  - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (indicate dates of mtgs)

- Advisory Committee Meeting(s)
  - Date(s) of Meeting(s)

- Decisional and Summary Memos
  - Office Director Decisional Memo (indicate date for each review)
  - Division Director Summary Review (indicate date for each review)
  - Cross-Discipline Team Leader Review (indicate date for each review)
  - PMR/PMC Development Templates (indicate total number)

Reference ID: 4009378
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<td>Financial Disclosure reviews(s) or location/date if addressed in another review</td>
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<td>Page 3 of Clinical Review</td>
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<td>(include copies of OSI letters to investigators)</td>
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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
Nonclinical

- Pharmacology/Toxicology Discipline Reviews
  - ADP/T Review(s) *(indicate date for each review)*: No separate review
  - Supervisory Review(s) *(indicate date for each review)*: No separate review
  - Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*: None 10/12/16

- Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*: None

- Statistical review(s) of carcinogenicity studies *(indicate date for each review)*: No carc

- ECAC/CAC report/memo of meeting: None

- OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*: None requested

Product Quality

- Product Quality Discipline Reviews
  - Tertiary review *(indicate date for each review)*: None
  - Secondary review (e.g., Branch Chief) *(indicate date for each review)*: None
  - Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*: None 10/12/16

- Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*: None CDRH ODE 10/6/16

- Environmental Assessment (check one) (original and supplemental applications)
  - Categorical Exclusion *(indicate review date)* *(all original applications and all efficacy supplements that could increase the patient population)*: 10/12/2016-Page 46 of Integrated Quality Assessment
  - Review & FONSI *(indicate date of review)*
  - Review & Environmental Impact Statement *(indicate date of each review)*

- Facilities Review/Inspection
  - Facilities inspections *(action must be taken prior to the re-evaluation date)* *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*: Acceptable CDRH OC 10/03/2016 Quality Assessment 10/11/16 Re-evaluation date:
    - Withhold recommendation
    - Not applicable

---

6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
### Day of Approval Activities

<table>
<thead>
<tr>
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<th>Status</th>
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</tr>
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<td>□ Send approval email within one business day to CDER-APPROVALS</td>
<td>□ Done – 11/4/2016</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW A GENTLES
11/04/2016
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>22128</th>
<th>NDA Supplement #</th>
<th>17</th>
<th>If NDA, Efficacy Supplement Type:</th>
<th>SE-5</th>
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<tr>
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<td></td>
<td>BLA Supplement #</td>
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<td>(an action package is not required for SE8 or SE9 supplements)</td>
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<tr>
<td>Proprietary Name:</td>
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<td>Established/Proper Name:</td>
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<td>DOSAGE FORM:</td>
<td>tablet</td>
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<tr>
<td>Applicant:</td>
<td>ViiV Healthcare Company</td>
<td>Agent for Applicant (if applicable):</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RPM:</td>
<td>Linda Onaga</td>
<td>Division:</td>
<td>DAVP</td>
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<tr>
<td>NDA Application Type:</td>
<td>☒ 505(b)(1)</td>
<td>☐ 505(b)(2)</td>
<td></td>
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<td>☒ 351(a)</td>
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**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- Review the information in the 505(b)(2) Assessment and submit the draft\(^2\) to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - No changes
  - New patent/exclusivity (notify CDER OND IO)
  - Date of check:

**Note:** If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- Proposed action
- User Fee Goal Date is November 6, 2016
- Previous actions (specify type and date for each action taken) [☑ AP, ☐ TA, ☐ CR]

### If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

**Note:** Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain [☐ Received]

### Application Characteristics

\(^1\) The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

\(^2\) For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

\(^3\) Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.
**Review priority:**  [ ] Standard  [x] Priority  
**Chemical classification (new NDAs only):**  
(Confirm chemical classification at time of approval)
- [ ] Fast Track  
- [ ] Rolling Review  
- [ ] Orphan drug designation  
- [ ] Breakthrough Therapy designation  

*(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)*

### NDAs: Subpart H
- [ ] Accelerated approval (21 CFR 314.510)  
- [ ] Restricted distribution (21 CFR 314.520)  
- [ ] Approval based on animal studies

### BLAs: Subpart E
- [ ] Accelerated approval (21 CFR 601.41)  
- [ ] Restricted distribution (21 CFR 601.42)  
- [ ] Approval based on animal studies

### Subpart I
- [x] Submitted in response to a PMR  
- [ ] Submitted in response to a PMC  
- [x] Submitted in response to a Pediatric Written Request

### REMS:
- [ ] MedGuide  
- [ ] Communication Plan  
- [ ] ETASU  
- [ ] MedGuide w/o REMS  
- [ ] REMS not required

**Comments:** Partial response to a WR

---

- **BLAs only:** Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)  
  - [ ] Yes  
  - [ ] No

- **Public communications (approvals only):**
  - Office of Executive Programs (OEP) liaison has been notified of action  
    - □ Yes  
    - □ No
  - Indicate what types (if any) of information were issued
    - □ None  
    - □ FDA Press Release  
    - □ FDA Talk Paper  
    - □ CDER Q&As  
    - □ Other

- **Exclusivity**
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  
    - □ No  
    - □ Yes
  - If so, specify the type

- **Patent Information (NDAs only):**
  - Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    - □ Verified
    - □ Not applicable because drug is an old antibiotic.

---

### CONTENTS OF ACTION PACKAGE

#### Officer/Employee List
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  
  - □ Included

- Documentation of consent/non-consent by officers/employees  
  - □ Included

---

Reference ID: 4009321
## Action Letters
- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s)
    - November 4, 2016

## Labeling
### Package Insert *(write submission/communication date at upper right of first page of PI)*
- Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Included
- Original applicant-proposed labeling
  - Included

### Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*
- Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
  - Included
- Original applicant-proposed labeling
  - Included

### Labels *(full color* carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*
- Most-recent draft labeling
  - Included

### Proprietary Name
- Acceptability/non-acceptability letter(s) *(indicate date(s))*
- Review(s) *(indicate date(s))*
  - N/A

### Labeling reviews *(indicate dates of reviews)*
- RPM: 11.4.16 [ ] None SRPI 6/30/16
- DMEPA: [ ] None 11.3.16 & 8/10/16
- DMPP/PLT (DRISK): [ ] None 10/7/16
- OPDP: [ ] None 10/7/16
- SEALD: [ ] None
- CSS: [x] None
- Product Quality [ ] None
- Other: [x] None

## Administrative / Regulatory Documents
- RPM Filing Review 4/Memo of Filing Meeting *(indicate date of each review)*
- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee
  - July 1, 2016
  - Not a (b)(2)

- NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*
  - Included 11.4.16

- Application Integrity Policy (AIP) Status and Related Documents
  - [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)
  - Applicant is on the AIP
    - [ ] Yes
    - [x] No

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
• This application is on the AIP
  o If yes, Center Director’s Exception for Review memo \(\text{(indicate date)}\) [Yes  \(\square\) No  \(\square\)]
  o If yes, OC clearance for approval \(\text{(indicate date of clearance communication)}\) [Not an AP action  \(\square\)]

 Pediatrics (approvals only)
  • Date reviewed by PeRC October 12, 2016
  If PeRC review not necessary, explain: ___

 Breakthrough Therapy Designation
  • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) [N/A  \(\square\)]
  • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes) [N/A  \(\square\)]
  • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes) [N/A  \(\square\)]

 (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)

 Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package) [Included  \(\square\)]

 Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) [N/A  \(\square\)]

 Minutes of Meetings
  • If not the first review cycle, any end-of-review meeting \(\text{(indicate date of mtg)}\) [N/A or no mtg  \(\square\)]
  • Pre-NDA/BLA meeting \(\text{(indicate date of mtg)}\) [No mtg  July 14, 2015  \(\square\)]
  • EOP2 meeting \(\text{(indicate date of mtg)}\) [No mtg  \(\square\)]
  • Mid-cycle Communication \(\text{(indicate date of mtg)}\) [N/A  \(\square\)]
  • Late-cycle Meeting \(\text{(indicate date of mtg)}\) [N/A  \(\square\)]
  • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) \(\text{(indicate dates of mtgs)}\) [N/A  \(\square\)]

 Advisory Committee Meeting(s) [No AC meeting  \(\square\)]

 Decisional and Summary Memos

 Office Director Decisional Memo \(\text{(indicate date for each review)}\) [None  \(\square\)]
 Division Director Summary Review \(\text{(indicate date for each review)}\) [None  \(\square\)]
 Cross-Discipline Team Leader Review \(\text{(indicate date for each review)}\) [None  \(\square\)]
 PMR/PMC Development Templates \(\text{(indicate total number)}\) [None  \(\square\)]

 Clinical
<table>
<thead>
<tr>
<th>Section</th>
<th>Review Details</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Reviews</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical Team Leader Review(s) <em>(indicate date for each review)</em></td>
<td>☒ No separate review</td>
<td></td>
</tr>
<tr>
<td>• Clinical review(s) <em>(indicate date for each review)</em></td>
<td>10.7.16</td>
<td></td>
</tr>
<tr>
<td>• Social scientist review(s) <em>(if OTC drug)</em> <em>(indicate date for each review)</em></td>
<td>☒ None</td>
<td></td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not <em>(indicate date of review/memo)</em></td>
<td>Clinical Review 10/7/16 Page 3</td>
<td></td>
</tr>
<tr>
<td>• Clinical reviews from immunology and other clinical areas/divisions/Centers <em>(indicate date of each review)</em></td>
<td>☒ None  DMPH Review 10/11/16</td>
<td></td>
</tr>
<tr>
<td>• Controlled Substance Staff review(s) and Scheduling Recommendation <em>(indicate date of each review)</em></td>
<td>☒ N/A</td>
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<tr>
<td><strong>Risk Management</strong></td>
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<tr>
<td>• REMS Documents and REMS Supporting Document <em>(indicate date(s) of submission(s))</em></td>
<td>None</td>
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<td>None</td>
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<tr>
<td>• Risk management review(s) and recommendations (including those by OSE and CSS) <em>(indicate date of each review and indicate location/date if incorporated into another review)</em></td>
<td>☒ None</td>
<td></td>
</tr>
<tr>
<td>**OSI Clinical Inspection Review Summary(ies) <em>(include copies of OSI letters to investigators)</em></td>
<td>☒ None requested</td>
<td></td>
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<tr>
<td><strong>Clinical Microbiology</strong></td>
<td>☐ None</td>
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</tr>
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<tr>
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<td>☒ None requested  6/26/16</td>
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</table>

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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

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### Nonclinical

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<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td>- ADP/T Review(s) <em>(indicate date for each review)</em></td>
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<td>- Supervisory Review(s) <em>(indicate date for each review)</em></td>
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<td>- Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
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<td></td>
<td>- None 10/12/16</td>
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<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer</td>
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</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
<td>- No carc</td>
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<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>- None</td>
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<td>OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
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### Product Quality

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<th>Review Category</th>
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<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
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<td>- None</td>
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<tr>
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<td>- Secondary review *(e.g., Branch Chief) <em>(indicate date for each review)</em></td>
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<td>- None</td>
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<td>- Integrated Quality Assessment *(contains the Executive Summary and the primary reviews from each product quality review discipline) <em>(indicate date for each review)</em></td>
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<td>- None Product Quality 10/24/16</td>
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<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
<td>- None BioPharm 10/24/16</td>
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### Environmental Assessment

<table>
<thead>
<tr>
<th>Environmental Assessment *(check one) <em>(original and supplemental applications)</em></th>
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<tbody>
<tr>
<td>Categorical Exclusion <em>(indicate review date)</em>(all original applications and all efficacy supplements that could increase the patient population)*</td>
<td>Product Quality Review Page 28</td>
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<tr>
<td>Review &amp; FONSI <em>(indicate date of review)</em></td>
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<td>Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
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/s/

KAREN D WINESTOCK
11/04/2016
Mark,
Please attached as DAVP’s final proposed label. I will need a response no later than 12pm tomorrow. Please confirm receipt of this email.

Thanks,
AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
Andrew.Gentles@fda.hhs.gov

"The only person you are destined to become is the person you decide to be"

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/s/

ANDREW A GENTLES
10/31/2016
Hello Mark,

Please see attached with DAVP’s proposed labeling changes. A response is required from Viiv before or by 12pm this Thursday, October 27, 2016. Please confirm receipt of this email.

Thanks,
AG
Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
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/s/

ANDREW A GENTLES
10/25/2016
Sent: 10/17/2016 11:14:59 AM  
To: mark.a.baumgartner@gsk.com  
CC: thomas.f.kline@gsk.com  
BCC: Avani.Patel@fda.hhs.gov  
Subject: NDA-022128-SUPPL-17 Information request 2

ViiV Healthcare Company  
Attention: Mark Baumgartner  
Director, Global Regulatory Affairs  
Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC 27709-3398

Dear Baumgartner:

Please see attached and kindly send an acknowledging receipt to Avani.Patel@fda.hhs.gov.

Thank you,  
Avani
NDA 022128/S-017

INFORMATION REQUEST

ViiV Healthcare Company
Attention: Mark Baumgartner
Director, Global Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709-3398

Dear Baumgartner:

Please refer to your supplemental New Drug Application (sNDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SELZENTRY® (maraviroc) Tablets, 25 mg, 75mg, 150mg, and 300mg.

We also refer to your May 6, 2016 submission, Prior Approval Supplement to register: SELZENTRY Tablets, 25 mg and 75mg strength; labeling changes; and pediatric data for Required Pediatric Study commitment.

We are reviewing the Drug Product (Biopharmaceutics) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA. Please provide your comments by October 19, 2016.

1. We acknowledge your Response dated 10/13/2016 to our IR dated 10/05/2016, including your commitment to [redacted] once these data are collected.

2. Regarding the newly proposed 25 mg and 75 mg Selzenty® (maraviroc) Tablets, the proposed dissolution acceptance criterion of $Q = \frac{t}{t_0} \%$ at 15 minutes is not acceptable. Based on the provided dissolution data, we recommend that you implement a dissolution acceptance criterion of $Q = \frac{t}{t_0} \%$ at 15 minutes for the proposed 25 mg and 75 mg Selzentry® (maraviroc) Tablets. Provide an updated drug product specification table accordingly.
Send your submission through the Electronic Submission Gateway
http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
PRODUCT QUALITY (BIOPHARMACEUTICS)

If you have questions, contact Avani Patel, Regulatory Business Process Manager, at (240) 402-1845 or avani.patel@fda.hhs.gov.

Sincerely,

Avani Patel, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Good Morning Mark,
Please see the proposed labeling changes for this application. A response from ViiV Healthcare is required by October 19th, 2016 before 4pm. Let me know if you have any questions and in the meantime, please confirm receipt of this email.

Thanks,
AG
Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
Andrew.Gentles@fda.hhs.gov

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/s/

ANDREW A GENTLES
10/13/2016
Good Morning Mark,

Please see the IR below as it pertains to the container and carton labeling. Response is due before October 17th, 2016 and in the meantime, please confirm receipt of this email.

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

**Container Label and Carton Labeling For Oral Solution**

1. As presented, the labels and labeling for the oral solution and the marketed 300 mg tablet strength are similar in color. Revise the colored box for the strength of the oral solution to a dissimilar color to help differentiate the labels and labeling to prevent strength selection errors.

2. Include “[see USP Controlled Room Temperature].” after storage temperatures.

3. Per 21 CFR 201.25(c)(2) place barcode on container and carton

**Carton Labeling For Oral Solution**

1. As presented, the carton lists the contents of the carton on the PDP; however we recommend to use clarifying terminology. Revise the following contents, (b)(4) to read “1 oral dosing syringe” and (b)(4) to read, “1 press-in bottle adapter”.

Thanks,

AG

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager

Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
Andrew.Gentles@fda.hhs.gov
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Reference ID: 3997876
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/s/

ANDREW A GENTLES
10/12/2016

Reference ID: 3997876
Dear Baumgartner:

Please refer to your supplemental New Drug Application (sNDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SELZENTRY® (maraviroc) Tablets, 25 mg, 75 mg, 150 mg, and 300 mg.

We also refer to your May 6, 2016 submission, Prior Approval Supplement to register: SELZENTRY Tablets, 25 mg and 75 mg strength; labeling changes; and pediatric data for Required Pediatric Study commitment.

We are reviewing the Drug Product (Biopharmaceutics) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA. Please provide your comments by October 7, 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= 80% at 15 minutes for all strengths of your drug product (25 mg, 75 mg, 150 mg and 300 mg). Please provide an updated drug product specification Table(s) accordingly.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:
INFORMATION REQUEST
PRODUCT QUALITY (BIOPHARMACEUTICS)

If you have questions, contact Avani Patel, Regulatory Business Process Manager, at (240) 402-1845 or avani.patel@fda.hhs.gov.

Sincerely,

Avani Patel, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
ViiV Healthcare Company
Attention: Mark Baumgartner
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709-3398

Dear Baumgartner:

Please see attached and kindly send an acknowledging receipt to Avani.Patel@fda.hhs.gov.

Thank you,
Avani
Good Morning Mark,

Please submit the following information on or before October 3, 2016 before 4pm.

1. More transparency regarding samples excluded from the population PK analysis for the maraviroc + CYP3A inhibitor model:
   a. The Nonmem data that was submitted does not contain excluded samples. Submit a revised Nonmem dataset that contains all samples (i.e. prior to excluding data).
      i. Add a column that identifies which samples were excluded from the analysis. There is no need to include samples not eligible for the analysis (i.e. subjects treated with inhibitors other than those used in the pediatric trial).
      ii. Add a column stating the reason for exclusion.
   b. A summary table of number of samples excluded by category.

2. Individual subject posthoc PK parameter (Cmax, AUC, Cmin) estimates for all pediatric and adult subjects in the maraviroc + CYP3A inhibitor dataset. Include columns for dose and OBT category.

3. Individual subject PK parameters (Cmax, AUC, Cmin) for the 375 TE adults in the maraviroc label who received maraviroc 150 mg BID plus a CYP3A inhibitor. Include a column for the identity of the inhibitor(s).

As always let me know if you have any questions and please confirm receipt of this email.

Thanks,

AG
Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAR/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
Andrew.Gentles@fda.hhs.gov

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supplier.

Please respond to the following with a submission to your NDA by Friday, September 16, 2016.

Please confirm receipt of this email.

Thanks,
Florence.

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.

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Good Morning Mark,

Please submit the following information on or before October 3, 2016 before 4pm.

1. More transparency regarding samples excluded from the population PK analysis for the maraviroc + CYP3A inhibitor model:
   a. The Nonmem data that was submitted does not contain excluded samples. Submit a revised Nonmem dataset that contains all samples (i.e. prior to excluding data).
      i. Add a column that identifies which samples were excluded from the analysis. There is no need to include samples not eligible for the analysis (i.e. subjects treated with inhibitors other than those used in the pediatric trial).
      ii. Add a column stating the reason for exclusion.
   b. A summary table of number of samples excluded by category.

2. Individual subject posthoc PK parameter (Cmax, AUC, Cmin) estimates for all pediatric and adult subjects in the maraviroc + CYP3A inhibitor dataset. Include columns for dose and OBT category.

3. Individual subject PK parameters (Cmax, AUC, Cmin) for the 375 TE adults in the maraviroc label who received maraviroc 150 mg BID plus a CYP3A inhibitor. Include a column for the identity of the inhibitor(s).

As always let me know if you have any questions and please confirm receipt of this email.

Thanks,

AG
Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Center for Drug Evaluation and Research
OND/OAP/Division of Antiviral Products
U.S. Food and Drug Administration
Tel: 240-402-5708
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sender immediately at Andrew.Gentles@fda.hhs.gov
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/s/

ANDREW A GENTLES
09/27/2016
Hi Florence, Confirming receipt of the IR and confirming we will submit a response on Friday. Let me know if you would like a email copy of that response sent to you as well.

Regards,

Chris

---

EXTERNAL

Hello Chris,

1. ViiV Healthcare is listed as the applicant for NDA 208984. Please explain the responsibility ViiV healthcare assumes in regards to the devices constituents of the combination product. Please also provide the name of the company listed on the final product.

2. Please explain who is responsible for the following:
   a. Purchasing controls, as outlined in 21 CFR 820.50,
   b. Design controls, as outlined in 21 CFR 820.30
   c. Corrective Actions and Preventative Actions (CAPA), as outlined in 21 CFR 820.100, and
   d. Management controls, as outlined in 21 CFR 820.20

Please respond to the following with a submission to your NDA by Friday, September 23, 2016.

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691
HI Florence,

With respect to the question below to “update your 356h form with ViiV Healthcare Company as the dosing/unit”:

To clarify, there is no ViiV Healthcare manufacturing site to be listed on the 356H form. ViiV Healthcare is a specialist company formed as a collaboration between GlaxoSmithKline (GSK) and Pfizer Inc.

GSK serves as the Authorized US Agent for the NDA 208984 on behalf of ViiV Healthcare.

Under contract service agreements between ViiV Healthcare and GSK, GSK performs on behalf of ViiV Healthcare.

Under contract service agreement between ViiV Healthcare and Pfizer Inc, Pfizer Inc performs manufacturing.

Please let me know if you require further clarity. Thanks.

Chris Musteikis
Director, CMC Product Lifecycle
Global Regulatory Affairs
RD Chief Regulatory Office
GSK
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States
Email chris.r.musteikis@gsk.com
Tel +1 919 483 5866

gsk.com | Twitter | YouTube | Facebook | Flickr

Hi Chris,

Can you please update your 356h form with ViiV Healthcare Company as the dosing/unit
supplier.

Please respond to the following with a submission to your NDA by Friday, September 16, 2016.

Please confirm receipt of this email.

Thanks,
Florence.

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GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.
Hello Mark,

Please see attached, the Division’s review of the proposed labeling. We would like to obtain Viiv’s response to these labeling recommendations no later than September 15, 2016 before 4pm.

Please let me know if you have any questions and confirm receipt of this email.

Thanks,

AG

Andrew Gentles, PharmD, BCPS-AQ ID, NCPS
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
Room 6211
Ph:240-402-5708
Email: Andrew.Gentles@fda.hhs.gov

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/s/

ANDREW A GENTLES
09/12/2016
Hello Chris,

Another set of IR.

Please submit the intermediate precision data for the validation of analytical methods regarding assay and degradation products to include analytical conditions, acceptance criteria, and results.

Please respond to the following with a submission to your NDA by Tuesday, September 13, 2016.

Please confirm receipt of this email.

Thanks,

Florence

Florence Aisida, Pharm.D,BCPS  
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)  
Office of Pharmaceutical Quality/CDER/FDA. T: 240.602.2691
Hello Chris,

My CMC Reviewer is requesting a TCON to discuss the Information request below.

1. Update section 3.2.P.3.4 to include the maximum manufacturing time limit from.

2. Update section 3.2.P.3.3 with proposed tentative acceptance criteria for the actual yields and percentages of theoretical yield for the individual processing steps and the overall manufacturing process beyond which investigation is required. Refer to CFR 211.103 and CFR211.186(b)(7).

Teleconference Schedule

Date: September 13 2016,
Time: 2:30 p.m-3:30 p.m. E.S.T
Phone Arrangements: 
Meeting ID: 

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.602.2691

Hi Florence, Confirming receipt of the IR below. Thanks and have a great weekend!

Regards,

Chris
Hello Chris,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, September 2, 2016.

We have completed the review of your Information request response from August 17th, 2016. Please update your application based on the following:

A. Your proposed [redacted] (Section 1.14.1.1). Revise the [redacted] (b)(4).

B. Time limits for the completion of drug product manufacturing assure the quality of the drug product. Deviations from established time limits must be documented and justified to ensure drug product quality. As you have noted, [redacted] (b)(4) you evaluated through development studies; however, the impact of [greenacted] (b)(4) on drug product quality has not been assessed. Specify a time limit for the completion of total production that is supported by data to assure the quality of the drug product as per 21 CFR 211.111.

C. The purpose of actual yield and batch reconciliation is to demonstrate manufacturing capability and batch to batch consistency. Actual yield and batch reconciliation specifications are established as quality control limits beyond which an official investigation will be triggered. Batch accountability should be close to 100% with explanation and justifications for any significant waste or rejects [redacted] (b)(4) and batch to batch variability. Actual batch yield specifications should be based on manufacturing capabilities, prior experience and data. Provide the actual yield and batch reconciliation acceptance criteria for the overall manufacturing process from the site cGMP procedures that are applicable to the commercial manufacturing of maraviroc oral solution.

Please confirm receipt of this email.

Thanks,

-Florence

Florence Aisida, Pharm.D,BCPS
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From: Abida, Bamidele (Florence)
To: "Chris Mustelkis"
Cc: Gentles, Andrew
Subject: NDA 208984 IR
Date: Friday, August 19, 2016 1:45:08 PM

08/19/16

Hello Chris,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, September 2, 2016.

We have completed the review of your information request response from August 17th, 2016. Please update your application based on the following:

A. Your proposed [(b)(4)] (Section 1.14.1.1). Revise the [(b)(4)]

B. Time limits for the completion of drug product manufacturing assure the quality of the drug product. Deviations from established time limits must be documented and justified to ensure drug product quality. As you have noted, [(b)(4)] you evaluated through development studies; however, the impact of [(b)(4)] on drug product quality has not been assessed. Specify a time limit for the completion of total production that is supported by data to assure the quality of the drug product as per 21 CFR 211.111.

C. The purpose of actual yield and batch reconciliation is to demonstrate manufacturing capability and batch to batch consistency. Actual yield and batch reconciliation specifications are established as quality control limits beyond which an official investigation will be triggered. Batch accountability should be close to 100% with explanation and justifications for any significant waste or rejects [(b)(4)] and batch to batch variability. Actual batch yield specifications should be based on manufacturing capabilities, prior experience and data. Provide the actual yield and batch reconciliation acceptance criteria for the overall manufacturing process from the site cGMP procedures that are applicable to the commercial manufacturing of maraviroc oral solution.

Please confirm receipt of this email.

Thanks,

-Florence

Florence Alsida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.602.2691

Reference ID: 4011885
Hello Chris,

I have additional information requests from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, August 17, 2016:

1. The dispensing operations of the API as described in the registration batch records do not account for API purity. The drug substance specifications in section 3.2.5.4.1 allow for [b](4) wt-% pure Maraviroc to be used during commercial manufacturing which would result in drug product intentionally formulated at [b](4) mg/mL which is below the labeled claim of 20 mg/mL. Refer to 21 CFR 211.101(a). The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. Update section 3.2.P.3.3 to include manufacturing procedures for material dispensing to account for variability in API purity.

2. Section 3.2.P.3.3 and 3.2.P.3.4 do not contain sufficient information regarding intended controls over the manufacturing process for future commercial production. Update these sections with the intended process parameters and controls to be implemented during commercial manufacturing as requested below. Note that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process Validation: General Principles and Practices, 2011)

   A. The development data provided for

   B. Please provide the GMP procedures including sampling plan and acceptance criteria

   C. Update 3.2.P.3.4 with maximum manufacturing times for the individual processing steps

   D. Update 3.2.P.3.4 with yield reconciliation acceptance criteria for the individual processing steps

   E. Update 3.2.P.3.4 to establish

Reference ID: 4011885
Please verify receipt of this Email.

Thanks,

-Florence

Florence Aisida, Pharm.D.,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.602.2691

---

From: Chris Musteikis [mailto:chris.r.musteikis@gsk.com]
Sent: Monday, August 08, 2016 8:57 PM
To: Aisida, Bamidele (Florence)
Cc: Gentles, Andrew
Subject: RE: NDA 208984 IR

Hello Florence,

Confirming receipt of the IR request email. Thanks.

Chris Musteikis
Director, CMC Product Lifecycle
Global Regulatory Affairs
RD Chief Regulatory Office

GSK
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States
Email christ.r.musteikis@gsk.com
Tel +1 919 483 5866

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gsk
do more feel better live longer

---

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Monday, August 08, 2016 4:26 PM
To: Chris Musteikis
Cc: Gentles, Andrew
Subject: NDA 208984 IR

EXTERNAL

Hello Mr. Musteikis,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Monday, August 15, 2016:

Reference ID: 4011885
1. You have provided a table that lists the specifications and verification/validation testing for the essential performance requirements of your combination product. For the essential performance requirement, please include the accuracy specification in the essential performance requirements and specifications table you provided on July 28, 2016. Please include this document within the NDA submission 208984 (e.g. under 3.2.P or 3.2.R).

2. In an IR sent on June 15, 2016, the Agency requested the lot release specifications for the essential performance requirements of the device. You referred to section 3.2.P.7.1 Packaging Description which included [b](4) Please include the lot release specifications for the device constituent under section 3.2.P.5. Additionally, the analytical procedure [b](4) does not provide any information on what is being inspected. Please clarify if verification of the component which are essential for the accurate dosing of the product, is included in the testing criteria.

3. On July 14, 2016, the Agency requested a biocompatibility evaluation for all of the patient contacting components of the syringe, which includes the drug contacting components. The IR stated that the biocompatibility evaluation should take into account the repeated use of the device, which includes the re-use of the each syringe (i.e. 2X a day for up to 47 days) for the duration the patient is receiving the treatment, as a new syringe is provided with each bottle (indicated for patients ages 2-12). The Agency requested the test protocols and test reports to address the following endpoints: cytotoxicity, sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity. The Agency stated that you may provide testing demonstrating that the device meets the requirements of USP <661> Containers-Plastic to support the biocompatibility evaluation of your device. In addition to the USP <661> testing, the Agency requested a risk assessment addressing the above biocompatibility endpoints including a discussion of the materials and manufacturing of the oral syringe, including any additives or processing agents. Your response on July 28, 2016 included cytotoxicity testing per USP <87>. You also included a list of [b](4) You did not include a risk assessment within your response addressing the appropriate endpoints. If you would like to provide a risk assessment in lieu of biocompatibility testing for sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity endpoints, please provide a risk assessment which addresses all of the above endpoints (i.e. sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity) as previously requested on July 14, 2016. The risk assessment should include information on the materials, manufacturing and processing to support the biocompatibility of the final finished device for the intended use of the device. The intended use of the device should take into account the worst case total exposure of the device to the patient which includes the repeated use of the device (i.e. drug contact of single syringe for up to 94 doses/47 days, and new syringe with every new dose for patients 2-12 years of age). For more information, please refer to Use of International Standard ISO 10993-1, “Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process”.

Please verify receipt of this Information Request.

Reference ID: 4011885
Thanks,

Florence Aisida, Pharm.D,BCPS  
Regulatory Business Process Manager  
HHS | FDA | CDER  
Office of Pharmaceutical Quality  
Office of Program and Regulatory Operations  
Bamldele.aisida@fda.hhs.gov | 240.402.2691

GSK monitors email communications sent to and from GSK in order to protect GSK, our employees, customers, suppliers and business partners, from cyber threats and loss of GSK Information. GSK monitoring is conducted with appropriate confidentiality controls and in accordance with local laws and after appropriate consultation.
Hello Mr. Musteikis,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Monday, August 15, 2016:

1. You have provided a table that lists the specifications and verification/validation testing for the essential performance requirements of your combination product. For the essential performance requirement, please include the accuracy specification in the essential performance requirements and specifications table you provided on July 28, 2016. Please include this document within the NDA submission 208984 (e.g. under 3.2.P or 3.2.R).

2. In an IR sent on June 15, 2016, the Agency requested the lot release specifications for the essential performance requirements of the device. You referred to section 3.2.P.7.1 Packaging Description which included a Please include the lot release specifications for the device constituent under section 3.2.P.5. Additionally, the analytical procedure does not provide any information on what is being inspected. Please clarify if verification of the which are essential for the accurate dosing of the product, is included in the that is part of your release criteria.

3. On July 14, 2016, the Agency requested a biocompatibility evaluation for all of the patient contacting components of the syringe, which includes the drug contacting components. The IR stated that the biocompatibility evaluation should take into account the repeated use of the device, which includes the re-use of the each syringe (i.e. 2X a day for up to 47 days) for the duration the patient is receiving the treatment, as a new syringe is provided with each bottle (indicated for patients ages 2-12). The Agency requested the test protocols and test reports to address the following endpoints: cytotoxicity, sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity. The Agency stated that you may provide testing demonstrating that the device meets the requirements of USP <661> Containers-Plastic to support the biocompatibility evaluation of your device. In addition to the USP <661> testing, the Agency requested a risk assessment addressing the above biocompatibility endpoints including a discussion of the materials and manufacturing of the oral syringe, including any additives or processing agents. Your response on July 28, 2016 included cytotoxicity testing per USP <87>. You also included a list of You did not include a risk assessment within your response addressing the appropriate endpoints. If you would like to provide a risk assessment in lieu of biocompatibility testing for sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity endpoints, please provide a risk assessment which address all of the above endpoints (i.e. sensitization, irritation, acute systemic toxicity, and subchronic systemic toxicity) as previously requested on July 14, 2016. The risk assessment should
include information on the materials, manufacturing and processing to support the biocompatibility of the final finished device for the intended use of the device. The intended use of the device should take into account the worst case total exposure of the device to the patient which includes the repeated use of the device (i.e. drug contact of single syringe for up to 94 doses/47 days, and new syringe with every new dose for patients 2-12 years of age). For more information, please refer to Use of International Standard ISO 10993-1, "Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process".

Please verify receipt of this Information Request.

Thanks,

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691
As a follow-up and in order to meet our internal timelines. Please confirm this receipt of this request as soon as possible. I will need this request to be received no later than August 4th, 2016.

Thanks,
AG
Andrew Gentles, PharmD, BCPS-AQ ID, NCPS
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
Room 6211
Ph:240-402-5708
Email: Andrew.Gentles@fda.hhs.gov

"The only person you are destined to become is the person you decide to be"

Hi and Good Morning Mark,
As indicated in our conversation earlier. We are requesting 6 bottles along with the corresponding syringe and adapter system associated with this NDA. Please confirm receipt of this email and let me know if you have any questions.

Thanks,
AG
Andrew Gentles, PharmD, BCPS-AQ ID, NCPS
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
Room 6211
Ph: 240-402-5708
Email: Andrew.Gentles@fda.hhs.gov

“The only person you are destined to become is the person you decide to be”

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Andrew.Gentles@fda.hhs.gov
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/s/

----------------------------------------------------
ANDREW A GENTLES
07/25/2016
NDA 208984

INFORMATION REQUEST

ViiV Healthcare Company.
Attention: Chris Musteikis,
Director, CMC Product Lifecycle, Global Regulatory Affairs
Five Moore Dr, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Musteikis:

Please refer to your New Drug Application (NDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Selzentry® (maraviroc) Oral Solution.

We are reviewing the Chemistry Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by July 29, 2016. A partial response by that date with a timeline for response to the remaining questions is also acceptable.

Microbiology

Reference ID: 4011885
Device Requirements/Performance

6. The table below represents the information needed to complete an adequate review of the device constituents. Please provide this information, preferably in tabular format, for
each essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary.

<table>
<thead>
<tr>
<th>Essential Performance Requirement</th>
<th>Specification</th>
<th>Verification</th>
<th>Validation</th>
<th>Aging (Y/N)</th>
<th>Lot Release Testing (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>{Insert requirement}</td>
<td>{Insert specification}</td>
<td>{Insert Document Number}</td>
<td>{Insert Document Number}</td>
<td>{Insert Yes if specification was verified after aging the device to the labeled date of expiry}</td>
<td>{Insert Yes if specification is a part of the lot release testing of the final finished combination product}</td>
</tr>
</tbody>
</table>

Ex: dose accuracy

If you have questions, call me at (240) 402-2691.

Sincerely,

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208984

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Mark Baumgartner
Sr. Director, Global Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Baumgartner:

Please refer to your New Drug Application (NDA) dated May 6, 2016 received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for SELZENTRY® (maraviroc) oral solution 20 mg/ml.

We also refer to your amendments dated June 10, 2016, June 14, 2016, June 22, 2016, June 27, 2016, June 29, 2016, and July 5, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have reviewed your July 5, 2016 submission submitted in response to the FDA’s June 22, 2016 information request related to your pharmacokinetic simulation data and we have the following requests:

1. Maraviroc (MVC) with neutral concomitant medications model:
   a. Provide the full PopPK report, model codes, dataset, and output files for this model.
   b. Regarding the simulations submitted July 5, 2016, tabulate the demographic characteristics (for all characteristics that are model covariates) of the patients used for simulations. Compare the patient demographics used for the simulations to the patients enrolled in study A4001031.
   c. Submit the model codes, simulation dataset (containing patient characteristics and simulated MVC exposures), output files, and analysis scripts used for constructing figures and tables based on the output.
   d. Discuss physiologically why body weight is not a significant covariate (weights ≥ 20 kg) for MVC exposure when coadministered with neutral concomitant medications while weight is a significant covariate for MVC exposure when coadministered with CYP3A inhibitors.

Reference ID: 3961128
2. MVC with potent CYP3A inhibitors model:
   a. The response dated July 5, 2016 stated that simulations were conducted for the typical pediatric subject. Please provide additional simulations using a patient dataset that is reflective of subjects enrolled in study A4001031. In the response, tabulate the demographic characteristics (for all characteristics that are model covariates) of the patients used for simulations. Compare the patient demographics used for the simulations to the patients enrolled in study A4001031.
   b. Submit the model code, simulation dataset (containing patient characteristics and simulated MVC exposures), output files, and analysis scripts used for constructing figures and tables based on the output.
   c. Discuss mechanistically why food effect is not a significant covariate for MVC exposure when coadministered with CYP3A inhibitors while food effect is a significant covariate for MVC exposure when coadministered with neutral concomitant medications.

3. In report PMAR-EQDD-A400b-DP4-195, pediatric and adult concentration-time data were graphically compared (Figures S1-3). Please provide additional graphs comparing pediatric and adult concentration-time data stratified by pediatric body weight groups corresponding to proposed dosing (10-19 kg, 20-29 kg, 30-39 kg, 40+ kg). On each graph overlay adult observations with those from the listed body weight groups.

Please respond only to the above requests for information on or before July 28, 2016. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and Patient Package Insert (PPI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Patient Package Insert (PPI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.
We acknowledge receipt of your request for a partial waiver of pediatric studies for pediatric patients from birth to at least 2 years of age in this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 2 to 18 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, at (240) 402-5708 or the mainline (301) 796-1500.

Sincerely,

[See appended electronic signature page]

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

JEFFREY S MURRAY
07/19/2016
INFORMATION REQUEST

ViiV Healthcare Company.
Attention: Hemant Goswami, Regulatory Project Manager, CMC Regulatory
Five Moore Dr
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Goswami:

Please refer to your New Drug Application (NDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Selzentry® (maraviroc) Oral Solution.

We are reviewing the Chemistry Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by July 28, 2016 in order to continue our evaluation of your NDA.

Drug Substance
1. 

Process
2. 

3. 

4.
**Drug Product**

9. Section 3.2.1 P.7.2, Container Closure System – Specifications, provides the test and acceptance criteria for the oral dosing syringe. Tests include [redacted]. Please provide [redacted].

10. Evaluate which components of the [redacted]. Analyze the drug product solution from long-term and accelerated stability studies to determine the levels of those components, and perform a risk assessment to determine if there is any risk to patients.
11. On June 15, 2016, the Agency requested information on the Biocompatibility of the device constituent of the combination product commensurate with the level and duration of patient contact including leachable/extractable studies. However, the Agency recommends that a biocompatibility evaluation is performed for devices that have direct or indirect patient contact which includes devices that are used for oral administration of drugs.

a. The syringe is part of the combination product and should be tested according to the intended use for the intended patient population per the G95-1 Blue Book memo, Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/guidancedocuments/ucm080742.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/guidancedocuments/ucm080742.htm))
12. Please provide the address and contact information (and FEI number if available) for the ViiV facility where records, e.g. Design History Files, are maintained relating to the device components (oral syringe and bottle adapter) used with Maraviroc Oral Solution. Additionally, please provide a summary of the following:

a. The current management structure which outlines who has the executive responsibility to manage, perform, and assess work affecting quality of the product and related controls to ensure that the quality policies are appropriately implemented and followed, and the product is appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements, as per 21 CFR 820.20.

b. Information as to who is responsible for the design of the device components. This should include all necessary design controls described in 21 CFR 820.30. If the device constituents are not subject to design controls, the summary should identify the scope of the design control activities applicable to the combination product.

c. Purchasing controls and documentation for components, products, or services (example sterilization) received at the sponsor’s facility for use in the manufacture of the combination product, per 21 CFR 820.50. The summary should include the applicant’s evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm’s Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product.

d. Corrective and Preventive Action (CAPA) documentation. The CAPA process is used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituents. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm’s CAPA System as described in 21 CFR 820.100.

13. Please verify that the [redacted] is the site where the oral dosing syringe and bottle adapter are packaged with the Maraviroc Oral Solution.
If you have questions, call me at (240) 402-2691.

Sincerely,
Bamidele F.
Aisida -A

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 208984

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Mark Baumgartner
Sr. Director, Global Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Mr. Baumgartner:

Please refer to your New Drug Application (NDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Selzentry® (maraviroc) oral solution, 20 mg/mL.

We also refer to your submissions dated June 10, 2016, June 14, 2016, June 22, 2016, June 27, 2016, and June 29, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Priority. Therefore, the user fee goal date is November 6, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 17, 2016.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before July 19, 2016.
If you have any questions, call Andrew Gentles, Regulatory Project Manager, at (240) 402-5708.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

JEFFREY S MURRAY
07/05/2016
ViiV Healthcare Company  
c/o: GlaxoSmithKline  
Attention: Mark Baumgartner  
Sr. Director, Global Regulatory Affairs  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709-3398  

Dear Mr. Baumgartner:

Please refer to your supplemental New Drug Application (sNDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Selzentry® (maraviroc) tablets, 25 mg, 75 mg, 150 mg, and 300 mg.

We also refer to your amendments date June 8, 2016 and June 27, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is November 6, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 17, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.
PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and Instructions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:
Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and Instructions for Use, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUdPED  PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application for pediatric patients 2 to less than 18 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Linda C. Onaga, MPH, Senior Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

[See appended electronic signature page]

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

JEFFREY S MURRAY
07/05/2016
Please find attached the Division’s comments for NDA 208984 and NDA 22128/S-17.

1. Simulate the distribution of Cavg for each of the weight/concomitant medication categories in the proposed pediatric dosing regimen:
   a. Provide box plots of Cavg, AUC, Cmax, and Cmin by bodyweight/concomitant medication category
   b. Tabulate median, 5th, and 95th percentiles of Cavg, AUC, Cmax, and Cmin by bodyweight/concomitant medication category
   c. For each concomitant medication category, plot continuous body weight versus median, 5th, and 95th percentiles of pediatric Cavg, AUC, Cmax, and Cmin. On each plot include reference adult median, 5th, and 95th percentile values.

Please provide your response by June 29, 2016.

We are providing this above information via e-mail for your convenience. Please feel free to contact me at 301-796-0759 or Andrew Gentles at 240-402-5708 if you have any questions regarding the contents of this transmission.

Linda Onaga, MPH
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
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/s/

LINDA C ONAGA
06/22/2016

Reference ID: 3949828
INFORMATION REQUEST

ViiV Healthcare Company,
Attention: Hemant Goswami, Regulatory Project Manager, CMC Regulatory
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Goswami:

Please refer to your New Drug Application (NDA) dated and received May 6, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Selzentry® (maraviroc) Oral Solution.

We are reviewing the Chemistry Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Wednesday, June 22, 2016. Your response to comment #1 by that date, with a timeline for response to the remaining questions is also acceptable.
If you have questions, call me at (240) 402-2691.

Sincerely,

Bamidele F. Aisida -A

Florence Aisida, Pharm.D, BCPS
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 6, 2016
Application Number: NDA 208984 and NDA 22128/S-17
Product Name: Selzentry (maraviroc)
Sponsor/Applicant Name: Viiv Healthcare

Subject: PSP and Labeling Information Request

FDA Participants:
Linda Onaga, MPH (Senior Regulatory Project Manager)
Andrew Gentles, PharmD, BCPS AQ-ID (Regulatory Project Manager)

Sponsor/Applicant Participants:
Mark Baumgartner
Sr. Director, Global Regulatory Affairs, Infectious Diseases

1.0 BACKGROUND:
NDA 208984 and 22128/s-17 are submissions in to a PREA requirement as this product was approved prior to FDASIA and no iPSP was available at that time. A PSP is still required for NDA 208984 which is a new formulation which triggers PREA. The new NDA 208984 fulfils PREA requirement 1357-2 issued under NDA 22128.

2.0 DISCUSSION:
Contacted US sponsor via telephone and requested:
- PSP to be submitted to NDA 208984
- Submit word, pdf and SPL format of label to NDA 22128/S-17

3.0 ACTION ITEMS: Sponsor verbalized understanding of request and indicated they would submit the requested information as soon as possible.
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/s/

ANDREW A GENTLES
06/06/2016
Good Afternoon Mark,

We have a question pertaining to location of specific information within the current submission. Please the following question from our review team below and provide a response by Thursday, June 2, 2016, COB.

We had requested the sponsor submit tropism data from both the Trofile phenotypic tropism assay and Siemens genotypic tropism assay (prospective and retrospective), but we are unable to find the Siemens genotypic tropism data in the submission. Can the sponsor please direct us where to find these data?

Thanks,

AG

Andrew Gentles, PharmD, BCPS-AQ ID, NCPS

LCDR, U.S. Public Health Service

Regulatory Health Project Manager
FDA/CDER/OND/OAP/Division of Antiviral Products
Room 6211

Ph: 240-402-5708

Email: Andrew.Gentles@fda.hhs.gov

“The only person you are destined to become is the person you decide to be”

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/s/

ANDREW A GENTLES
05/31/2016
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ViiV Healthcare Company
Attention: Mark Baumgartner
Sr. Director, Global Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Mr. Baumgartner:

We have received your New Drug Application (NDA) and supplemental NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number/ Supplement Number: 208984/S-017

Drug Product: SELZENTRY® (maraviroc) oral solution, 20mg/ml
SELZENTRY® (maraviroc) tablet, 25 mg, 75 mg, 150 mg, 300 mg

Date of Submission: May 6, 2016
Date of Receipt: May 6, 2016

The supplemental application proposes the following change:

- To expand the patient population to include pediatric subjects from 2 to less than 18 years of age

Unless we notify you within 60 days of the receipt date the applications are not sufficiently complete to permit a substantive review, we will file the applications on July 5, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21
CFR 314.101(d)(3) . The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA and supplemental NDA numbers provided above should be cited at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact Andrew Gentles, PharmD, BCPS AQ-ID Regulatory Project Manager, at (240) 402-5708.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA C ONAGA
05/18/2016
Dear Dr. Balderson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Selzentry (maraviroc).

We also refer to your April 22, 2015, correspondence, received April 22, 2015, requesting a meeting to discuss the content and format of the new NDA for the oral solution formulation, and the content and format of the supplemental NDA for a lower strength tablet.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.
If you have any questions, call Mammah Sia Borbor, M.S., M.B.A, Regulatory Project Manager at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
  Preliminary Meeting Comments
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 16, 2015 11:00 AM – 12:30 PM Eastern Standard Time
Meeting Location: Teleconference

Application Number: IND 65229
Product Name: Selzentry (maraviroc)
Indication: Treatment of HIV-1 Infection
Sponsor/Applicant Name: ViiV Healthcare Company

FDA ATTENDEES (tentative)
Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, M.D., M.P.H., Deputy Director DAVP
Poonam Mishra, M.D., Medical Officer/ Deputy Director for Safety DAVP
Kim Struble, Pharm.D., Medical Team Lead DAVP
Charu Mullick, M.D., Medical Officer DAVP
Yodit Belew, M.D., Clinical Reviewer DAVP
Shirley K. Seo, PhD, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Jenny Zheng, Ph.D., Clinical Pharmacologist (OCP) (DCP IV)
Lisa Naeger, Ph.D., Virology Reviewer DAVP
Julian O’Rear, Ph.D., Virology Team Lead DAVP
Peter Verma, Ph.D., Pharmacologist DAVP
Hanan Ghantous, Ph.D., DABT, Pharmacology/ Toxicology Team Lead DAVP
Stephen Miller, Ph.D., CMC-Lead, OPQ
Shrikanth N. Pagay, Chemist, OPQ
Mammah Sia Borbor, M.S., M.B.A. DAVP
Karen Winestock, Chief, Project Management Staff, DAVP
Antoine El-Hage, PhD, Office of Scientific Investigations
Danyal Chaudhry, MPH, Regulatory Project Management Staff, Office of Surveillance and Epidemiology
Jessica Fox, PharmD., RAC, Regulatory Review Officer, Office of Prescription Drug Promotion
Brantley Dorch, PharmD., Program Management Officer, Office of Medical Policy Initiatives, Division of Medical Policy Programs
Katherine Schumann, M.S., Senior Project Manager DAVP
Stacey Min, PharmD., Associate Director of Labeling DAVP
Rosemary Addy, M.H.S., Lead Project Management Officer, Pediatric & Maternal Health
Kathleen FitzGerald, Nurse Consultant, CDRH/ODE/DAGRID/GHDB

Reference ID: 3791747
Jasminder Kumar, PharmD, Risk Management Analyst, Division of Risk Management
Jamie Wilkins Parker, PharmD, Acting Team Leader, Division of Risk Management
Monica Calderon, PharmD, BCPS, Safety Evaluator
Jeen Min, RPh, User Fee Staff

**SPONSOR ATTENDEES**
 Kimberly Smith, M.D., M.P.H., Vice President, Global Medical Strategy, VHC
 Neil Shortman, Vice President, Regulatory Affairs, VHC
 Andrew Clark, M.D., Global Medical Leader Selzentry, VHC
 Nassrin Payvandi, PhD, VP Safety and Pharmacovigilance, VHC
 James Demarest, Ph.D., Director Microbiology Strategy, VHC
 Karen Grainger, Director, Regulatory Affairs, VHC
 Diane Balderson, PhD, Senior Director, Global Regulatory Affairs, GSK
 Rebecca Zhang-Roper, MD, PhD, Director, Global Clinical Safety & Pharmacovigilance, GSK
 Anne Mariathas, MRPharm S, Director, Global Clinical Safety and Pharmacovigilance, GSK
 Jayvant Heera, MD, MFPM, Senior Director, Clinical HIV, Pfizer
 Srinivas Rao Valluri, PhD, Director, Biostatistics, Pfizer
 Annie Fang, MD, PhD, Director, Clinical HIV, Pfizer
 Lynn McFadyen, PhD, Senior Director, Pharmacometrics, Global Clinical Pharmacology, Pfizer
 Manoli Vourvahis, PharmD, Director, Clinical Pharmacology, Pfizer
 Charles Craig, PhD, on contract with Pfizer, Virology, Pfizer
 Barry Weatherly, PhD, on contract with Pfizer, Pharmacometrics
 Amanda Matthews, Associate Director, Global Chemistry Manufacturing & Controls (Medical Devices), Pfizer
 Elna van der Ryst MBChB, MMed, DTM&H, PhD, FFPM, on contract with Pfizer, Clinical HIV and Virology
 Maria Vasaka, Clinical Project Manager, Pfizer

**Introduction:**
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 16, 2015, 11:00 AM – 12:30 PM (EST), Teleconference between ViiV Healthcare Company and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the
purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

SELZENTRY (maraviroc), a C-C chemokine receptor type 5 (CCR5) co-receptor antagonist was first approved on August 06, 2007 for the treatment of subjects with CCR5-tropic HIV-1. In the final labeling approval of SELZENTRY (maraviroc), two post-marketing requirements were issued for pediatric studies required under PREA. ViiV initiated Study A4001031 entitled: An Open-Label, Multicenter, Multiple-Dose Pharmacokinetic, Safety, and Efficacy Trial of Maraviroc in Combination with Optimized Background Therapy for the Treatment of Antiretroviral-Experienced CCR5-Tropic HIV-1 Infected Children 2 to < 18 Years of Age as a result of post marketing requirements. Study A4001031 has completed the last-subject last Week-48 visit and will be used to support expanding the indication to include pediatric patients.

On April 22, 2015, ViiV Healthcare Company submitted a Type B, Pre- NDA meeting request for SELZENTRY (maraviroc). The purpose of the requested meeting is to discuss the content and format of the new NDA for the oral solution formulation, and the content and format of the supplemental NDA for lower strength tablets. There will be 2 submissions; a NDA for a new oral solution and a supplement to the existing NDA (22128) to add two lower tablet strengths of 25 mg and 75 mg. ViiV Healthcare Company is targeting a goal date of the first quarter of 2016 to submit the applications to the Division for review. ViiV Healthcare Company is seeking guidance along with detailed feedback from the Division on the following questions.

2.0 DISCUSSION

General Questions

Question 1: Currently, the Sponsor provides the Agency with an annual listing of non-serious adverse events of special interest from a clinical trial source for maraviroc; none were reported in the 2013 to 2014 annual reporting period. At this juncture, maraviroc has been available for more than 8 years. The Sponsor requests that this listing is waived from here onwards as much of the clinical program is now complete.

Does the Agency agree with this proposal?

DAVP’s Preliminary Response:
We agree with the proposal.

Question 2: Prescription Drug User Fee Act fees require a full user fee for an NDA and a reduced fee for a supplement with efficacy data. Efficacy data would be provided in the NDA supporting the new oral solution and the lower strength tablets from the same clinical study, and the sNDA would cross-reference these data back to the oral solution NDA such that only appropriate module 1 components and Chemistry, Manufacturing and Control information would be provided in the sNDA.
Does the Agency agree that only one full NDA user fee is required in this instance?

**DAVP’s Preliminary Response:**
Based upon the information provided, both the NDA and supplement would incur a user fee because the NDA and supplement require clinical data for approval. Please note the final determination for user fee requirements occurs when the application and/or supplement is submitted in their entirety to the Agency.

**Question 3:** There are essentially two submissions being prepared; an NDA for a new oral solution (20mg/mL), and a supplement to the existing tablet NDA (#22128) for lower strength tablets (25mg and 75mg). The Table of Contents in Appendix F of this briefing document provides an overview of the content for this electronically filed common technical document (eCTD) NDA for the new oral solution and the sNDA for adding lower tablet strengths as a side by side view. The sNDA would be filed to the existing tablet NDA #22128. The Table of Contents indicates which modules would contain information/content on both formulations in black text. Modules/submodules where no content will exist have been removed from the Table of Contents. Where cross-referencing would occur from the sNDA to the original NDA components or to the new oral solution NDA, this has been stated. Essentially cross-referencing would be included in the lower strength tablet sNDA back to the original NDA or to the new oral solution NDA for all modules except module 1 (as appropriate), module 2.3 and module 3.

a. Does the Agency support submitting these two submissions such that the NDA for oral solution will be filed first and the sNDA for the lower strength tablets will be filed to the original tablet NDA within a few days of the oral solution NDA?

**DAVP’s Preliminary Response:**
Submitting the two applications on different days is acceptable provided this is within a reasonable time-frame e.g., within 7 days.

b. Does the Agency support cross-referencing as proposed?

**DAVP’s Preliminary Response:**
Yes. Sponsors options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission...
serial number, volume number, electronic folder, file name, etc.,) of the referenced document along with a hypertext link to the location of the information, when possible.

To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. (e.g. xlink:href="../nda022128/0009/m2/24-nonclin-over/nonclinical-overview.pdf">). In the leaf titles of the documents, it is recommended that the leaf title indicate the word “cross reference to” and the application number (e.g. Cross Ref to nda 022128-nonclinical-overview). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

**Question 4:** The NDA for oral solution will contain pharmacokinetic, safety, efficacy and virology data provided from the various studies supplied in this submission (A4001034 and A4001031 [Week 48 clinical study report and a Post-Week 48 supplemental clinical study report]), along with pharmacokinetic modeling reports (PMAR-00309/EQDDA400b-DP4-193 and PMAR-EQDD-A400b-DP4-195) as outlined in the Table of Contents in Appendix F of this briefing document. The supplemental NDA (sNDA) for the lower strength tablets will cross-reference these reports from the NDA for oral solution. The Table of Contents indicates which modules would contain information/content on both formulations in black text. Modules/submodules where no content will exist have been removed from the Table of Contents. Where cross-referencing would occur from the sNDA to the original NDA components or to the new oral solution NDA, this has been stated.

Does the Agency agree that this is sufficient to support a submission for maraviroc in antiretroviral treatment-experienced pediatric patients?

**DAVP’s Preliminary Response:**
From a technical standpoint (not content related) yes. However, please see general comments below:-

- Providing Table of Contents in 2.1 and 5.1, is not necessary in the eCTD structure. If possible, provide a linked reviewer’s aid/reviewer’s guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application.
- Provide m2.7.6 in tabular format and link to the referenced synopsis in module 5
• The tabular listing in module 5.2, should be provided in tabular format and linked to the referenced studies in m5.

• Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study’s STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study’s STF to which they belong, organized by site as per the specifications and tagged as “case report form”. Subject Data Listings (16.4) should be file tagged as “data-listing-dataset”. For documents with no specific file tags, “study-report-body" or “legacy-clinical-study-report” file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

• To submit post marketing reports (descriptive portion only) in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Please ensure that the leaf title of the report includes the reporting period. Since each report is for a specific time period, we recommend that the leaf title follows a standard format, so reviewers can quickly differentiate one report from another (e.g. Periodic Safety Update Report (PSUR-january19-2013-june18-2014).

**Question 5: Module 1.4.4 will provide a table that lists NDA 022128 and IND 065229 for SELZENTRY.**

Is there anything else the Agency would expect in this module?

*DAVP’s Preliminary Response:*
If possible, provide hyperlinks.

**Question 6: Module 1.6 will contain only official correspondence related to the two pediatric research equity act post-marketing requirements.**

Does the Agency agree?

*DAVP’s Preliminary Response:*
Module 1.6 is for meeting related correspondence. If the correspondence is related to a meeting it can be placed in this module. All other pediatric related information should be placed in Module 1.9.

**Question 7: The Sponsor considers a risk evaluation and mitigation strategy (REMs) or a risk management plan (RMP) is not needed in Module 1.16 in either the NDA or sNDA**
given the current safety profile of maraviroc. Note that currently there is no REMS in place for maraviroc.

Does the Agency agree with this proposal?

**DRISK’s Preliminary Response:**
At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

**Question 8:** For module 5.3.6, Reports of Post Marketing Experience, the Sponsor proposes to include the following information

- A summary of spontaneous adverse events reports in pediatric patients using maraviroc identified from the Sponsor’s global safety database
- Post-marketing surveillance reports of serious adverse events in pediatric subjects using maraviroc identified from the Sponsor’s global safety database
- Published literature relating to the safety of maraviroc used in pediatric populations.

The proposed cut-off date for post marketing data is 6th July 2015, which is consistent with the annual Development Safety Update Report (DSUR).

Does the Agency agree with the content and the cut-off date for module 5.3.6?

**DAVP’s Preliminary Response:**
The proposed content for module 5.3.6 is reasonable. At this time, we cannot commit to the proposed cut-off date and this will depend on the submission dates.

**Question 9:**

For the post-NDA submission safety update, the Sponsor anticipates this application will be assigned priority review and hence a 4 month safety update as outlined in CFR §314.50 (d)(5)(vi)(b) may be more appropriate at 2 months, in time for the Agency’s mid-cycle review meeting. As such the Sponsor proposes to submit updated safety information covering the period from the Last-Subject Last-48-week Visit date (14 April 2015) to the date of submission of the NDA for oral solution (date to be confirmed). This safety update will be submitted to the NDA 2 months after that application is submitted, and should be cross-referenced when reviewing the sNDA.
It is proposed to include the following information for this safety update:

- Listings and a brief discussion of all adverse events leading to discontinuation from study A4001031. Data will be retrieved from the study clinical database.

- Listings and a brief discussion of all serious adverse events, deaths and pregnancies. Data will be retrieved from the Sponsor’s global safety database.

If no events occur, no update will be provided. The Sponsor will send a formal communication to the Agency at the end of the 2-month period if this is the case. Safety updates after approval will be provided as required for NDA annual reporting.

Does the Agency agree with this proposal for the post-NDA submission safety update?

**DAVP’s Preliminary Response:** A single safety update should be submitted to support both applications. We agree, in general, with submitting an update two months after the clock begins for the first NDA (for oral solution). Please note that if there are unanticipated delays in the sNDA submission then we may request another safety update for the sNDA. In addition to the proposed elements for the update, include any events of special interest. Please ensure the safety update only includes new findings not included in the NDA submissions.

**Question 10:** For study A4001031 there were a total of 9 protocol amendments. The Sponsor proposes to concatenate all protocol amendments for study A4001031 into a single new file for inclusion in the eCTD as is outlined in the Table of Contents Appendix F.

Does the Agency agree with the concatenation?

**DAVP’s Preliminary Response:**
Yes. Please make sure you provide table of contents, hyperlink, clear and proper bookmarks.

**Question 11:** For the NDA, there is one pivotal pediatric clinical study (A4001031) and one relative bioavailability study (A4001034) supporting this submission. There will be no pooling of efficacy or safety data. Therefore the Summary of Efficacy (module 2.7.3) and Summary of Safety (module 2.7.4) will contain the same information as the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) typically required in module 5.3.5.3. Module 5.3.5.3 will contain data sets for the pharmacokinetic modeling report; the corresponding modeling report will be located in module 5.3.3.5. All these modules for the sNDA would be cross-referenced to the oral solution NDA.

As the ISE and ISS would be identical to m2.7.3 and m2.7.4 respectively, does the Agency want these summaries to be included in m5.3.5.3 as well as m2.7.3 and m2.7.4 or can they be omitted from m5.3.5.3 in the oral solution NDA?

**DAVP’s Preliminary Response:**
It is acceptable to submit the Summary of Clinical Efficacy and Summary of Clinical Safety as well as datasets for PK modeling report in module 5.3.5.3.

Non-Clinical

**Question 12:** A list of all non-clinical studies conducted with maraviroc is available in Appendix G.

Does the Agency agree that no further nonclinical studies are necessary to support the submission and approval of maraviroc in pediatric patients from birth to 18 years of age?

**DAVP’s Preliminary Response:**
Yes, we agree.

Clinical Data Format and Content of NDA

**Question 13:** According to the latest FDA Submission Guidance published on 17 Dec 2014 under Section 745A(a), any studies with a start date after December 17, 2016 (for NDA), are required to submit the study data with Clinical Data Interchange Standards Consortium (CDISC) compliance. Since the maraviroc pediatric study A4001031 started more than 5 years prior to this date with first subject screened in April 2009, the Sponsor believes that this maraviroc submission does not meet the mandated requirement for CDISC compliance. Therefore, the following are the proposals for presenting the datasets and programs for analyses and reporting in the oral solution NDA (the sNDA would contain cross-references back to the oral solution NDA for these aspects):

**Study Data Format for Submission**

- Safety/efficacy/Laboratory/Pharmacokinetic study data

Sponsor proposes to submit all the study data in the Pfizer data standard (PDS), non-CDISC format.

(13a) **Does the Agency agree with this proposal?**

**DAVP’s Preliminary Response:**
Your approach for submitting non-CDISC-formatted data is acceptable, though we recommend submitting standardized data to help facilitate review. In addition to the dataset submissions, please also include all relevant metadata (e.g. define.xml) associated with each study in both .xml and .pdf formats, as indicated in the Study Data Technical Conformance Guide and previous Study Data Specifications documents.

We recommend that you submit a sample or mock dataset including definition files in advance of the NDA for an assessment and feedback.
• **Virology/Resistance data**

Sponsor proposes to perform the virologic analysis on the protocol-defined virologic failure population using the listings and summary tables from the PDS standards. In addition, the Sponsor proposes to submit all available HIV-1 resistance data in SAS transfer files described in the FDA draft guidance document titled “*Guidance for Submitting HIV-1 Resistance Data*” dated February 2014 and following the associated template. Appendix I provides a spreadsheet of the proposed variables to be included for study A4001031. Also included in Appendix I is a word document that describes the variables and presents questions for the Agency, which need to be addressed for the submission of the virology data.

(13b) Does the Agency agree that the draft guidance from February 2014 should be applied to these data?

**DAVP’s Preliminary Response:**
Yes, we agree.

(13c) Will the Agency please provide responses to the clarifications contained in the associated word document in Appendix I as part of the written responses to this meeting in order to assist the Sponsor to submit virology data for study A4001031?

**DAVP’s Preliminary Response:**
These questions were already addressed in IND65229 SDN649 and 650.

**SAS Programs for Primary and Secondary Endpoints Analysis and Reporting**

• **Pharmacokinetic**

The non-compartmental pharmacokinetic analysis is performed within Pfizer’s electronic non-compartmental analysis (eNCA) system which serves as the Pfizer corporate clinical data repository for the pharmacokinetic bioanalytical/concentration data (21 CFR part 11 compliant). The system uses S_PLUS scripting. The Sponsor does not intend submitting any specific programs in support of the pharmacokinetic analyses and reporting.

(13d) Does the Agency agree with this proposal?

**DAVP’s Preliminary Response:**
Yes, we agree.

• **Safety Reporting**

Pfizer’s internal Clinical Data Analysis and Reporting System (CDARS) is being used for standard safety reporting. The reporting system has been standardized and validated over the years. However, the system’s codes involve system level macros which are not
standalone SAS programs and cannot be delineated easily. Therefore, the Sponsor is not planning to submit the system codes for generating the key safety reports.

(13e) Does FDA agree with this proposal?

**DAVP’s Preliminary Response:**
The proposal to not submit in the NDA programs used to generate the safety reports is acceptable as long as the NDA includes the standard safety-related data in the standard NDA format.

- **Efficacy Reporting**

  Efficacy endpoints (e.g. HIV-1 RNA, CD4 and CD4%) are secondary endpoints in this study. The Sponsor is not planning to submit the SAS programs for generating the efficacy analyses and reports.

(13f) Does the Agency agree with this proposal?

**DAVP’s Preliminary Response:**
Yes, we agree.

- **Virology/Resistance summaries**

  Simple descriptive summaries are produced and therefore the Sponsor does not plan to submit the associated SAS programs on these data.

(13g) Does the Agency agree with this proposal?

**DAVP’s Preliminary Response:**
Yes, we agree.

- **Bioavailability study data**

  Study A4001034 is a 3-way crossover study that investigated the relative bioavailability and effect of food on the pharmacokinetics of the pediatric maraviroc oral solution. The final clinical study report for this study will be provided in support of the submission. The Sponsor is not planning to submit either raw data or value added datasets for the study.

(13h) Does the Agency agree with this proposal?

**DAVP’s Preliminary Response:**
Please provide all raw and derived PK datasets. In addition, please provide bioanalytical and assay validation reports.

**Question 14:** The initial statistical analysis plan for A4001031 was written in 2008 and was reviewed by the Agency prior to the first-subject first-visit. Since then, there have been a
number of changes to guidelines and procedures as well as the change to report adverse events using Division of AIDS (DAIDS) grading criteria instead of the AIDS Clinical Trials Group (ACTG) system. During the course of the study to date, there have been 9 amendments to the protocol to reflect these required changes. Therefore, the Sponsor thought it appropriate to revise the statistical analysis plan to address any changes relevant to the analysis including additional clarification on efficacy summarization and specific virologic analyses planned to be conducted. The statistical analysis plan is provided in Appendix H.

Does the Agency agree with the planned analyses as described in the amended statistical analysis plan, included in Appendix H?

**DAVP’s Preliminary Response:**
The proposal appears reasonable. Please ensure the safety analyses are performed using data from all subjects who received at least one dose of treatment i.e. the FAS dataset. Ensure laboratory analyses include the following parameters in addition to those proposed: hemoglobin, platelet count, and absolute neutrophil count.

**Question 15:** The Sponsor will provide SAS transport files for the final modeling datasets, together with a definition document and the final NONMEM models and output files or R scripts (as .txt files) for the Agency to independently analyze pharmacokinetic (PK)/noncompartmental analysis (NCA) data.

Does the Agency agree this is an appropriate format?

**DAVP’s Preliminary Response:**
Your approach seems acceptable. Please review the Study Data Technical Conformance Guide and previous Study Data Specifications documents for additional instructions on preparing and submitting relevant study data. Similarly, additional details on the submission of the pharmacokinetic modeling datasets, control streams, output files, and analysis scripts can be found at the following link: [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm).

**Clinical Safety**

**Question 16:** The Agency provided feedback from a Type C meeting held in 9 May 2014 which discussed stopping enrolment into pediatric study A4001031, indicating that the amount and robustness of Week 96 safety data would be considered when determining if the Sponsor had met their pediatric research equity act post-marketing requirement (Appendix E). The cut-off date for all safety data in the A4001031 study will be the last subject last-48 week visit date, which occurred on 14 April 2015.

- Module 2.7.4 will include the following information from study A4001031:
- Analysis of Week 48 safety data (based on the Week 48 clinical study report in module 5.3.5.2)
- Analysis of available Week 96 and 5 year safety data (based on Post Week 48 supplemental clinical study report in module 5.3.5.2)

Does the Agency support the proposal for the cut-off date and the content structure for module 2.7.4?

DAVP’s Preliminary Response:
Yes, we agree.

**Question 17** Given that the mean and range for the stage 1 (intensive) pharmacokinetic maraviroc average concentration (Cavg) is similar between Cohorts 2 (liquid) and 3 (tablet) in the same age group, the Sponsor proposes to combine safety data from these two cohorts to support a submission for maraviroc dosing in antiretroviral treatment-experienced children 6 to 12 years of age.

Does the Agency agree with this proposal to combine these cohorts to summarize safety data?

**DAVP’s Preliminary Response:**
In addition to the proposed combined safety summary, please include safety summaries for individual cohorts to allow adequate evaluation of the oral solution and tablet formulations.

**Question 18** The Sponsor proposes to provide listings of deaths, serious adverse events, pregnancies, and withdrawals due to adverse events from pediatric study A4001031 as part of the Week 48 clinical study report and the Post Week 48 supplemental clinical study report. Case narratives for all serious adverse events will be provided in these reports. The safety data will have a data cut-off date of 14 April 2015 (last-subject last-Week 48 visit). There were no deaths, serious adverse events, pregnancies, and withdrawals reported in the relative bioavailability study A4001034, therefore no narratives will be provided for this study.

Does the Agency agree with this proposal?

**DAVP’s Preliminary Response:**
In addition to the proposal, please submit narratives for any grade 3 or 4 adverse events in study A4001031.

**Question 19** The Sponsor proposes to submit case report forms for all subjects in pediatric study A4001031 who died or discontinued due to an adverse event. Case report forms for other subjects in this study will be available upon request. There were no deaths or discontinuations in the relative bioavailability Study A4001034, therefore no case report forms will be provided for this study.

Does the Agency agree with this proposal?
DAVP’s Preliminary Response:
Please include CRFs for all SAEs.

Clinical Virology

**Question 20** Does the Agency agree with the proposed virology analysis and that this analysis is sufficient to support the current proposed extension of the indication to a pediatric population?

**DAVP’s Preliminary Response:**
Yes, we agree.

Dosing, Labelling, PK Modelling and Dosing Device

**Question 21** The pediatric study A4001031, supporting the NDA/sNDA submissions, utilised body surface area bands to determine dose. However, for simplicity and to reduce potential dosing errors when calculating dose using body surface area, the Sponsor proposes to use weight bands to determine dose. This will lead to a reduction in the number of dosing bands, and an increase in dose for those subjects who have a body-surface area of 1.31 to 1.73m² from a clinical study dose of 125mg (2x25mg and 1x75mg tablets) to a marketed dose of 150mg (1x 150mg tablet). The Sponsor is confident that the submission will provide the necessary data and justification to support weight-based dosing. Notwithstanding that the data will be needed for a final decision, and that this will be a review issue, does the Agency support the approach to utilize weight based dosing in preference to body surface area as outlined in Appendix A?

**DAVP’s Preliminary Response:**
Yes, we agree.

**Question 22** The Sponsor is planning a tabular presentation for pediatric dosing by weight (kg) and concomitant medications due to potential drug interactions as outlined in Appendix A. The concomitant medication groupings proposed will be consistent with those for adult patients (that is potent CYP3A inhibitors [with or without a potent CYP3A inducer], other concomitant medications [neutral agents], and potent CYP3A inducers [without a potent CYP3A inhibitor].

Does the Agency agree with this proposal?

**DMEPA’s Preliminary Response:**
Yes, the Agency agrees with the proposal for the tabular presentation; however, we recommend adding kilograms (kg) next to each weight band (e.g 10 kg to 20 kg) to provide clarity and to remove all symbols (> ) from the table and replace with “greater than”. For improved readability, the Sponsor may consider bolding the weight ranges or doing something to distinguish that particular row.
**Question 23** Discussions were held with FDA and EMA after submission of an interim modeling report based on pharmacokinetic data available when stage 1 (intensive pharmacokinetic sampling phase) completed in 2013. Recommendations were received from FDA and EMA to simplify models with sub-setting of pharmacokinetic data to improve NONMEM termination behaviour and data fitting (Appendix E). These recommendations have been implemented in two analysis plans provided as Appendix J and Appendix K to the briefing document.

Analysis Plan 1 proposes (Appendix J):

- Graphical analysis/comparison of data from A4001031 and adult patient data (sparse sampling) with appropriate background therapy on labelled twice-daily maraviroc doses

- Simplified pharmacokinetic compartmental modeling of A4001031 data from subjects on background therapy with CYP3A4 inhibitors combined with healthy volunteer adult data from appropriate phase 1 studies

Analysis Plan 2 (Appendix K) proposes graphical analysis of non-compartmental analysis parameters from adult healthy volunteer and HIV patient studies with non-compartmental analysis data from A4001031 to compare observed exposure ranges.

Does the Agency agree that this is an appropriate way forward for the modeling component of the submission and aligned with prior recommendations from the Agency?

**DAVP’s Preliminary Response:**
The Agency acknowledges the sponsor’s proposed updated analysis plans. These analysis plans address the majority of the concerns raised by the Agency at the May 2014 Type C meeting. We agree that these analyses represent a potential path forward for the modeling component; however, determination of the appropriateness of the analyses will ultimately be a review issue. One suggestion for the analysis plan in Appendix J is to include at least a subset of adults patients on background therapy with CYP3A4 inhibitors in the planned analysis of pediatric patients and healthy volunteers.

**Question 24** In order to deliver the oral solution doses, the Sponsor is proposing to provide
(24a) Does the Agency agree the proposed dispensing device in Figure 6 is appropriate for its intended use?

Please see the Agency’s response to question 24b. Within your future NDA submission, the Agency expects that you will provide information supporting the performance of the device constituent parts, including descriptive information and test reports for the press-in bottle adaptor and 10 ml syringe.

DMEPA’s Preliminary Response:

We recommend maintaining the milliliter measurements to maintain one unit of measure and minimize risk for confusion. We also recommend the Dosage and Administration section of the full prescribing information be congruent with the recommendations to maintain only metric units of measurement.

The syringe contains the following statement, We recommend removing from the statement as this syringe will only be used for oral administration. We also recommend adding the following statement, as this oral syringe will be specific to dosing with this product.

To minimize such errors, we recommend presenting the measurement in whole numbers, (e.g., 2 mL) To improve readability while drawing up the dose, we recommend inverting the measurements so that the numbers are read upright when the syringe is upside down.

(24b) Does the Agency agree this combination product is exempt from additional cGMP requirements under 21 CFR Part 4?

CDRH Preliminary Response:

After review of IND 65229 meeting package is instead considered the device constituent part of a combination

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product and requires premarket review. The co-packaged Selzentry (maraviroc) drug product, together with the press-in bottle adaptor and the 10 ml syringe devices is a combination product subject to 21 CFR Part 4 requirements. Please provide complete device related information and performance test reports regarding the press-in bottle adaptor and 10 ml syringe in the applications.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.
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/s/

MAMMAH S BORBOR
07/14/2015