CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-145 SUPPL # N/A HFD # 530

Trade Name ISENTRESS

Generic Name raltegravir

Applicant Name Merck & Co., Inc.

Approval Date, If Known October 12, 2007

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)

c) 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:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

e) 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.

YES ☐ NO ☒

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

NDA#

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:

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"):

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 # 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:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: Monica Zeballos, Pharm.D.
Title: Sr. Regulatory Project Manager
Date: Oct 1, 2007

Name of Office/Division Director signing form: Debra Birnkrant, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Debra Birnkrant
10/1/2007 01:55:49 PM

PEDIATRIC PAGE ADDEMDUM REPLACES THE ORIGINAL SIGNED-OFF ON OCT 1, 2007

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-145 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: April 13, 2007 **PDUFA Goal Date:** October 13, 2007

HFD 530 **Trade and generic names/dosage form:** ISENTRESS™ (raltegravir) 400 mg tablets

Applicant: Merck & Co., Inc. **Therapeutic Class:** Antiviral, integrase strand transfer inhibitor (INSTI)

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: Treatment of HIV-1 infection in treatment-experienced adults patients

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- ☒ No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- ☒ No: Please check all that apply: X Partial Waiver X Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo. birth yr._____ Tanner Stage_____
Max_____ kg_____ mo. up to 4 weeks yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☒ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo. 4 weeks yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr. 18 Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ☒ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): June 30, 2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Monica Zeballos, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Monica Zeballos
10/12/2007 05:17:45 PM

Monica Zeballos
10/12/2007 05:17:45 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 22-145 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: April 13, 2007 **PDUFA Goal Date:** October 13, 2007

HFD 530 **Trade and generic names/dosage form:** ISENTRESS™ (raltegravir) 400 mg tablets

Applicant: Merck & Co., Inc. **Therapeutic Class:** Antiviral, integrase strand transfer inhibitor (INSTI)

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☒ **Yes. Please proceed to the next question.**
- ☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: Treatment of HIV-1 infection in treatment-experienced adults patients

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☒ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply:** ____**Partial Waiver** _X_**Deferred** ____**Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__18__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ☒ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): June 30, 2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: N/A

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Monica Zeballos
10/1/2007 09:41:13 AM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # **22-145**	BLA STN# NDA Supplement # **N/A**	If NDA, Efficacy Supplement Type **N/A**	
Proprietary Name: **Isentress** Established Name: **Raltegravir** Dosage Form: **400 mg tablets**		Applicant: **Merck & Co., Inc.**	
RPM: **Monica Zeballos, Pharm.D.**		Division: **Division of Antiviral Products (DAVP)**	Phone # **(301) 796-1500**

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): **N/A** Provide a brief explanation of how this product is different from the listed drug. **N/A** ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	**October 13, 2007** **October 12, 2007**
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☒ Received but not reviewed yet

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): 1

NDAs, BLAs and Supplements:
☒ Fast Track
☒ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: Internal Informational Advisory

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A** ☐ No paragraph III certification Date patent will expire - **N/A**
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified **N/A**
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	**N/A**
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	**October 12, 2007**
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	**N/A**
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	**No**
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**Included**
• Original applicant-proposed labeling	**No**
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	**N/A**
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	**No**
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**Included**
• Original applicant-proposed labeling	**No**
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	**N/A**
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	**N/A**
• Original applicant-proposed labeling	**N/A**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	**No**
• Most recent applicant-proposed labeling	**Included only immediate container label**

❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS **February 13, 2007** ☒ DSRCS **July 19, 2007** ☒ DDMAC **July 25, 2007** ☒ SEALD **dated October 4, 2007 informal review not DFS'd** ☒ Other reviews: **RPM Format PLR Review dated July 20, 2007** ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	**RPM Regulatory Filing Review & Memo of Filing Meeting dated October 2, 2007**
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ **Included**
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	 **N/A** **N/A**
❖ Pediatric Page (all actions)	☒ **Included**
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ **Verified, statement is acceptable**
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	**See facsimile correspondence dated October 1, 2007**
• Incoming submission documenting commitment	**N/A**
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	**Included**
❖ Internal memoranda, telecons, email, etc.	**Included**
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	**Mgt held on September 7, 2007 but there were no meeting minutes**
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg **Dec 1, 2006**
• EOP2 meeting *(indicate date)*	☐ No mtg **Dec 5, 2005**
• Other (e.g., EOP2a, CMC pilot programs)	**EOP1 on June 29, 2005; Type C mgt. on August 9, 2006**
❖ Advisory Committee Meeting	☐ No AC meeting
• Date of Meeting	**September 5, 2007**
• 48-hour alert or minutes, if available	**Included**
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**Included**
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	**Included dated September 26, 2007**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None **Manufacturing Science Branch review dated September 28, 2007**
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and*	**See CMC review dated**

all efficacy supplements that could increase the patient population)	**September 26, 2007**
• ☐ Review & FONSI *(indicate date of review)*	**N/A**
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: **August 7, 2007** ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	**N/A** ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**Included dated October 11, 2007. Reference IND 69,928 and Tx IND**
❖ 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	**November 1, 2005**
❖ Nonclinical inspection review Summary (DSI)	☒ None requested

Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**Included and dated October 11, 2007**
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	**See clinical review**
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☐ Not needed **Included and dated Oct 10, 2007**
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	**See clinical review**
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	*Included in Consults section and dated August 24, 2007*
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	**Included**
• Bioequivalence Studies	**N/A**
• Clin Pharm Studies	**N/A**
❖ Statistical Review(s) *(indicate date for each review)*	☐ None **Included and dated October 11, 2007**
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **Pharmacometrics and pharmacogenomics are included with it and dated October 1, 2007**

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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

/s/

Monica Zeballos
10/12/2007 05:09:17 PM

MEMORANDUM

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

DATE: October 9, 2007

TO: Division of Antiviral Products, Division File

FROM: Monica Zeballos, Pharm.D., Sr. Regulatory Project Manager

SUBJECT: **Information Requests from reviewers (queries)**
NDA 22-145, raltegravir (formerly MK-0518)

The following Query Table attachment represents all communications with the applicant via email correspondence (queries from reviewers) only, from the receipt date of the final NDA rolling submission (April 13, 2007) to October 9, 2007. Also included are the word documents with the specific queries all attached in the order they were sent to the applicant via email correspondence. The purpose of this memo is to batch all communications via email correspondence for reference to the NDA via the Division File System. This Query Table states date sent and when the response was received.
For all other communications via facsimile correspondence (CMC IR, labeling recommendations), please refer to the Division File System.

NDA 22-145, Raltegravir Potassium (first integrase inhibitor)
Query Table

Applicant: Merck & Co., Inc.

Review Team: Sarah Connelly (MO, 6-2085); Ita Yuen (Pharm/tox, 6-0838); Derek Zhang (ClinPharm, 6-1634); Pravin Jadhav (ClinPharm, 6-1510); Shashi Amur (ClinPharm, 6-1631); Sung Rhee (Mic, 6-0794); George Lunn (CMC, 6-1701); Ted Chang (CMC, 6-1974); Karen Qi (Stats, 6-0792); Fraser Smith (Stats, 6-0814); Monica Zeballos (PM, 6-0840)

DATE SENT	REQUEST TYPE	VIA TYPE	RESPONSE RECEIVED DATE	EDR Rec'd
May 4, 07	Four clinical queries	Email	• May 8-MRL requested clarification for no. 4 to include actual data vs. dates. May 10-Sarah provided clarification to include actual data w/ corresponding dates. May 10-received via email responses for nos. 2 & 3. Beth forwarded them to Sarah. May 14-received via email response to no. 1. Monica forwarded it to Sarah. May 15-received via EDR/gateway response for no. 4 and forwarded to Sarah.	
May 18, 07	Follow-up queries to MRL's responses to queries 1 & 4 from our May 4, 2007 email request	Email	• May 23 –received via email response to query 1 but not sent to Sarah b/c waiting for response to query 4. May 29-sent both responses for queries 1 & 4 to Sarah.	Yes 5/24/07
May 7, 07	DSI information for patient datasets from 4 clinical sites to be inspected to be submitted to the NDA & CDs (one per site)	Tecon/ Email	• May 11-received via email & sent to Tony as well. • May 14-Tony confirmed receipt of CDs.	
May 7, 07	Clinical query regarding dataset discrepancies between study site data in NDA (studies 005, 019) and IND ~~~~ (SN414)	Fax	• May 11-received via email. Monica forwarded them to Sarah & Kendall (sent to Tony, Fraser, Karen on May 14).	Yes 5/18/07
May 25, 07	Sent Kendall's explanation about dataset discrepancies	Email	• Jun 5-received via email and forwarded to Kendall.	
May 7, 07	One clinical and one mic query	Email	• May 10-received via email to both. Beth forwarded them to Sarah & Sung.	
May 7, 07	One clinical query regarding date of death for 16 subjects	Email	• May 10-received via email. Beth forwarded it to Sarah and Sarah to Karen	
May 11, 07	Five clinical queries	Email	• May 16-received via email for all queries. Forwarded them to Sarah	Yes 5/18/07
May 18, 07	Four clinical queries re Mycosi fungoides, Kaposi's sarcoma X2, squamous cell carcinoma	Email	• May 29-received via email responses to 1-3. Forwarded them to Sarah. Response to 4 will be sent via gateway 5/30 or 5/31	

			• May 30-received via email word response to 4. Forwarded it to Sarah. Not is the EDR yet or GS. Also sponsor performed QA for all SAS files for P04, 05, 019, 018. Forwarded to Kendall, Greg, Fraser, Karen & Sarah. Rerequested updated SAS files for P018 (due to corruption).	
May 25, 07	One clinical response (Kendall's), 3 statistical (2 SAS datasets: screening, OBT & 1 re QT study), 2 CMC (IND 69,928: debossed marking on Kaletra in SN528, info raltegravir placebo for P018 & P019)	Email	• Jun 5-received via email and forwarded to Sarah, Kendall, Steve, George, Fraser, Karen, Rafia and Joanne (QT study) on Jun 6, 07. The SAS datasets for the 2 stats (Fraser & Karen) queries will be in the EDR by Friday, Jun 8 but not received as of 6/20/07	
Jun 5, 2007	Five queries (1 clinical, 3 stats, 2 mic)	Email	• Jun 11-emailed clarification responses to Abey/Bob for the 3 stats queries and had a Webacasting/WebEx meeting on Jun 12 for additional clarification. • Jun 21-received pending responses Seq019 via email and forwarded it.	
Jun 8, 2007	Two queries for INDs 75,635 (SN110, missing CV for Dr. McClelland) and 69,928 (SN575, unreadable safety report)	Email to Abey	• Jun 21-received via email partial for 75,635. Jun 25-received paper official for 69,928 and assigned it Sarah.	NA
Jun 12, 07	Action Items captured at a Webcasting/WebEx meeting: **1. DAVP will provide the protocol number and allocation numbers for the 2 patients who discontinued study prematurely and MRL will follow-up with the reasons why only 1 placebo patient is represented on proposed label Table 7 in the label.** *Note: On Jan 13, 2007, DAVP sent the excel table from the DISPOS datasets for Protocols 018, 019 pertaining to subjects who discontinued (2 subjects in the placebo arm who discontinued due to "other reasons" versus 1 subjects in Table 7 in the label) to Dr. Abey via email correspondence.* **2. Merck will provide analysis datasets (SAS XPT files with DEFINE.PDF) for all the laboratory data included in** [redacted] **3. Merck will provide logic to support and describe the apparent discrepancies in the examples above.** **4.** [redacted] **will provide hard copy of the laboratory reports of Week 16 and 24 for efficacy endpoints directly to the FDA for the 4 sites to be inspected and for the 2 additional sites. (Original query sent Jun 5, 07)**	Email our version of AI to Abey/ Bob on Jun 25, 07	• Jun 25-received via email response (from Abey) to action item #1 and Jun 27 received via email response (from Abey) to action item #3 and forwarded them both to Sarah on Jun 27, 07. • Jun 25-received via DHL hard copy of the lab reports (computer generated) from [redacted], thus completing action item #4. • Jun 29-received via gateway/EDR (Seq021) all the responses to 1, 2, 3, and 5. Also see Seq030 (query 2) and Seq031 (query 1) forwarded links to Sarah. • July 31-received in EDR (Seq037), additional datasets for P4, 5, 18, & 19 including all scheduled and unscheduled laboratory measurements and supplemental site-specific lab tests. Forwarded link to Fraser, Karen, & Sarah. Complete responses to all action above are as follows: EDR (BM dated June 28, 07, Seq021 in GS EDR (BM dated July 25, 07), Seq030 in GS EDR (BM dated July 26, 07), Seq031 in GS EDR (BS dated July 31, 07), Seq037 in GS	YES Seq021 Seq030 Seq031 Seq037 dated July 31, 07

	5. Merck will provide PDF files of the data mentioned above and submitted them officially to the FDA (to the EDR).			
June 20, 07	One extensive pharmacometric query (Pravin) for P018 & 019	Email	• Jun 21-MRL requested a tecon to discuss clarifications, comments, proposals re this query. Tecon on Jun 26 to clarified request and MRL agreed to provide responses by **Jul 10, 07. MLR provided responses by agreed time in the EDR (BB, dated Jul 10) Seq025**	Seq025
Jun 22, 07	Stats/clinical query re death dates in raw dataset for P04,05,18, and 19	Email	• July 5-received EDR path location and forwarded to Sarah, Fraser & Karen.	YES Seq022
Jun 26, 07	Two clinical queries (5 subject discrepancies in P019)	Email	• July 5-received responses via email and forwarded to Sarah. EDR submission (BM) dated July 9, 07.	YES Seq023
Jun 26, 07	Comment in the filing letter to submit CAC update report for the 2 year ongoing study	Faxed	• July 23-received response via email in PDF format & forwarded to Ita, Sarah and Hannan. Located in EDR (BP dated July 20, 07 and the V drive.	YES Seq028
July 5, 07	CMC IR (George) with 29 comments/recommendations	Faxed received receipt confirmation	• July 27-received response via email and expect the eCTD submission to include updates impacted by these responses. Forwarded to George and he'll have replies. EDR (BC, dated July 27, 07) link was forwarded to George on Aug 6, 07. • Aug 9-sent via fax CMC replies for queries 3 & 14 towards Merck's responses dated July 27, 07. • Aug 17-received via EDR (BC, Seq049, dated Aug 16. 07) responses to follow-up CMC replies for queries 3 & 14 towards Merck's responses dated July 27, 07. Forwarded link to George on Aug 20. • Aug 10-received via EDR (BC, Seq048, dated Aug 10, 07) further response to comment 28: stability update along w/ stats analysis of FSS along w/ info to justify extension of proposed expiry to 30 months. Forwarded link and Seq to George & Steve on Aug 16.	Seq035 Seq049 Seq048
July 6, 07	Four queries (2XKaren, 1XFraser, 1XPravin)	Email	• Back and forth discussion on July 17, 18 and our final response on July 20 re the stats query no 3 (Fraser). • July 23-received responses Seq029 for all except Fraser's and forwarded them to Karen, Pravin & Sarah but waiting for stats datasets in the EDR. July 24-received the EDR (BZ, dated July 23, 07) link &forwarded to Karen, Pravin, Fraser. Fraser's query is still pending w/ new date of July 20.	YES Seq029 Seq033

			• July 26-received response Seq033 via email for Fraser's last query reclarified on July 20 & forwarded it to him, Karen, Greg and Sarah. July 26-received response via email & forwarded to Fraser, who formulated a follow-up query dated July 31, 2007. • Aug 13-received via EDR (C, Seq046 dated Aug 8, 07) response re original source documents of tx allocation codes from external vendor and forwarded GS link to Fraser, Tony, Karen, Greg & Karen.	Seq046
July 12, 07	• Two queries for the RMP to submit all details of all meds errors occurred in clinical trial & pink table (Todd Bridges, TL of DMETS) • Two clinical queries for NDA 22-145 re MedDRA used in SUR & revised FDALAB dataset w/ toxi grades for P2, P3	Email Email	• July 18-received responses via email & forwarded to Todd and Sarah. • July 16-received response via email for no. 2 & clarification question for no. 1. Forwarded to Sarah. Response for no. 1 is pending but requested to be submitted by July 19 instead of July 27 per Merck. • July 25-received in EDR partial response for no. 1 (P018 & P019)*.	YES Seq026 *Seq030 Seq031
July 18, 07 **July 23, 07**	One query (subject mapping file) from the IRT for the QT study report (Devi Kozeli) Follow-up query (mine) to resubmit the uncorrupted dataset for P024	Email Email	• July 23-received response via email & forwarded it to Devi. • Aug 6-sent EDR link (C, dated July 27, 07) to Devi to complete this query.	Seq034 for both
July 20, 07	One query From Shashi re Protocol 013 (UGTA1)	Email but not in word	• July 24-received response: *"Merck states that it can provide a further update report around August 21, 2007, but the Clinical Study Report (complete data) and related raw datasets (properly QC'ed) will not be available until well after the Advisory meeting in September"* forwarded to Shashi, Derek, Kellie and requested from Merck to submit the update report & raw datasets for the already submitted interim analysis. Aug 1-received response in EDR and forwarded link Seq to Shashi, Sarah, Pravin, and Derek. Merck'll provide a further update report around Aug 21, 07. Aug 22-received via EDR (Seq052 dated Aug 21, 07) the promised updated preliminary results for Protocol 013 (UGT1A1 study & send Seq info to PK team, Shashi, and Sarah. • Sept 21-received response via EDR (Seq064 dated Sept 20, 07) for the complete raw data for P013 & sent EDR link to Shashi, Derek, Pravin, Sarah & Kellie	Seq037 dated Jul 31, 07 Seq051 Seq052 Seq064
Aug 1, 07	One query from Derek re status of all phase 1 clinpharm	Email	• Aug 1-received responses for Derek's and below query re P035	Seq042

	studies (5)	but not in word	(Seq042 dated Aug 3, 07) and forwarded to Derek, Pravin, Kellie and Sarah. Response located in Seq042.	
	One query re current status of P1 Protocol 035 (low, moderate, and hight-fat meals of MK-0518) submitted on May 11, 2007 in SN548	Email but not in word	• See above for response	
July 26, 07	One PK/PD (Pravin) re discrepancy of Seq004 for P019	Email	• July 31-received responses to both queries via email and requested a tecon for Aug 1 to get additional clarification re "phase3.xpt" dataset for P018 & P019.	Seq040 dated Aug 1, 07
July 27, 07	One PK/PD (Pravin) re discrepancies of Seq004 & Seq025 for P018 and P019	Email		
Aug 1, 07	During Aug 1, 07 tecon: submit PK raw datasets for P005, P018, P019	Confirmed action item per email	• Aug 6-received response Seq043 to Pravin's queries dated July 26 & July 27 (updated version of "phase3.xpt, programming code to calculate pk values) and proposed response for query re PK raw datasets on Aug 8, 07. • Aug 13-received via EDR (Seq045 dated Aug 8, 07) responses to the Aug 1 query re PK raw datasets (12 source files containing raw data provided to outside vendor in SAS transport and excel format). Emailed global submit link to Pravin, Kellie, Derek and Sarah.	Seq043 Seq045
Not queries, just submissions				
July 20, 07	Merck's final neoplasm update using 9July07 cut-off-date included in the backgrounder with the note "These data have not been reviewed by FDA"	Email	In the EDR (C, dated July 20, 07), Seq027 in GS. Located in the V drive	
July 20, 07	Merck's preclinical updated report on the ongoing 2-yr animal carcinogenicity study is in reply to the request in the filing letter dated June 26, 2007.	Email	In the EDR (BP, dated July 20, 07), Seq028 in GS. Located in the V drive	
July 31, 07	Merck's full 24-week efficacy data for Protocols 018 & 019 provided as statistical reports included in Merck's backgrounder with the note "These data have not been	Email	In the EDR (BZ, dated Aug 1, 07), Seq036 in GS. Located in the V drive	

	reviewed by FDA". Also included are 24-week combined meta-analysis for P018 & 019, and 24-week statistical reports for P018 & P019. (Seq036 using global submit)			
Aug 1, 07	Merck's Advisory Committee Background Package for public disclosure	Email	In the EDR (C, dated Aug 1, 07). Seq039 in GS. Draft BP was submitted on July 19, 07 (EDR C, Seq024)	
Aug 7, 07	Merck's Revised Final Advisory Committee Background Package for public disclosure	Email	In the EDR (C, dated Aug 7, 07). Seq044 in GS. Located in the V drive.	
Sept 12, 07	Merck's AC original & back up slides presented at the Sept 5, 07 AC		In the EDR (Seq057 dated Sept 12, 07).	
July 31, 07	• Two clinical queries re subject AN16235 and table 1 in labeling • Three AC queries re MLR's slides (basic PK & clinpharm info, submit slides by Aug 17, 07, and webex mgt for Aug 29 to provide feedback)	Email in same word doc	• Aug 3-received responses Seq041 only for 2 clinical queries & forwarded to Sarah. • Aug 6-received clarification questions for 3 AC queries and on Aug 7 & 8 sent responses (to submit MRL's slides by Aug 13, to have web/ex mgt on Aug 17, and PK info). • Aug 13-received responses re specific PK info (Derek) we want included in Merck's AC slides & sent it to the PK team along with Merck's AC slides.	Seq041
Aug 6, 07	One stats (Karen) query re updated datasets using raw listing data in SUR for P5, 018 & 019	Email	Aug 13-received via EDR (BM, Seq047 dated Aug 9, 07) & sent link to Karen.	Seq047
Aug 7, 07	One clinical query if Merck submitted datasets and narratives corresponding to the updated malignancy info using 9July07 cut-off-date	Email but not in word	• Aug 9-received following response via email: "We did not submit narratives or datasets with the memo submission. "We'll try to provide them (perhaps WAES based) sometime next week", forwarded to Sarah. • Aug 21-received via EDR (BM, Seq050 dated Aug 17, 07) narratives and datasets corresponding to the updated malignancy info using Jul 9,	Seq050

			07 cut-off date. Forwarded link to Sarah & Ita. • Aug 22-received via EDR (Seq053 dated Aug 21, 07) a malignancy report (WAES 0705DNK00005, Bowen's disease) inadvertently omitted from Seq050.	Seq053
Aug 8, 07		Email	• Aug 17-received responses via email & forwarded to Sarah, Kendall, PK team. • Received EDR (Seq051 dated Aug 20, 07) response, which was the same as the one emailed on Aug 17, 07.	Seq051
Not a query Aug 16, 07	Two comments (Sarah's) to cover during web/ex mgt to discuss Merck's AC slides on Aug 17, 07: 100% 24-week efficacy data was not included, 2 pts discrepancies (slide 14, 39)	Email	• Aug 17-two comments were addressed satisfactory per Sarah during web/ex meeting.	
Aug 21, 07	Four statistical queries (Fraser) re the need of verification that the tx allocation codes for P04, 05, 018, and 019	Email	Tecon to discuss queries is scheduled for Aug 23, 07 Tx codes sources from ICON & ALMAC were received and given to Greg/Fraser. Sept 4-Greg's assessment: "I compared the treatment codes submitted by Merck (specifically dataset "Demodata") and treatment codes submitted by the ICON, the randomization vendor for Merck. I took a 10% random sample from Study 018 and Study 019 and went through case by case, they all matched. A total of 75 subjects were cross examined."	Seq055
Aug 22, 07	One clinical query (updated lab data for subject AN 3243 in Protocol 05	Email	• Received response via EDR (Seq054, dated Aug 29, 07) and informed Sarah.	Seq054

Sept 4, 07	One pharm/tox query historical control values for increased ossification of hyoid in rabbits and on mating performance (# mated, # pregnant etc.) for both male and female rats for both fetal & litter values in table format.	Email	• Sept 12-received response via email in word format & forwarded to Ita. • EDR submission (Seq058 dated Sept 13, 07).	Seq058
Sept 7, 07	Five queries (items captured during our Sept 7 pre-approval safety conference) re PK wording for PI, RMP, complete raw data for P013.	Email	• Sept 14-received responses via email and proposed PI language & sent it to Sarah, Derek, Shashi.	Seq062
Sept 12, 07	CMC IR dated Sept 12, 07 from George containing 3 queries re HPLC method not being acceptable. Last CMC issue for this NDA.	Email confirmed receipt 13Sept07	• Sept 14-received response via email & sent it to George.	Seq061
Sept 14, 07	Three queries 1xpcl (multi-generation reproductive study in rats) and 2x clinical re PI (different # for patient-years/labs; additional less common ARs)	Email	• Sept 20-received response via email & sent it to Sarah & Ita. MRL has agreed to add labeling info.	Seq065
Sept 21, 07	To add to PI (following laboratory values to the PI Table 3: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Patients: CK, WBC, ANC, Amylase, and Lipase.	Email but not in word	• Received response in EDR (Seq066 dated Sept 25, 07) & forwarded to Sarah	Seq066
Oct 1, 2007	CMC IR (Ted, 3 comments, no response/action require prior to PDUFA due date).	Email & confirmed	• Sept 5-received responses via email & forwarded to Ted, George & Steve. Received in the EDR (Seq068 dated Oct 8, 07)	Seq068
Oct 2, 2007	Two clinical queries for INDs 69928, ——regarding updated narratives and other cases of myopathy, rhabdo, acute hepatic failure	Email	• Sept 3-received responses via email & forwarded to Sarah on Oct 4, 07.	

Four clinical queries for NDA 22-145

1. Please obtain the following data regarding determination of duration of treatment/follow up and patient-years:

Mean/Median duration of treatment (min,max)		Mean/Median duration of follow-up (min,max)		Patient-Years for total exposure (min,max)		Patient-Years for total follow-up (min,max)	
MK-0518	Placebo	MK-0518	Placebo	MK-0518	Placebo	MK-0518	Placebo

Protocol 05
Protocol 018
Protocol 019
Protocol 018/019

2. In our analysis of baseline CD4 counts, using the QCD4CC dataset, we found 461 patients with a baseline CD4 cell count. Please assist us in determining why one patient's baseline CD4 cell count is missing.

3. In our analysis of Hepatitis Co-infection, we used the LABOTHR dataset and came up with 38 subjects in the MK-0518 arm with (+)HCV versus 37 subjects presented in the label. Please assist us in determining the discrepancy.

4. Please construct the following laboratory table for all laboratories, including CD4 and HIV viral load, for Protocols 018 and 019.

AN	Protocol	Parameter	Baseline (day/date)	Max (day/date)	Min (day/date)	Last (day/date)	Treatment Arm	Age	Sex	Race
AN 001	018	CD4								
AN 002	018	CD4								
AN 003	018	CD4								
etc										
AN 110	019	CD4								
AN 111	019	CD4								
AN 112	019	CD4								
AN 001	018	viral load								
AN 002	018	viral load								
AN 003	018	viral load								
etc										
AN 110	019	viral load								
AN 111	019	viral load								
AN 112	019	viral load								
AN 001	018	Sodium								
AN 002	018	Sodium								
AN 003	018	Sodium								
etc										

Follow-up queries for responses to queries no. 1 and 4 from our May 4, 2007 email request

1. This for your response dated May 14, 07 to query no. 1 from our May 4, 2007 email request.

Currently the datasets FDALAB01 and FDALAB02 contain the variables:
PROTOCOL AN PARAMTER BASEDAY MAXDAY MINDAY LASTDAY TREATMENT AGE SEX RACE

Please adjust the **BASEDAY, MAXDAY, MINDAY, LASTDAY** variables to separate the numerical value from the characters of day and date. An example is provided below in blue:

BASEVALUE BASEDAY BASEDATE MAXVALUE MAXDAY MAXDATE MINVALUE MINDAY MINDATE LASTVALUE LASTDAY LASTDATE

We request submission of the study day (BASEDAY, MAXDAY, etc) in numerical format and in relation to the first of study medication. The study date (BASEDATE, MAXDATE, etc) will be a character variable.

2. This is for your response sent via EDR/gateway on May 15, 07 to query no. 4 from our May 4, 2007 email request. Please provide the data from **all** Protocol 005 MK-0518 arms (not the 400 mg bid arm only).

From: Zeballos, Monica
Sent: Monday, May 07, 2007 12:57 PM
To: 'Fromtling, Robert A.'
Cc: Zeballos, Monica
Subject: RE: Verification of CD Data Needs

Hello Bob,

Thanks for confirming the request.

Below are my edits in blue.

FDA would like the following data for each site on one CD per site:

Site No. 0011 (Protocol 018)

Site No. 0015 (Protocol 019)

Site No. 0018 (Protocol 019)

Site No. 0054 (Protocol 019)

Information needed for each subject enrolled,

1) CD4 counts and viral load measured by HIV RNA at baseline and Weeks 2, 4, 8, 12, 16 and 24

2) Subjects who discontinued and reason for discontinuation

3) Study visit variable and study day variable for each data point.

The CDs should be expressed to Dr. El-Hage by Friday, May 11, 2007:

Dr. Antoine El-Hage
Division of Scientific Investigation
Office of Compliance
CDER-FDA
7520 Standish Place, Room 125
Rockville, MD 20855

Thanks,

Monica

From: Fromtling, Robert A. [mailto:robert_fromtling@merck.com]
Sent: Monday, May 07, 2007 11:58 AM
To: Zeballos, Monica
Cc: Fromtling, Robert A.
Subject: Verification of CD Data Needs

Hello, Monica,

Just to make certain I have the request correct, would you please verify that I have the correct sites and data needs for the CDs for site inspections listed below?

Thank you,

Bob

FDA would like to following data per site each on a CD (one CD per site):

Site No. 0011 (Protocol 018) [redacted]

Site No. 0015 (Protocol 019) [redacted]

Site No. 0018 (Protocol 019) [redacted]

Site No. 0054 (Protocol 019) [redacted]

Information needed by site of each CD:

For each subject enrolled,

1) Baseline data at weeks 2, 4, 8, 12, 16 and 24 for CD4 counts and viral RNA

2) Subjects who discontinued and reason for discontinuation

3) Include study visit and study variable for each patient

The CDs should be expressed to:

Dr. Antoine El-Hage
Division of Scientific Investigation
Office of Compliance
CDER-FDA
7520 Standish Place, Room 125
Rockville, MD 20855

intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

"EMF <fda.hhs.gov>" made the following annotations.

This message was sent by Merck across the Internet in encrypted format and was successfully decrypted, unless otherwise noted. Merck & Co., Inc.

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Five clinical queries for NDA 22-145 dated May 11, 2007

1. Subject AN 16237 is listed in the AE dataset as experiencing an SAE of "Gastroenteritis cryptosporidial" on Days 66 and 118. The corresponding subject narrative listed in Protocol 019 (14.4 p. 433-434) does not describe a second episode of "Gastroenteritis cryptosporidial" on Day 118. Please resolve the discrepancy.

2. There is no SAE narrative for subject AN 8287 who experienced an SAE of overdose on Day 1. Please provide a narrative for this subject.

3. Subject AN 7036 is listed in the AE dataset as experiencing an SAE of "neutrophil count decreased" on Days 27, 34, and 37. The corresponding subject narrative list in Protocol 018 (14.4 p. 391) does not describe these episodes. Please provide further details.

4. Please let us know where we can locate the definitions for:

   Post Viral Fail Max
   Post-Treatment PVFM
   Post-Treatment PVFO
   Post Viral Fail Optm

5. We performed a subject discontinuation analysis from the DISPOS datasets from Protocols 018 and 019, limiting the analysis to subjects who received at least one dose of study medication. We came up with seven subjects who discontinued due to withdrawn consent. Table 2.7.3-trxexp:9 in the Summary of Clinical Efficacy reports six subjects who discontinued due to withdrawn consent. Please assist us in identifying the discrepancy. Below is a list of the allocation numbers resulting from our analysis.

	AN	Days_IN	Days_TRT	Period	Phase	RDStudy	REL_DY
019	15006	133	84	Post-Study DB	Post-Study	pat. withdrew consent	133
019	15100	132	85	Post-Treatment DB	Post-Treatment	pat. withdrew consent	132
019	16254	192	185	Post-Treatment OL	Post-Treatment	pat. withdrew consent	192
019	16367	43	9	Post-Study DB	Post-Study	pat. withdrew consent	29
019	16323	146	129	Post-Treatment DB	Post-Treatment	pat. withdrew consent	146
019	16404	117	117	Double-Blind	Treatment	pat. withdrew consent	117
018	7610	56	7	Post-Study DB	Post-Study	pat. withdrew consent	36

Four clinical queries dated May 16, 2007 for NDA 22-145

1. The AE dataset for Protocol 018 contains the REPTTERM and PREFTERM for subject AN 8325 of "Mycosis fungoides" occurring on 7/24/2006. Review of the corresponding subject narrative and case report form does not contain a diagnosis of mycosis fungoides. However, the case report form does note an adverse event of "buccal mycosis" occurring on 7/24/2006. Please provide an explanation for the discrepancy.

2. The AE dataset for Protocol 004 contains the REPTTERM and PREFTERM for subject AN 12 of "Kaposi's sarcoma" occurring on 5/17/2006. Review of the corresponding subject narrative does not contain a diagnosis of Kaposi's sarcoma. Please provide further details.

3. Please provide a subject narrative for subject AN 165 who has the PREFTERM of "Kaposi's sarcoma" in the AE dataset for Protocol 004.

4. The subject narrative for subject AN 163 in Protocol 004 describes a diagnosis of squamous cell carcinoma. However, the AE dataset for Protocol 004 does not have this diagnosis listed in the REPTTERM or PREFTERM columns. Please provide an explanation for the discrepancy.

One clinical response, 3 statistical and 2 chemistry queries for NDA 22-145 and IND 69,928 dated May 25, 2007

Clinical

1. This comment is in reply to your response dated May 11, 2007 to our clinical query dated May 7, 2007 regarding dataset discrepancies between study site data in your NDA and SN414 (IND 69.928).

   The patient enrollment numbers that were provided in SN414 were obtained from your CTMS (Clinical Trial Management Database), a "live" database used for study management. Although the total enrollment number was correct for Protocol 019, it was later discovered that enrollment numbers at some individual sites were incorrect by a few patients. In fact, the discrepancies appear to have resulted from a transcription error and likely did not come from errors in the database.

   As you can see below, the correct enrollment numbers are offset by 1 site from Site 3 through 18 (there is no Site 012). After a mistake is made on Site 019, the problem disappears.

	SN414	datasets
Site 002	6	6
Site 003	3	6
Site 004	7	3
Site 005	7	7
Site 006	6	7
Site 007	6	6
Site 008	7	6
Site 009	6	7
Site 010	7	6
Site 011	5	7
Site 013	6	5
Site 014	6	6
Site 015	12	6
Site 016	6	12
Site 017	5	6
Site 018	9	5

   Site 019 mislabeled as Site 001
   No more discrepancies after Site 019

Statistics

2. Please submit an additional SAS dataset including all screening information from all subjects screened for Studies 005, 018, 019, and if possible for Study 004. The dataset should include all variables used for the screening, demographics and subject characteristics variables. Variables describing if a subject met the entry criteria, major violation of entry criteria, randomization, and actual treatment should also be included.

3. Please submit an additional SAS dataset for Studies 004, 005, 018. and 019 as follows:

   - Optimized background therapy (OBT) dataset. The dataset should be one record per patient, and include the variables describing what OBT the patient initially received, whether OBT changed or not during the double-blind treatment period, the date and the reason the OBT changed, and the name(s) of new OBT.

4. Dr. Rafia Bhore, Statistical Reviewer, for Study Clinical Report for the QT study (Protocol 24) would like to have a teleconference with your statisticians and programmers to discuss the following:

   a. The analysis tables in the study report do not match the output files submitted in the appendices. Please explain how you got the numbers.

Chemistry

5. For IND 69,928 (SN528), please provide your assessment of the issues for placebo-controlled trials 032 and 033 caused by the debossed markings on the Kaletra tablets. Please submit your response to the IND.

6. Please also indicate which amendment contained information on the raltegravir placebo tablets used in trials 018 and 019. Please submit your response to the IND.

Six queries for NDA 22-145 dated June 5, 2007

Clinical

1. Please provide us with a dataset for Studies 05, 018, and 019 combined with variables for outcome classification at the Week 16 and Week 24 visits, if possible by COB Thursday, June 7, 2007. Please classify subjects as one of the following:

    1) Death
    2) Discontinued: Adverse event
    3) Discontinued: Consent withdrawn
    4) Discontinued: loss to follow-up
    5) Discontinued: other
    6) Discontinued; pregnancy
    7) Treatment response: $\geq$ 1 log decrease
    7) Treatment response: < 50 copies/mL
    8) Virologic failure: Nonresponder
    9) Virologic failure: rebound
    10) Open-label post-virologic failure
    11) Week 24 visit not reached

Statistics

2. Please submit Week 16 and 24 Laboratory Reports (not a listing of results) for efficacy endpoints from the 5 sites that are being inspected for Studies 018 and 019.

3. Please submit Laboratory Reports from the largest site 16 at [redacted].

4. In addition, please confirm if these laboratory data are available at the 5 sites.

Microbiology

5. Please conduct cell culture combination antiviral activity studies to evaluate the effects of MK-0518 in combination with the recently approved HIV PIs, darunavir (TMC114) and tipranavir. These studies should include a positive antagonism control (ribavirin and zidovudine combination as chosen in your Study PD004) and the cytotoxicity evaluation of the combinations.

6. Please confirm if you are using either of these [redacted]
   Pharmacology facilities: [redacted]

From: Zeballos, Monica
Sent: Monday, June 11, 2007 1:30 PM
To: 'Abeygunawardana, Chitrananda'
Cc: 'Robert A. Fromtling Ph. D. (robert_fromtling@merck.com)'; Zeballos, Monica
Subject: Clarification responses for queries dated June 5, 2007 for NDA 22-145

Hello Abey,

Please find below in blue our clarification responses for queries 2, 3, and 4 dated June 5, 07:

Q2. Please submit Week 16 and 24 Laboratory Reports (not a listing of results) for efficacy endpoints from the 5 sites that are being inspected for Studies 018 and 019.

- Please clarify what is meant by "Laboratory Reports". Merck does not receive hard copy laboratory reports from the Central Laboratory [redacted]. Data is electronically loaded from a flat, positional ASCII file into our CTS database.

FDA Clarification Response: We need the Laboratory Reports from [redacted]

- Please clarify the required efficacy endpoints. Do these include HIV RNA - Amplicor, HIV RNA - Ultrasensitive, and CD4 cell counts?

FDA Clarification Response: Yes, we like the laboratory reports for all three efficacy endpoints at Weeks 16 and 24.

- Please clarify if 5 sites have been chosen for FDA inspection. We are aware of only 4 sites: 019 Sites [redacted] (Atlanta, Georgia), [redacted] (New York, New York), [redacted] (New Haven, Connecticut), 018 Site - [redacted] (Barcelona, Spain).

FDA Clarification Response: Yes, there are 4 sites (as listed above) chosen for FDA inspection not 5. Sorry for the confusion.

Q3. Please submit Laboratory Reports from the largest site 16 at [redacted]

- Please clarify what is meant by "Laboratory Reports" (as in the question above).
- Are the same reports being requested as in the question above (efficacy results)?

FDA Clarification Response: Yes, the same laboratory reports for efficacy endpoints in the question above are being requested for the [redacted] site. In addition, please submit the same information requested in query 2 from Study 018: Site 18, [redacted]

Q4. In addition, please confirm if these laboratory data are available at the 5 sites.

- Please clarify if the data being referred to are the hard copy efficacy results from the central laboratory from Week 16 and 24. Do these include HIV RNA - Amplicor, HIV RNA - Ultrasensitive, and CD4 cell counts?

FDA Clarification Response: Yes, we are requesting hard copy efficacy results from the central laboratory from Week 16 and 24 for HIV RNA-Amplicor, HIV RNA-Ultrasensitive, and CD4 cell counts. In addition, please confirm if there are hard copy laboratory reports from [redacted] at each investigator's site.

Thanks,

Monica

Monica Zeballos, Pharm.D.
Senior Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6377
Silver Spring, MD 20993-0002
Phone (301) 796-0840
Fax (301) 796-9883
Email: Monica.Zeballos@fda.hhs.gov

From: Abeygunawardana, Chitrananda [mailto:abey@merck.com]
Sent: Thursday, June 07, 2007 5:00 PM
To: Zeballos, Monica
Cc: Abeygunawardana, Chitrananda
Subject: Update to availability of requested SAS data sets - Re NDA 22-145

Hi Monica,

We will not be able to submit SAS data sets related Q2 & Q3 of the 25May07 FDA queries by the end of the week as stated in Bob's email dated June 5th due to unforeseen internal delay. The revised target for submission via the Gateway is mid next week.

Also, we will not be able to provide the data set on COB June 7, 2007 as requested in Q1 of 05June07 FDA queries. We will submit this along with other two via Gateway by mid week.

Could you please provide clarification on Q2, 3 & 4 of 05June07 FDA queries as stated below.

Q2. Please submit Week 16 and 24 Laboratory Reports (not a listing of results) for efficacy endpoints from the 5 sites that are being inspected for Studies 018 and 019.

- Please clarify what is meant by "Laboratory Reports". Merck does not receive hard copy laboratory reports from the Central Laboratory [redacted] Data is electronically loaded from a flat, positional ASCII file into our CTS database.

- Please clarify the required efficacy endpoints. Do these include HIV RNA - Amplicor, HIV RNA - Ultrasensitive, and CD4 cell counts?

- Please clarify if 5 sites have been chosen for FDA inspection. We are aware of only 4 sites: 019 Sites - [redacted] Atlanta, Georgia), [redacted] (New York, New York), [redacted] (New Haven, Connecticut), 018 Site - [redacted] (Barcelona, Spain).

Q3. Please submit Laboratory Reports from the largest site 16 at [redacted]

- Please clarify what is meant by "Laboratory Reports" (as in the question above).
- Are the same reports being requested as in the question above (efficacy results)?

Q4. In addition, please confirm if these laboratory data are available at the 5 sites.

- Please clarify if the data being referred to are the hard copy efficacy results from the central laboratory from Week 16 and 24. Do these include HIV RNA - Amplicor, HIV RNA - Ultrasensitive, and CD4 cell counts?

Looking forward to your reply. Thanks,

Abey

Dr. C. Abeygunawardana
Associate Director
Worldwide Regulatory Affairs
Merck Research Laboratories
UG2D-68
PO Box 1000
North Wales PA 19454-1099
Phone: 267 305 5949
Fax: 267 305 6407
Cell: 215 828 5875
abey@merck.com

One PD/PK query dated June 20, 2007 for NDA 22-145 for Protocols 018 and 019

1. Please submit longitudinal dataset in the following format:

Please note that this is a standard data request template, ignore the variables that may not apply to the specific study design and/or add any variables that are relevant to the specific study design.

i. Study ID or Protocol number
ii. Unique patient identifier
iii. Dose group randomized
iv. Dose group actually treated, if not the same as above
v. Visit information
    1. Date and time of visit
    2. Type of visit (Planned/Unplanned)
    3. Visit number
    4. Planned week information (For example; Week 2)
    5. Date for first day of active treatment
    6. Date for last day of active treatment
    7. Time (days) since active treatment
    8. Visit information for endpoint analysis
        a. For example, if Week 12 then 99 for endpoint analysis, if Week 16 then 999 for endpoint analysis and if Week 24 then 9999 for endpoint analysis (using LOCF imputation for missing data).
        b. For example, if Week 12 then 88 for endpoint analysis, if Week 16 then 888 for endpoint analysis and if Week 24 then 8888 for endpoint analysis (using Baseline observation carried forward (BOCF) imputation for missing data).
        c. Include both (LOCF and BOCF) for sensitivity analysis.
    9. Discontinuation status (yes/no)
        a. If yes, create a numeric variable identifying discontinuation reasons and decode the variable in the define file.
vi. Patient disease information (to be replicated across individual patient records)
    1. Baseline viral load
    2. Baseline CD4+ count
    3. Screening tropism (if measured)
    4. Baseline Tropism (if measured)
    5. Baseline OSS (if measured)
    6. Time since diagnosis, years
    7. Time since first ART
vii. Plasma viral load
viii. Plasma CD4+ count
ix. Change from baseline log viral load

x. Change from baseline CD4+ count
xi. HIV outcome indicator, a binary variable
    1. Is RNA <50 copies/mL?
    2. Is RNA <400 copies/mL?
    3. Is at least 1 log drop?
    4. Is at least 2 log drop?
xii. Demographic information (to be replicated across individual patient records)
    1. Age
    2. Weight
    3. Race
    4. Sex
xiii. OBT information (to be replicated across individual patient records)
    1. Number of sensitive protease inhibitors (0= no PI in OBT or no sensitivity to PI in OBT, 1= sensitive to 1 PI in OBT and 2= sensitive to 2 PI in OBT etc.)
    2. Number of sensitive NRTIs in OBT
    3. Number of sensitive NNRTIs in OBT
    4. Presence and sensitivity to T20 (0=no T20, 1=T20 and sensitive, 2=T20 but insensitive)
    5. Previous treatment with T20 (0=No, 1=Yes)
    6. Presence of ritonavir (0=No, 1=Yes)
    7. Presence of tipranavir (0=No, 1=Yes)
    8. Presence of PI in OBT
        a. Identify protease inhibitor (for example; 0=not taking any protease inhbitior in the list: 1=amprenavir, 2=atazanavir, 3=fosamprenavir, 4=Indinavir...If combinations e.g. 12=amprenavir+atazanavir)
        b. Please create an informative list in the define file.
    9. Presence of NNRTI in OBT
        a. Follow similar structure as that of PI information above
    10. Presence of NRTI in OBT
        a. Follow similar structure as that of PI information above
xiv. Pharmacokinetic information
    1. Dose
    2. Dose frequency
    3. Predicted plasma concentration
    4. Predicted AUC (0-tau)

General instructions for data submission to the pharmacometrics team:
All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

One query dated June 22, 2007 for NDA 22-145 for Protocols 004, 005, 018 and 019

1. Please submit the death dates in a raw dataset. In addition, please submit any other omitted data that was captured in the case report forms but not submitted to the Division.

Two clinical queries dated June 26, 2007 for NDA 22-145

1. There are four subjects (AN 16283, 16299, 16303, and 16390) in the DEMODATA dataset for Protocol 019 who are listed as having no prior antiretrovirals (ARVS_CNT = 0); however, the CONXCLP dataset for Protocol 019 includes these subjects' antiretroviral history along with start and stop dates. Please clarify and, if a discrepancy is found, an update to Table 5 in the label will be indicated.

2. Subject AN 14403 (Protocol 019, placebo arm) was classified as HCV antibody negative in the original LABOTHR raw dataset; however, in the updated LABOTHR dataset submitted with the SUR, Subject AN 14403 is now classified as HCV antibody positive. Please clarify this discrepancy. In addition, please outline and describe any other changes that have been made to the updated raw datasets.

Four new queries for NDA 22-145 dated July 6, 2007

Statistical

1. The following questions are regarding the SAS datasets of SPRMTHR.XPT and SPATSTT.XPT for Study 005.

   a. The variables LABEL and PERD_NM are in SPRMTHR.XPT, but their definitions are not provided in the data definition table. Same for PERD_NM in SPATSTT.XPT. Please give the detail descriptions of the variables in particular for PERD_NM. There are 11 categories in the variable PERD_NM. Please explain their meanings.

   b. Please provide the descriptions of the coding of variable VT_NUM and the categories in variable PTNT_STT (e.g., no res con post viro fail) in SPATSTT.XPT.

   c. Please explain the data structure of SPATSTT.XPT. Some patients have one record for each of the multiple visits in spite that the levels in PTNT_STT and PERD_NM are same (please see Patient 2702 below as an example), but some do not.

```
ALLOCATION_NUMBER=2702
VT_NUM      VT_DT          PTNT_STT              RESN_DS1      PERD_NM
  1.0       05/17/05   pat. contin. trial                     Screening
  2.0       06/20/05   pat. contin. trial                     Dose-Ranging
  3.0       07/05/05   pat. contin. trial                     Dose-Ranging
  4.0       07/19/05   pat. contin. trial                     Dose-Ranging
  5.0       08/16/05   pat. contin. trial                     Dose-Ranging
 30.0       06/07/06   pat. complete contin.                  Dose-Ranging
```

   d. Please provide a dataset including the following variables:

      - patient ID
      - start and stop dates of receiving the double-blind treatment
      - whether the patient entered the open-label phase after the double-blinded treatment, if yes, the start and stop dates of receiving the open-label treatment and what dosage of MK-0518 the patient received
      - whether the patient entered the post-virologic failure open-label phase, if yes, the start and stop dates of receiving the post-virologic failure open-label treatment, and what dosage of MK-0518 the patient received

2. Please provide the date of last visit for all patients in Studies 004, 005, 018 and 019. Note that you provided the last visit number in SDEMOS.XPT, but not the date of last visit.

3. Please provide the original randomization schedules generated for each patient in Studies 004, 005, 018, and 019.

MRL Response dated July 17, 2007: Randomization schedules are included in the appendix of each individual Clinical Study Report (CSR). They can be found in Section 16.1.7 (Randomization Scheme and Codes) as subsection 16.1.7.1 (Patient Allocation Schedule).

FDA Response dated July 17, 2007: Although the codes are given in appendix 16.1.7.1 of the CSR, they do not appear to be original source documents. For example, the patient allocation schedule for Protocol 019 has a creation date of 16-Nov-2005 but the date at the top of the page is 21-Feb-2007. We are requesting original source documents that generated the treatment codes for each study.

MRL Reply dated July 18, 2007: The allocation schedules provided with the CSRs are identical to the original schedules. In the example provided, 21-Feb-2007 is the date the schedule was printed from the Clinical Allocation Schedule System (CASS) for inclusion in the CSR. It is not the date the allocation schedule was generated. Prior to study initiation, an allocation schedule is generated in the CASS system. For Protocol 019, this schedule was created on 16-Nov-2005.

At the time of the allocation schedule generation, only a "masked" allocation schedule is printed which has the treatment assignments covered. The masked schedule allows for emergency unblinding only. So that the study blind is strictly maintained, we do not print "unmasked" allocation schedules at the time of schedule generation. The allocation schedules reside in the electronic CASS system and access to the system is limited. Unmasked schedules are printed only as needed for inclusion in CSR appendices.

FDA Response dated July 20, 2007: Unfortunately, what you have provided us in Appendix 16.1.7.1 in the Clinical Study Report entitled 'Patient Allocation Schedule' is not a source document. Please clarify what source documents pertaining to randomization schedules are available at the sites. In addition, we would like to know more about your standard operating procedures for generating and storing randomization treatment codes and the corresponding documentation process. Please submit your SOPs that pertain to this topic.

Pharmacometrics

4. Please provide raw PK datasets for all patients in Studies 004, 005, 018, and 019, as well as the original bioanalytical reports.

Two clinical queries for NDA 22-145 dated July 12, 2007

1. For Protocols 004, 005, 018, and 019, please submit a revised dataset that includes the FDALAB dataset information (submitted on 5/24/07) plus the incorporation of the corresponding toxicity grades.

2. The Safety Update Report dated June 15, 2007, has tables that refer to adverse experience terms from MedDRA Version 9.0 and 9.1. Please clarify the version of MedDRA used.

   Examples:

   Protocol 04

   Table 2.7.4: 15 lists version 9.0
   Table 2.7.4: 43 lists version 9.1

   Protocols 05, 018, 019

   Table 2.7.4: 26 lists version 9.0
   Table 2.7.4: 28 lists version 9.1

MRL Responses (and clarification sought) on Two clinical queries for NDA 22-145 dated July 12, 2007

1. **For Protocols 004, 005, 018, and 019, please submit a revised dataset that includes the FDALAB dataset information (submitted on 5/24/07) plus the incorporation of the corresponding toxicity grades.**

MRL Response (Request for clarification):

This request appears to refer to the dataset provided in reply to an FDA Query #4 dated May 4, 2007 (shown below). Our reply was that the data could be found in Module 5.3.5.1.

We would like clarification on this current query for additional data. In the revised dataset you request, do you wish to have the DAIDS grading or are you interested in the more recent laboratory dataset involving the label table for lab abs?
Yes to both.
Does FDA need this for Protocols 004 and 005 as well?
Yes.
We would like to note that the DAIDS criteria do not cover all of the lab tests in the datatset.
Noted.

MRL Responses to FDA E-Mail Dated 04 MAY 2007
Four clinical queries for NDA 22-145

FDA Query 4

Please construct the following laboratory table for all laboratories, including CD4 and HIV viral load, for Protocols 018 and 019.

AN	Protocol	Parameter	Baseline (day/date)	Max (day/date)	Min (day/date)	Last (day/date)
Treatment Arm	Age	Sex	Race			
AN 001	018	CD4				
AN 002	018	CD4				
AN 003	018	CD4				
etc						
AN 110	019	CD4				
AN 111	019	CD4				
AN 112	019	CD4				
AN 001	018	viral load				
AN 002	018	viral load				
AN 003	018	viral load				
etc						
AN 110	019	viral load				
AN 111	019	viral load				
AN 112	019	viral load				
AN 001	018	Sodium				
AN 002	018	Sodium				

AN 003 018 Sodium
etc

2. ***The Safety Update Report dated June 15, 2007, has tables that refer to adverse experience terms from MedDRA Version 9.0 and 9.1. Please clarify the version of MedDRA used.***

Examples:

Protocol 04

Table 2.7.4: 15 lists version 9.0
Table 2.7.4: 43 lists version 9.1

Protocols 05, 018, 019

Table 2.7.4: 26 lists version 9.0
Table 2.7.4: 28 lists version 9.1

MRL Response:

Merck's MedDRA dictionary update occurs every May and November. MedDRA version 9.1 was made available in Merck's Clinical Trial System (CTS) on 06-Nov-2006. All data frozen on or after 06-Nov-2006 used version 9.1.

For the Original WMA Application, data from Protocol 004 was frozen on 20-Oct-2006, thus Protocol 004 tables in the Original Application were generated using MedRA version 9.0. Data for Protocols 005, 018 and 019 were frozen after 06-Nov-2006, thus tables in the Original Application from these protocols were generated using version 9.1. In the SUR, all "Cumulative Period" tables were generated using version 9.1

We have reviewed the SUR tables noted in the examples, and agree that there were typographical errors in the MedRA versions listed for Tables 2.7.4: 15 and 2.7.4: 26 as detailed below in bold type. It should be noted that Table 2.7.4: 27 (Protocols 005, 018, 019) was also generated using version 9.1.

Protocol 04

Table 2.7.4: 15 lists version 9.0 - **version should be 9.1**
Table 2.7.4: 43 lists version 9.1 - **version is correct**

Protocols 05, 018, 019

Table 2.7.4: 26 lists version 9.0 - **version should be 9.1**
Table 2.7.4: 28 lists version 9.1 - **version is correct**

One query dated July 18 for NDA 22-145 regarding data for the QT study

1. Please submit a subject mapping file. The subject IDs in the clinical datasets are different from the ones in the ECG Warehouse. Our Data Manager can not match them at all. Enclosed are both subject IDs for your convenience.

Warehouse	Clinical
1001	331
1003	332
1004	333
1005	334
1008	335
1009	336
1011	337
1012	338
1015	339
1016	340
1017	341
1018	342
1022	343
1024	344
1027	345
1029	346
1031	347
1033	348
1038	349
1039	350
1043	351
1046	352
1047	353
1048	354
1049	355
1054	356
1055	357
1056	358

1057		359
1059		360
1065		1332

Appears This Way
On Original

One PK query for NDA 22-145 dated July 26, 2007

1. In your submission dated April 13, 2007 (final component), for P019, in the "phase3.xpt" dataset, the allocation number #16295 is associated with unusual time since first dose (~2000 days). The concentration dataset indicate first dosing in the year 2000, however, the viral data indicate first dosing in the year 2006. Please clarify this discrepancy.

One PK query for NDA 22-145 dated July 27, 2007

1. In your submission dated April 13, 2007 (final component), for P019 and P018, there are some discrepancies in dosing records between datasets. For example: According to "phase3.xpt", the 1st dosing for the allocation number 6401 happens on 08MAY2006. However, according to "fda-pkpd.xpt" (submission dated July 10, 2007) "jhivrna.xpt" (submission dated April 13, 2007), the 1st dosing for the allocation number 6401 is indicated on 11APR2006. Please clarify this discrepancy or understand if there are errors in our processing of the datasets as we convert the numeric variables to SAS date format.

New queries for NDA 22-145 dated July 31, 2007

Clinical

1. Subject AN 16235 in Protocol 019 experienced elevated AST, ALT, and bilirubin on Day 174. Please provide a subject narrative and any updated information as to the subject's current status.

2. We performed an analysis of the AE database for Protocols 05, 018, and 019, limited to the double-blind treatment period and either the 400 mg bid raltegravir dose or placebo. Our results are similar but do not replicate Table 1 in the Label as listed below:

	Raltegravir 400 mg bid + OBT	Placebo + OBT
Nausea	2.2%	3.5% (vs ——, in Label)
Headache	2.4% (versus——, in Label)	1.8% (versus ——, in Label)

Please see enclose Excel spreadsheet (Phase 3 and Protocol 05…) of the subject ANs used to generate my results. Please assist me in determining the discrepancies.

Advisory Committee

3. Please include basic PK and clinical pharmacology information for raltegravir in your slides that will be presented at the Advisory Committee meeting on September 5, 2007.

MRL Response dated Aug 6, 2007: We plan to include this information. We would like to ask if there are any specific areas of concern or questions FDA may have on this subject. Is this considered a "normal" request, or is there particular information for which FDA is interested. We would appreciate your thoughts on this.

FDA Response dated August 7, 2007: Thank you for your response. We are interested in the following information:

a. Raltegravir plasma concentrations were highly variable in clinical studies either in healthy subjects (e.g., Protocols 25, 28) or in HIV patients (e.g., intensive PK data in Protocols 004 and $C_{12\,hr}$ data in Protocol 018 and 019), which implies a large degree of uncertainty in raltegravir exposure level. Thus, it is challenging to define a clinically significant threshold for dose adjustment.

   - Within the concentration range studied, the virologic success rate is similar (77%) for patients with lower C_{12hr} (median C_{12hr} 76nM) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM). This relationship needs careful interpretation in the presence of high within subject variability.

- It is difficult to define the maximum safe raltegravir concentration because of the size of the current safety database at high exposure levels and the high pharmacokinetic variability.

Please comment on high PK variability of raltegravir in terms of defining a clinically significant threshold.

b. The high pharmacokinetic variability observed across these clinical studies could be due to the combination of the following factors:

- High variability in hepatic UGT1A1 protein expression levels (>50-fold) from human liver samples.
- UGT1A1 polymorphism
- High variability in intestinal P-gp expression levels
- pH-dependent solubility. Solubility increases with increasing pH.
- Food effect on $C_{12\,hr}$ values (raltegravir was administered with or without food in Phase II/III trials)
- Drug interactions affecting UGT1A1 and/or P-gp

Please comment on the sources of pharmacokinetic variability.

c. Please provide rationale for dose adjustment.

4. Please submit your advisory committee slides for the Division's review by COB August 17, 2007.

MRL Response dated Aug 6, 2007: We will provide the slides by the August 17, 2007 date COB.

FDA Response dated August 7, 2007: Please send me your AC slides via email by Aug 13, 2007.

5. The Division proposes a WebEx meeting (E-Meeting) for August 29, 2007 from 2-3 p.m. to provide our comments for your advisory committee slides.

MRL Response dated Aug 6, 2007: We look forward to such a meeting and value FDA feedback on our slides. The proposed date of August 29 is very close to the Advisory Committee and would not provide much time for us to respond to major FDA comments and alter slides. Is it possible to conduct this meeting earlier, such as August 22-24? Please let Dr. Robert Fromtling know if an earlier time can be arranged (August 27 is our only exclusion date). Once receiving our slides (T-Aug 17), we would appreciate it if FDA could provide high level comments to us as early as possible so that we may discuss/address any outstanding issues or concerns. Is this possible? We may be able to achieve this objective if we can move to any earlier meeting date from the proposed August 29. Also, may we receive the FDA slides as well before the AC meeting?

FDA Response dated August 7, 2007: As requested, the Web/Ex meeting is scheduled for August 17, 2007, from 11:45 a.m.- 12:45 p.m. EST. Due to our limited limited resources, we will not be able to provide you with our slides or backgrounder package. Please note that both will be posted in the FDA website 48 hours prior to the AC meeting.

14403	Placebo	Injection sit	severe	def
14404	MK-0518 4	Cellulitis	mod	prob
15001	Placebo	Diarrhoea	mod	poss
15001	Placebo	Nausea	severe	poss
15001	Placebo	Vomiting	mod	poss
15002	Placebo	Diarrhoea	mod	poss
15002	Placebo	Rash	mod	poss
15005	MK-0518 4	Chills	mod	poss
15005	MK-0518 4	Dizziness	mod	poss
15005	MK-0518 4	Pyrexia	mod	poss
15005	MK-0518 4	Rash	mod	poss
15006	MK-0518 4	Injection sit	mod	def
15007	MK-0518 4	Diarrhoea	mod	prob
15007	MK-0518 4	Injection sit	mod	def
15007	MK-0518 4	Weight dec	mod	poss
15012	MK-0518 4	Injection sit	mod	def
15016	MK-0518 4	Asthenia	mod	poss
15019	Placebo	Nausea	mod	poss
15023	MK-0518 4	Injection sit	mod	def
15023	MK-0518 4	Nausea	mod	poss
15029	MK-0518 4	Injection sit	mod	def
15033	MK-0518 4	Diarrhoea	mod	poss
15036	MK-0518 4	Diarrhoea	mod	prob
15036	MK-0518 4	Nausea	mod	prob
15036	MK-0518 4	Vomiting	mod	poss
15055	MK-0518 4	Injection sit	mod	def
15056	Placebo	Diarrhoea	mod	prob
15056	Placebo	Fatigue	mod	poss
15056	Placebo	Injection sit	mod	def
15057	MK-0518 4	Diarrhoea	severe	poss
15057	MK-0518 4	Nausea	severe	poss
15057	MK-0518 4	Vomiting	severe	poss
15063	Placebo	Injection sit	mod	def
15063	Placebo	Nausea	mod	def
15063	Placebo	Vomiting	mod	def
15064	MK-0518 4	Abnormal c	mod	poss
15064	MK-0518 4	Headache	mod	poss
15067	MK-0518 4	Abdominal	mod	prob
15067	MK-0518 4	Diarrhoea	mod	prob
15071	MK-0518 4	Pyrexia	mod	poss
15079	MK-0518 4	Muscle spa	severe	poss
15079	MK-0518 4	Myositis	mod	poss
15079	MK-0518 4	Pain in extı	severe	poss
15092	Placebo	Injection sit	mod	def
15094	MK-0518 4	Headache	severe	poss
15100	MK-0518 4	Hypersens	mod	def
15100	MK-0518 4	Hypersens	severe	def
15103	MK-0518 4	Dizziness	mod	poss
15105	MK-0518 4	Injection sit	mod	def
15111	MK-0518 4	Injection sit	mod	def
15111	MK-0518 4	Xeroderma	mod	poss
15115	MK-0518 4	Renal failu	severe	poss

15116	Placebo		Paraesthes	mod	poss
15121	MK-0518	4	Fatigue	mod	poss
15121	MK-0518	4	Injection si	mod	def
15121	MK-0518	4	Neuropath	mod	poss
15129	MK-0518	4	Anaemia	mod	def
15601	Placebo		Anaemia	mod	prob
15607	Placebo		Dry mouth	mod	poss
16201	Placebo		Hyperglyca	severe	prob
16201	Placebo		Pollakiuria	mod	prob
16201	Placebo		Weight dec	mod	poss
16204	MK-0518	4	Hyperlipida	mod	poss
16210	MK-0518	4	Flatulence	mod	poss
16210	MK-0518	4	Flatulence	severe	poss
16210	MK-0518	4	Nausea	severe	poss
16213	MK-0518	4	Tension he	mod	poss
16215	MK-0518	4	Lipodystro	severe	poss
16222	Placebo		Neutropeni	mod	poss
16227	MK-0518	4	Asthenia	mod	poss
16245	MK-0518	4	Diarrhoea	mod	def
16245	MK-0518	4	Nausea	mod	def
16258	MK-0518	4	Insomnia	mod	poss
16263	MK-0518	4	Fatigue	mod	prob
16266	MK-0518	4	Headache	mod	poss
16270	Placebo		Neuropath	mod	poss
16275	MK-0518	4	Abdominal	mod	poss
16275	MK-0518	4	Abdominal	mod	poss
16275	MK-0518	4	Fatigue	mod	poss
16275	MK-0518	4	Night swea	mod	poss
16278	MK-0518	4	Headache	severe	poss
16279	MK-0518	4	Abdominal	mod	poss
16279	MK-0518	4	Abdominal	mod	poss
16279	MK-0518	4	Diarrhoea	mod	poss
16279	MK-0518	4	Fatigue	mod	poss
16281	MK-0518	4	Neuropath	mod	prob
16284	Placebo		Nausea	mod	poss
16284	Placebo		Nausea	severe	prob
16286	MK-0518	4	Asthenia	mod	poss
16286	MK-0518	4	Hyperhidro	mod	poss
16287	MK-0518	4	Chest disc	mod	prob
16287	MK-0518	4	Ventricular	mod	poss
16289	MK-0518	4	Diarrhoea	mod	poss
16289	MK-0518	4	Headache	mod	poss
16291	MK-0518	4	Rash	mod	prob
16296	MK-0518	4	Diarrhoea	mod	prob
16303	MK-0518	4	Abdominal	mod	poss
16303	MK-0518	4	Dizziness	mod	poss
16303	MK-0518	4	Headache	mod	poss
16303	MK-0518	4	Nausea	mod	prob
16305	Placebo		Injection si	mod	poss
16310	MK-0518	4	Constipatic	mod	poss
16315	MK-0518	4	Abdominal	severe	poss
16315	MK-0518	4	Constipatic	mod	poss

16315	MK-0518	4	Musculosk	mod	poss
16322	MK-0518	4	Vomiting	mod	poss
16347	MK-0518	4	Allodynia	severe	poss
16351	MK-0518	4	Nausea	mod	poss
16353	MK-0518	4	Dyspepsia	mod	poss
16353	MK-0518	4	Rash macu	mod	prob
16355	Placebo		Rash	mod	prob
16357	MK-0518	4	Abdominal	mod	poss
16359	MK-0518	4	Diarrhoea	mod	poss
16369	Placebo		Myalgia	mod	prob
16374	Placebo		Fatigue	mod	poss
16374	Placebo		Libido decr	mod	poss
16377	Placebo		Neutropeni	severe	poss
16377	Placebo		Prurigo	mod	poss
16378	MK-0518	4	Diarrhoea	mod	prob
16379	MK-0518	4	Asthenia	mod	poss
16379	MK-0518	4	Dizziness	mod	poss
16379	MK-0518	4	Increased a	mod	poss
16379	MK-0518	4	Nausea	mod	poss
16379	MK-0518	4	Somnolenc	mod	poss
16384	Placebo		Abdominal	mod	prob
16385	Placebo		Diarrhoea	mod	prob
16385	Placebo		Myalgia	mod	prob
16386	MK-0518	4	Nausea	mod	def
16389	Placebo		Gastritis	mod	poss
16389	Placebo		Gastrooesc	mod	poss
16389	Placebo		Hepatomeg	mod	poss
16389	Placebo		Hypertrigly	mod	poss
16389	Placebo		Nephrolithi	mod	poss
16389	Placebo		Pancreatiti	mod	poss
16394	MK-0518	4	Diarrhoea	mod	prob
16395	Placebo		Somnolenc	mod	poss
16399	Placebo		Pruritus	mod	poss
16402	MK-0518	4	Headache	mod	poss
16402	MK-0518	4	Headache	severe	poss
2956	Placebo		Cardiovasc	mod	poss
2956	Placebo		Dysgeusia	mod	poss
2956	Placebo		Hypersens	mod	def
2956	Placebo		Stomach d	mod	poss
2964	MK-0518	4	Arthralgia	mod	poss
2964	MK-0518	4	Facial wast	mod	poss
2964	MK-0518	4	Glossitis	mod	poss
2964	MK-0518	4	Hyperhidro	mod	prob
2964	MK-0518	4	Injection sit	mod	def
2964	MK-0518	4	Lipoatroph	mod	poss
2964	MK-0518	4	Lipodystro	mod	poss
2964	MK-0518	4	Pollakiuria	mod	poss
2969	Placebo		Injection sit	mod	def
2973	Placebo		Anaemia	mod	prob
2982	Placebo		Skin nodul	mod	def
2986	MK-0518	4	Myalgia	mod	poss
2997	Placebo		Arrhythmia	mod	poss

2997	Placebo	Syncope	mod	poss
3225	Placebo	Dyspepsia	mod	prob
3225	Placebo	Nausea	mod	prob
3229	Placebo	Diarrhoea	mod	prob
3232	MK-0518 4	Paraesthes	mod	prob
3241	Placebo	Nausea	mod	poss
3241	Placebo	Rash macu	mod	poss
3241	Placebo	Vomiting	mod	poss
3249	MK-0518 4	Diarrhoea	mod	poss
3265	MK-0518 4	Dyslipidaer	mod	prob
3272	Placebo	Abdominal	mod	poss
3272	Placebo	Diarrhoea	severe	poss
3272	Placebo	Headache	mod	poss
3272	Placebo	Migraine	mod	poss
3272	Placebo	Migraine	severe	poss
3278	Placebo	Diarrhoea	mod	prob
3278	Placebo	Lipoatroph	severe	poss
3291	MK-0518 4	Dizziness	mod	poss
3291	MK-0518 4	Palpitation	mod	poss
3292	Placebo	Weight dec	severe	poss
3295	Placebo	Hypercholε	mod	def
3588	MK-0518 4	Abdominal	mod	poss
3588	MK-0518 4	Feeling hot	mod	poss
3591	Placebo	Drug intole	mod	def
3595	Placebo	Subcutane	mod	def
3598	Placebo	Injection sit	mod	def
3876	MK-0518 4	Erectile dy	mod	poss
3887	MK-0518 4	Central obε	mod	poss
3887	MK-0518 4	Lipodystroț	mod	poss
6402	Placebo	Vomiting	mod	def
6404	MK-0518 4	Drug hyper	severe	def
6404	MK-0518 4	Hypersens	severe	prob
7006	MK-0518 4	Injection sit	mod	def
7011	Placebo	Headache	mod	def
7011	Placebo	Headache	mod	prob
7016	Placebo	Abdominal	mod	poss
7017	Placebo	Injection sit	mod	def
7019	MK-0518 4	Injection sit	mod	def
7025	MK-0518 4	Injection sit	mod	def
7025	MK-0518 4	Skin infecti	mod	prob
7026	MK-0518 4	Headache	mod	poss
7032	MK-0518 4	Injection sit	mod	def
7032	MK-0518 4	Vertigo	mod	poss
7033	MK-0518 4	Injection sit	mod	def
7040	MK-0518 4	Inflammatic	mod	def
7040	MK-0518 4	Injection sit	mod	def
7041	Placebo	Injection sit	mod	def
7042	MK-0518 4	Dizziness	mod	def
7043	MK-0518 4	Injection sit	mod	def
7046	MK-0518 4	Neuropath	mod	poss
7047	MK-0518 4	Dermatitis	mod	poss
7047	MK-0518 4	Diarrhoea	mod	poss

7047	MK-0518 4	Subcutane	mod	poss
7051	MK-0518 4	Injection sit	mod	prob
7051	MK-0518 4	Neutropeni	mod	def
7056	Placebo	Anaemia	severe	poss
7056	Placebo	Nausea	mod	prob
7056	Placebo	Vomiting	mod	prob
7058	MK-0518 4	Rash	mod	def
7061	MK-0518 4	Injection sit	mod	def
7062	MK-0518 4	Nodule	mod	def
7066	MK-0518 4	Injection sit	mod	def
7071	MK-0518 4	Asthenia	mod	poss
7071	MK-0518 4	Diarrhoea	mod	prob
7071	MK-0518 4	Irritability	mod	prob
7071	MK-0518 4	Pain in ext	mod	poss
7073	MK-0518 4	Erythema	mod	poss
7073	MK-0518 4	Rash macu	mod	poss
7074	MK-0518 4	Injection sit	mod	def
7077	MK-0518 4	Visual distu	mod	poss
7078	MK-0518 4	Diarrhoea	mod	prob
7078	MK-0518 4	Fat atrophy	mod	prob
7080	MK-0518 4	Epistaxis	mod	poss
7080	MK-0518 4	Headache	mod	prob
7080	MK-0518 4	Herpes sim	mod	poss
7080	MK-0518 4	Nausea	mod	prob
7080	MK-0518 4	Vomiting	mod	prob
7082	Placebo	Headache	mod	prob
7083	MK-0518 4	Injection sit	mod	def
7086	MK-0518 4	Gastritis	severe	prob
7088	Placebo	Skin nodul	mod	prob
7092	MK-0518 4	Diabetes m	mod	prob
7102	Placebo	Injection sit	severe	def
7102	Placebo	Lipodystrop	severe	prob
7112	MK-0518 4	Injection sit	mod	def
7115	MK-0518 4	Injection sit	mod	def
7609	MK-0518 4	Depressior	mod	poss
7614	Placebo	Dyspepsia	mod	poss
7614	Placebo	Nausea	mod	poss
8204	MK-0518 4	Nephrotic s	severe	poss
8209	MK-0518 4	Abdominal	mod	poss
8217	MK-0518 4	Vertigo	mod	poss
8226	MK-0518 4	Asthenia	mod	poss
8226	MK-0518 4	Back pain	mod	poss
8236	MK-0518 4	Arthralgia	mod	poss
8236	MK-0518 4	Asthenia	mod	poss
8251	Placebo	Dizziness	mod	poss
8251	Placebo	Headache	mod	poss
8255	Placebo	Abdominal	mod	poss
8255	Placebo	Diarrhoea	mod	poss
8257	MK-0518 4	Diabetes m	mod	poss
8257	MK-0518 4	Hypertrigly	severe	poss
8262	MK-0518 4	Rash	mod	poss
8265	MK-0518 4	Body fat di	mod	poss

8265	MK-0518	4	Gynaecom	mod	poss
8270	Placebo		Depressior	severe	poss
8274	MK-0518	4	Abdominal	mod	prob
8274	MK-0518	4	Diarrhoea	mod	poss
8286	MK-0518	4	Fatigue	mod	poss
8287	MK-0518	4	Gastrointes	mod	poss
8288	MK-0518	4	Depressior	mod	def
8289	Placebo		Diarrhoea	mod	poss
8308	Placebo		Mouth ulce	mod	poss
8314	MK-0518	4	Lipodystro	mod	prob
8315	MK-0518	4	Hepatitis	mod	def
8318	MK-0518	4	Arthralgia	mod	poss
8318	MK-0518	4	Diarrhoea	mod	poss
8318	MK-0518	4	Nephropatl	severe	prob
8318	MK-0518	4	Renal impa	mod	prob
8325	MK-0518	4	Hepatitis	mod	poss
8325	MK-0518	4	Hepatitis	severe	poss
8334	Placebo		Nausea	mod	prob
8343	Placebo		Diarrhoea	mod	poss
8346	Placebo		Asthenia	mod	poss
8346	Placebo		Defaecatio	mod	poss
8348	MK-0518	4	Abdominal	mod	poss
8348	MK-0518	4	Gastrointes	mod	poss
8353	MK-0518	4	Hepatome	mod	prob
8353	MK-0518	4	Hyperlacta	mod	prob
8360	MK-0518	4	Pyrexia	mod	prob
8361	MK-0518	4	Insomnia	mod	poss
8362	Placebo		Mental disc	mod	poss
8367	MK-0518	4	Polyneurop	mod	prob
8367	MK-0518	4	Pyrexia	mod	poss
8368	MK-0518	4	Headache	mod	poss
8372	MK-0518	4	Myocardial	mod	poss
8378	Placebo		Rash macu	mod	poss
8380	MK-0518	4	Anaemia n	mod	prob
8380	MK-0518	4	Anxiety	mod	prob
8380	MK-0518	4	Drug hyper	mod	poss
8393	Placebo		Cholestasi	mod	poss
8395	MK-0518	4	Diarrhoea	mod	poss
8395	MK-0518	4	Headache	mod	poss
8395	MK-0518	4	Nausea	mod	poss
8395	MK-0518	4	Nocturia	mod	poss

Response to Original FDA Query Dated July 6 (Most Recent Request Dated July 20)

3. Please provide the original randomization schedules generated for each patient in Studies 004, 005, 018, and 019.

MRL Response dated July 17, 2007: Randomization schedules are included in the appendix of each individual Clinical Study Report (CSR). They can be found in Section 16.1.7 (Randomization Scheme and Codes) as subsection 16.1.7.1 (Patient Allocation Schedule).

FDA Response dated July 17, 2007: Although the codes are given in appendix 16.1.7.1 of the CSR, they do not appear to be original source documents. For example, the patient allocation schedule for Protocol 019 has a creation date of 16-Nov-2005 but the date at the top of the page is 21-Feb-2007. We are requesting original source documents that generated the treatment codes for each study.

MRL Reply dated July 18, 2007: The allocation schedules provided with the CSRs are identical to the original schedules. In the example provided, 21-Feb-2007 is the date the schedule was printed from the Clinical Allocation Schedule System (CASS) for inclusion in the CSR. It is not the date the allocation schedule was generated. Prior to study initiation, an allocation schedule is generated in the CASS system. For Protocol 019, this schedule was created on 16-Nov-2005.

At the time of the allocation schedule generation, only a "masked" allocation schedule is printed which has the treatment assignments covered. The masked schedule allows for emergency unblinding only. So that the study blind is strictly maintained, we do not print "unmasked" allocation schedules at the time of schedule generation. The allocation schedules reside in the electronic CASS system and access to the system is limited. Unmasked schedules are printed only as needed for inclusion in CSR appendices.

FDA Response dated July 20, 2007: Unfortunately, what you have provided us in Appendix 16.1.7.1 in the Clinical Study Report entitled 'Patient Allocation Schedule' is not a source document. Please clarify what source documents pertaining to randomization schedules are available at the sites. In addition, we would like to know more about your standard operating procedures for generating and storing randomization treatment codes and the corresponding documentation process. Please submit your SOPs that pertain to this topic.

MRL Response dated July 26: Protocols 004, 005, 018 and 019 used central randomization via an Integrated Voice Response System (IVRS) which was managed by an external vendor. The allocation schedules for these studies were generated by the Clinical Biostatistics Department at Merck, and uploaded into the IVRS system. Prior to enrolling each patient, the site called the IVRS system to provide necessary information and obtain an allocation number. A fax confirmation of this allocation number was sent to the site. For each enrolled patient, this fax is the source document that resides at the site. The full allocation schedule was not supplied to each site. The IVRS system was the only method for a primary investigator to directly unblind a patient.

Per your request, the Clinical Study Blinding Global Development Procedure (GDP) is attached as a pdf for your reference.

FDA **Response dated July 31, 2007:** Please submit the original source document of treatment allocation codes from the external vendor.

Statistical query for NDA 22-145 dated August 6, 2007

1. Please submit the following updated datasets using the raw listing data provided in the Safety Update Report dated June 15, 2007 as soon as possible.

    a. Updated SPATSTT.XPT for Studies 005, 018 and 019, including date and reason for discontinuation;
    b. Updated last visit dates for all subjects in Studies 005, 018 and 019:
    c. Updated THERAPY005.XPT for Study 005.

Two PK queries dated August 9, 2007 for NDA 22-145

1. In Protocol 009, raltegravir AUC in four subjects did not change or slightly increased with co-administration of rifampin. Please justify a dose increase of raltegravir to 800 mg twice daily when co-administered with rifampin in these patients with regards to safety.

2. There seems to be no substantial data (in vitro or in vivo) of the relative UGT1A1 induction potency on rifampin, phenytoin and phenobarbital. Please provide your rationale to rank phenytoin and phenobarbital in the same group with rifampin.

Division's Comments for Merck's AC slides for NDA 22-145 dated August 16, 2007

1. We note that 100% 24-week efficacy data were not included in the current slide presentation (Slides 25 and 26 contain 24-week data from the 60% subjects at the time of original database lock). Please comment if 24-week efficacy data will be presented.

2. Please provide assistance in rectifying protocol subject numbers.
   (a) Protocol 004: Slide 14 has N=206 subjects in Phase 2. We have N=198 subjects and this is the number we use in the denominator for safety analysis. Attached below are the ANs for the 198 subjects. We do not include the 3 subjects from Phase 1 who did not continue into Phase 2, however, that leaves 3 additional subjects unaccounted for. Please provide comments to explain the discrepancy.

Protocol 004
subjects.xls (28 ...

   (b) Phase 2 and Phase 3 Safety Database: Slide 39 lists 323 subjects on control for Protocols 004, 005, 018, 019, whereas we have N=320 and this is the number we use in the denominator for safety analysis. Are these the same subjects from Protocol 004? Attached are the ANs for the 320 subjects.

Phase 2 and 3
placebo_comparat...

Four statistical queries for NDA 22-145 dated August 21, 2007

Thank you for your August 8, 2007 response (Seq046) to our July 31, 2007 query regarding original source documents of treatment allocation codes from the external vendors. In the treatment allocation codes you sent to us, there were no dates for the code generation and no name of the code generator. We need verification that the treatment allocation codes were generated prior to study initiation and would like the external vendors to certify that these were the actual dates the treatment allocation codes were generated. We also acknowledged receipt of your August 20, 2007 email correspondence of the allocation scheduled release memos for Protocols 04, 05, 018, and 019 containing the dates on which the test files were transferred to the external vendors.

Please provide the following information to FDA to further clarify the issues:

1. Please provide the addresses and telephone numbers of the External Vendors (i.e., ————) used to generate the treatment allocation codes for Studies 004, 005, 018 and 019.

2. Please have the External Vendors (i.e., ————) send the original source documents of the treatment allocation codes to FDA directly. Information on when the vendors received/generated the original codes should be provided.

3. We need certification from the external vendors that the documents they send us were the original source documents and that the treatment allocation codes were generated prior to study initiation.

4. Please submit all other source documents of treatment allocation codes (e.g., from your Clinical Pharmaceutical Operations or drug packaging group).

5. Please disclose to FDA any financial or partnering agreements between Merck and the external vendors.

One clinical query dated August 22, 2007 for NDA 22-145

1. Please submit an updated laboratory data for subject AN 3243 in Protocol 05. The safety update report contains laboratory data up to study Day 113; however, the subject was subsequently hospitalized and died, and we request all available laboratory data corresponding to the subject's hospitalization.

One pharm/tox query dated September 4, 2007 for NDA 22-145

1. Please submit the historical control data for Segment II reproductive studies in rats and rabbits. If these data were submitted with the NDA, please help us locate them.

Queries dated September 7, 2007 for NDA 22-145

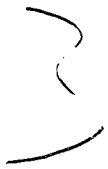
Risk Management Plan

1. Please revise the duration of your active surveillance program to at least five years post-launch and submit the protocol reflecting this revision for Division's review and comment as soon as possible.

MRL clarification question dated Sept 7, 07: Monica. We usually prepare a concept sheet of a study first for review by FDA followed later by the draft protocol. Will this be acceptable since a full protocol would take some time to write. Is the 5 yr period limited to the active surveillance study as noted in the query above?

FDA clarification dated Sept 12, 07 via phone: Concept sheets are acceptable and the 5 yr period is for the active surveillance program only.

Labeling



MRL clarification question dated Sept 7, 07: Monica. We'll provide wording. MRL confirmed that it will send wording on Sept 13, 07.

Clinical Pharmacology

3. Please provide your future plans to study raltegravir and other antitubercolosis agents.

Other

4. Please provide an update for the patient enrollment numbers by gender and race for the treatment-naïve study (Protocol 004) and expanded access study (Protocol 023).

MRL clarification question dated Sept 7, 07: Monica. The treatment-naïve study is protocol 021; is this the protocol in question rather than P004 as stated above?

5. Please submit the Clinical Study Report (complete data) and related raw datasets for Protocol 013 as soon as possible.

Three queries dated September 14, 2007 for NDA 22-145

Pharmacology/Toxicology

1. It is noted that the fertility indices for F1 generation were 95%, 95%, 100%, and 81% for the control, low, mid, and high dose groups in the oral developmental study in rats with pre-natal and post-natal evaluation. Eighty one percent (81%) is below the historical control data provided for the male and female fertility studies performed at conducting laboratories. In addition, it's unclear if statistical analysis was performed. Please provide explanation for the lower fertility index in the F1 generation and why statistical analysis was not performed. A similar trend of lower fertility index was observed in the male fertility study, though the value was within those in the historical control.

Clinical regarding proposed PI Labeling

2. In our analyses of Protocols 005, 018, and 019 comparing the 400 mg twice daily dose of raltegravir to placebo, results for patient-years and treatment-emergent laboratories differ from the data presented in the proposed PI label. Because the derived conclusions from each analysis are similar, we are not proposing changes to the label; however, we request review of our laboratory analyses to aid us in understanding the discrepancies. Our laboratory analyses are attached in the excel tables below. In addition, please provide your analysis for determination of patient-years.


Phase 3 and Prot 05 400 mg GLU...


Phase 3 and Prot 5 400 mg BILI...


Phase 3 and Prot 05 400 mg ALK...


Phase 3 and Prot 05 400 mg ALT...


Phase 3 and Prot 05 400 mg AST...

3. The less common adverse reactions section in the proposed PI label contains drug-related adverse reactions of moderate to severe intensity occurring between 1 and 2% of treatment-experienced adult patients. Our analysis has determined the following additional reactions meet this definition: lipodystrophy acquired and vomiting. Our analysis is attached in the excel tables below.


Phase 3 and Prot 05 400 mg Dru...


Phase 3 and rotocol 05 400 mg..

Two clinical queries dated October 1, 2007 for Tx IND [redacted] and IND 69,928

1. Please submit the updated narratives for the following patients enrolled in IND [redacted] (Protocol 023):

WAES numbers:	0707USC00004	Acute hepatic failure
	0705USC00012	Myopathy
	0705USC00027	Myopathy
	0706USC00003	Rhabdomyolysis

2. Please submit any other cases of myopathy, rhabdomyolysis, or acute hepatic failure that have occurred (1) since the July 20, 2007 Annual Report Date for IND [redacted] or (2) since the February 16, 2007 database lock for IND 69,928.

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/s/

Monica Zeballos
10/9/2007 05:37:39 PM
CSO

Monica Zeballos
10/9/2007 05:38:39 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 4, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Labeling recommendations # 5 for the PI and PPI for NDA 22-145

Total no. of pages including cover: 9 plus annotated and clean PI

Comments: This correspondence and annotated & clean PI and clean PPI were sent to Dr. Fromtling via email in PDF format on Oct 4, 2007.

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 4, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Sarah Connelly, M.D., Medical Reviewer, DAVP
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Ita Yuen, Ph.D., Pharm/Toxicology Reviewer, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader and Deputy Director , DCP4, OCP, OTS
Hanan, Ghantous, Ph.D., DABT, Acting Pharm/Tox Team Leader, DAVP

NDA: 22-145

Drug: Raltegravir potassium (formerly MK-0518)

Subject: Labeling recommendations # 5 for PI for PPI (NDA 22-145)

The following labeling comments are being conveyed on behalf of the Review Team, the SEALD Team, and the Interdisciplinary Review Team (IRT) for QT studies, and are directed towards your April 13, 2007, June 15, 2007, July 27, 2007, September 7, 2007, September 17, 2007, September 25, 2007, and October 3, 2007 submissions for this NDA. Reference is made to our labeling comments No. 1, No 2, No. 3, and No 4 sent to you on July 20, 2007 and July 31, 2007, August 30, 2007, and September 27, 2007 respectively via facsimile correspondence.

Please address the identified deficiencies/issues/recommendations and re-submit labeling by 11 a.m. on October 5, 2007. This updated version of labeling will be used for final labeling discussions during the teleconference scheduled for October 5, 2007 at 1:45 p.m. EST. Please find enclosed an annotated and clean version of the package insert (PI) and a clean version of package patient information (PPI).

34 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

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/s/

Monica Zeballos
10/9/2007 01:33:58 PM
CSO

Kendall Marcus
10/11/2007 04:17:36 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 3, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Proposed Postmarketing Study Commitment for NDA 22-145

Total no. of pages including cover: 3

Comments: see next page

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 3, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Sarah Connelly, M.D., Medical Reviewer, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP

NDA: 22-145

Drug: Isentress™ (raltegravir potassium) , formerly MK-0518

Subject: Proposed Postmarketing Study Commitment (PMC)

The following comment is being conveyed to you on behalf of the Review Team. Please refer to your new drug application (NDA) 22-145 submitted on April 13, 2007. Reference is made to our October 1, 2007 email correspondence sent to you proposing 14 PMCs and five non-PMCs for this application.

We proposed the following PMC that is not a condition of the accelerated approval regulations. The commitment is listed below:

Clinical

1. Conduct and submit a final report for [redacted] study to provide additional safety data including, but not limited to, the incidence of mortality, malignancy, herpes zoster, creatine kinase elevations, and other adverse events. [redacted] for a minimum of 5 years.

Protocol Submission Date: [redacted]
Final Study Report Submission Date: [redacted]

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Monica Zeballos
10/3/2007 09:02:27 AM
CSO

Kendall Marcus
10/3/2007 04:05:36 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Proposed Postmarketing Study Commitments and Non-Postmarketing Study Commitments for NDA 22-145

Total no. of pages including cover: 6

Comments: This correspondence was sent to Dr. Fromtling via email on Oct 1, 2007 in PDF format

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 1, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Sung Rhee, Ph.D., Microbiology Reviewer, Division of Antiviral Products (DAVP)
Sarah Connelly, M.D., Medical Reviewer, DAVP
Alan Shapiro, M.D., Ph.D., Medical Reviewer, DAVP
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Concur: Debra Birnkrant, M.D., Division Director, DAVP
Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Kendall Marcus, M.D., Medical Team Leader, DAVP
Hanan, Ghantous, Ph.D., D.A.B.T., Acting Pharm/Tox Team Leader, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader and Deputy Director , DCP4, OCP, OTS

NDA: 22-145

Drug: Isentress™ (raltegravir potassium) , formerly MK-0518

Subject: Proposed Postmarketing Study Commitments and Non-Postmarketing Study Commitments for NDA 22-145

The following comments are being conveyed to you on behalf of the Review Team. Please refer to your new drug application (NDA) 22-145 submitted on April 13, 2007. Please note that we will communicate additional proposed postmarketing study commitments (PMCs) and non-PMCs to you in a near future.

5 Page(s) Withheld

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Withheld Track Number: Administrative- 1A

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/s/

Monica Zeballos
10/2/2007 10:46:56 AM
CSO

Debra Birnkrant
10/3/2007 01:05:44 PM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **22-145** Supplement # **N/A** Efficacy Supplement Type SE- **N/A**

Proprietary Name: **Isentress™**
Established Name: **Raltegravir**
Strengths: **400 mg tablets**

Applicant: **Merck & Co., Inc.**
Agent for Applicant (if applicable): **N/A**

Date of Application: **April 13, 2007 (last piece received)**
Date of Receipt: **April 13, 2007**
Date clock started after UN: **April 13, 2007**
Date of Filing Meeting: **May 22, 2007**
Filing Date: **June 22, 2007**
Action Goal Date (optional): **October 12, 2007** User Fee Goal Date: **October 13, 2007**

Indication requested: **In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy**

Type of Original NDA:	(b)(1) ☒	(b)(2) ☐
AND (if applicable)		
Type of Supplement:	(b)(1) ☐	(b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) **1**
Other (orphan, OTC, etc.) **No**

Form 3397 (User Fee Cover Sheet) submitted: **ID # PD3006930** YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:
  No, confirmed a the FDA website
- If yes, has OC/DMPQ been notified of the submission? **N/A** YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☐ NO ☒
  If no, explain:

- Was form 356h included with an authorized signature? YES ☐ NO ☒
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☒ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

3. This application is an eCTD NDA. YES ☒
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐
- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐
- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-1O

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒
For eNDA is not required per guidance.
- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. **Done**
- List referenced IND numbers: **IND 69,928 and** ~~_____~~
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) **December 5, 2005** NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **December 1, 2006** NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) **Executive CAC recommendations sent to applicant on Nov 3, 2005** NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES ☐ NO ☒

If Rx-to-OTC Switch or OTC application: N/A for NDA 22-145

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A** YES ☐ NO ☒

Chemistry

•	Did applicant request categorical exclusion for environmental assessment?		YES	☒	NO	☐
	If no, did applicant submit a complete environmental assessment?		YES	☐	NO	☐
	If EA submitted, consulted to EA officer, OPS?		YES	☐	NO	☐
•	Establishment Evaluation Request (EER) submitted to DMPQ?		YES	☒	NO	☐
•	If a parenteral product, consulted to Microbiology Team?	**N/A** YES		☐	NO	☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: **May 22, 2007**

NDA #: **22-145**

DRUG NAMES: **Isentress™ (raltegravir)**

APPLICANT: **Merck & Co., Inc.**

BACKGROUND: **Raltegravir is a new molecular entity (NME) and is the first in a new class of antiretroviral drugs called integrase strand transfer inhibitor (INSTI)**
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: **Debra Birnkrant, Jeffrey Murray, Kendall Marcus, Sarah Connelly, Ita Yuen, Kellie Reynolds, Derek Zhang, Julian O'Rear, Sung Rhee, Greg Soon, Karen Qi, Fraser Smith, George Lunn, Stephen Miller, Anthony DeCicco, Ted Chang, Anne Marie Russell, Wendy Carter, Alan Shapiro, Tamiji Nakanishi, and Monica Zeballos**

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	**Sarah Connelly**
Secondary Medical:	**N/A**
Statistical:	**Karen Qi and Fraser Smith**
Pharmacology:	**Ita Yuen**
Statistical Pharmacology:	**Pravin Jadhav**
Chemistry:	**George Lunn and Ted Chang**
Environmental Assessment (if needed):	
Biopharmaceutical:	**Derek Zhang**
Microbiology, sterility:	**N/A**
Microbiology, clinical (for antimicrobial products only):	**Sung Rhee**
DSI:	**Antoine El Hage**
OPS:	
Regulatory Project Management:	**Monica Zeballos**
Other Consults:	**Genomics**

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known **Sept 5, 2007** NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒
  Note: Last GLP audit Feb 06, no significant deficiencies

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: **Complete eCTD submission and has been submitted through gateway**

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Pharmacology/Toxicology (Non RTF comment)

1. Please provide updated information on the status, mortality rate, and tumor findings on the ongoing carcinogenicity studies in rats and mice.

Monica Zeballos, Pharm.D.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No,**" skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes,**" skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No,**" to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes,**" (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No,**" to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Tony DeCicco
10/2/2007 01:13:49 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 1, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: CMC Information Request dated September 24, 2007 for NDA 22-145

Total no. of pages including cover: 3

Comments: This correspondence was sent to Dr. Fromtling via email on Oct 1, 2007

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 1, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, DAVP

Through: Ted Chang, Ph.D., Chemistry Reviewer, DPA2, ONDQA

Concur: Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA

NDA: 22-145

Drug: Raltegravir potassium (MK-0518)

Subject: CMC Information Request

These comments are provided for your information by the Manufacturing Science Branch Review Team regarding NDA 22-145 for raltegravir potassium (MK-0518). No response or action is required before the PDUFA action date but we appreciate an informational response.

1.

2.

3.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

Monica Zeballos
10/1/2007 12:44:41 PM
CSO

Norman Schmuff
10/1/2007 07:35:54 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 12, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: CMC Information Request for NDA 22-145

Total no. of pages including cover: 3

Comments: see next page

Document to be mailed: No

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 12, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, Division of Antiviral Products (DAVP)

Through: George Lunn, Ph.D., Chemistry Reviewer, DPA2, ONDQA

Concur: Elaine Morefield, Ph.D., Director, DPA2, ONDQA

NDA: 22-145

Drug: Raltegravir potassium (MK-0518)

Subject: CMC Information Request

Please address the following Chemistry, Manufacturing, and Controls (CMC) comments and recommendations that are related to NDA 22-145 for raltegravir potassium (MK-0518):

1.

a.

b.

c

2. 

3. At this stage in the application we would accept a commitment to work with FDA to achieve a satisfactory resolution of this issue post-approval if extensive experimental work is required.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 5, 2007

TO: Monica Zeballos, Regulatory Project Manager
Sarah Connelly, M. D., Medical Officer
Division of Antiviral Products, HFD-530

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-145

APPLICANT: Merck & Co., Inc.

DRUG: Raltegravir Potassium (MK-0518)

THERAPEUTIC CLASSIFICATION: Priority Review (6 months)

INDICATION: Treatment of experienced patients with evidence of HIV-1 replication despite ongoing therapy.

CONSULTATION REQUEST DATE: March 19, 2007

DIVISION ACTION GOAL DATE: October 1, 2007

PDUFA DATE: October 17, 2007

I. BACKGROUND:

The review division requested inspection of protocols 018 and 019: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0158- in Combination with an Optimized Background Therapy (OBT), Versus Optimized Background Therapy Alone, in HIV- Infected Patients With Documneted Resistance to at least 1 Drug in each of the 3 Classes of Lincensed Oral Antoretroviral Threapies." The sponsor submitted results from the two protocols in support of NDA 22-145. The primary efficacy endpoint is measured by the reduction in plasma HIV-1

RNA compared to OBT, as measured by proportion of subjects achieving HIV RNA < 400mL at week 16. The primary safety parameter is to evaluate results of clinical laboratory tests, vital sign and physical findings, blood chemistry (changes in LFT's when compared to baseline values), hematology, occurrence of adverse events and concomitant medication usage. The inspections targeted four clinical investigators who enrolled a relatively large number of subjects. One of the sites is a foreign site that conducted the study under protocol 018 (same as 019).

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
[redacted]	Barcelona, Spain	018	6/18/07	7/16/07	NAI
	St. New Haven, CT	019	7/17/07	pending	NAI*
	Atlanta , GA	019	5/30/07	8/20/07	NAI
	New York, NY	019	8/2/07	Pending	NAI*

* based on e-mail summary information or telephone call from the field investigators.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol 018

1. [redacted]

At this site a total of 19 subjects were screened, 5 subjects were reported as screen failures, and 14 subjects were randomized and completed the study. All 19 subjects were verified to have signed informed consent prior to entry into the study. The medical records for 14 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events. Subjects 005, 005, 010 and 013 were reported as virulence failures after week 16. Subject 012 experienced myocardial infarction and angina pectoris post infarction (11/15/06 and 11/24/06 respectively). The clinical investigator felt that myocardial infarction and angina were not related to study therapy. This subject had a history of ischemic cardiomyopathy and two stents prior to the study.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

Protocol 019

2. [redacted]

Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. A 1-item Form FDA 483 was issued with minor violation related to informed consent. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site a total of 8 subjects were screened, 2 subjects were discontinued, 6 subjects were randomized and entered the study. The medical records for all subjects randomized into the study were reviewed. Informed consent for all subjects was verified and no significant violations were found, except that for three subjects no documentation to show that the subjects were reconsented prior to entering the open-label phase. There was no underreporting of adverse events. There were no known limitations to this inspection. In general the records reviewed were accurate.

The data appear acceptable in support of the pending application.

3. [redacted]

At this site a total of 9 subjects were screened, 4 subjects were discontinued and 5 subjects were randomized. The records for 5 subjects were reviewed in depth and compared to case report forms and data listings for efficacy endpoints and adverse events. Informed consent for all subjects was verified and no significant violations found. For subject 16228, OBT regimen was changed during the double blind therapy by the primary physician to provide the subject with the convenience of taking less pills and not due to lack of efficacy. Both the sponsor and the IRB were notified. In general, the records reviewed were accurate and no significant problems were found that would impact the results. There were no known limitations to the inspection.

The data appear acceptable in support of the pending application.

4. [redacted]

At this site a total of 14 subjects were screened, 2 subjects were discontinued, 10 subjects were randomized and 3 subjects were enrolled in the open-label phase of the study. Five (5) subjects remain active on the study at the time of the inspection. Subjects 15014 and 15090 received prohibited medication TMC-125 by the primary care physician as part of OBT without the knowledge of the investigator or the sponsor. Subject 15062 did not meet the threshold for virologic efficacy to continue on the study. However, the clinical investigator sought the sponsor approval to continue all three subjects on the study. Informed consent for all subjects was verified and no significant violations found. In general, the records reviewed were accurate and no significant problems were noted that would impact the results. There were no known limitations to the inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of [redacted], revealed minor deviation from the protocol subjects for 15014 and 1590. The clinical investigator sought and obtained the sponsor approval to continue the subjects on the study. The inspection of [redacted] revealed minor deviation from the protocol subject 16228. However, in general these deviations do not adversely impact data acceptability; the division may elect to exclude the three subjects from the efficacy analysis. The remaining data submitted are acceptable in support of the pending application

The inspections of [redacted] revealed no significant problems that would adversely impact data acceptability. Therefore, the data from the inspected sites are acceptable in support of the pending application.

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Good Clinical Practice Branch I, HFD-46
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CONCURRENCE:

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/s/

Antoine El-Hage
9/18/2007 06:55:20 AM
PHARMACOLOGIST

Constance Lewin
9/18/2007 10:08:28 AM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: September 27, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Labeling recommendations # 4 for the PI for NDA 22-145

Total no. of pages including cover: 9 plus annotated and clean PI

Comments: This correspondence and annotated & clean PI were sent to Dr. Fromtling via email in PDF format on Sept 27, 2007.

[redacted]

Document to be mailed: No

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: September 27, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
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From: Sung Rhee, Ph.D., Microbiology Reviewer, Division of Antiviral Products (DAVP)
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Karen Qi, Ph.D., Division of Biometrics 4 (DB4), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Monica Zeballos, Pharm.D., Sr. Regulatory Project Manager, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader and Deputy Director , DCP4, OCP, OTS
Greg Soon, Ph.D., Statistical Team Leader, DB4, OB, OTS

NDA: 22-145

Drug: Raltegravir potassium (formerly MK-0518)

Subject: Labeling recommendations # 4 for PI (NDA 22-145)

The following labeling comments are being conveyed on behalf of the Review Team, the Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Interdisciplinary Review Team (IRT) for QT studies, and are directed towards your April 13, 2007, June 15, 2007, July 27, 2007, September 7, 2007, September 17, 2007, and September 25, 2007 submissions for this NDA. Reference is made to our labeling comments No. 1, No 2, and No. 3 sent to you on July 20, 2007 and July 31, 2007, and August 30, 2007, respectively via facsimile correspondence.

39 Page(s) Withheld

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X Draft Labeling

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Withheld Track Number: Administrative- 2

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/s/

Monica Zeballos
9/12/2007 11:15:12 AM
CSO

Elaine Morefield
9/12/2007 12:50:07 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 30, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
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Subject: Labeling recommendations # 3 for the PI and PPI for NDA 22-145

Total no. of pages including cover: 7 plus annotated PI, annotated and clean PPI

Comments: see next page

[redacted]

Document to be mailed: No