

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-187

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

22-187

NAME OF APPLICANT / NDA HOLDER

Tibotec, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

The following three names have been submitted for review: INTELENCE;

ACTIVE INGREDIENT(S)

etravirine

STRENGTH(S)

100 mg

DOSAGE FORM

tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 7,037,917	b. Issue Date of Patent 5/2/2006	c. Expiration Date of Patent 11/5/2019
d. Name of Patent Owner Janssen Pharmaceutica, N.V.	Address (of Patent Owner) TURNHOUTSEWEG 30	
	City/State B2340 BEERSE	
	ZIP Code BELGIUM	FAX Number (if available) 32 14 60 5491
	Telephone Number 32 14 60 6737	E-Mail Address (if available) jnjintlpatent@corus.jnj.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Philip S. Johnson, Esq. Chief Patent Counsel Johnson & Johnson	Address (of agent or representative named in 1.e.) One Johnson & Johnson Plaza	
	City/State New Brunswick, NJ	
	ZIP Code 08933	FAX Number (if available) (732) 524-2138
	Telephone Number (732) 524-2368	E-Mail Address (if available) pjohnso4@corus.jnj.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Yes

**APPEARS THIS WAY
ON ORIGINAL**

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Laura A. Donnelly

June 14, 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Laura A. Donnelly

Address

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933

Telephone Number

(732) 524-1729

FAX Number (if available)

(732) 524-2808

E-Mail Address (if available)

jnjuspatent@corus.jnj.com
ldonnel2@corus.jnj.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/foahtm/foahtm.htm>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1e) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,878,717

b. Issue Date of Patent

4/12/05

c. Expiration Date of Patent

11/5/2019

d. Name of Patent Owner

Janssen Pharmaceutica, N.V.

Address (of Patent Owner)

TURNHOUTSEWEG 30

City/State

B2340 BEERSE

ZIP Code

BELGIUM

FAX Number (if available)

32 14 60 5491

Telephone Number

32 14 60 6737

E-Mail Address (if available)

jnintlpatent@corus.jnj.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Philip S. Johnson, Esq.
Chief Patent Counsel
Johnson & Johnson

Address (of agent or representative named in 1.e.)

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933

FAX Number (if available)

(732) 524-2138

Telephone Number

(732) 524-2368

E-Mail Address (if available)

pjohnso4@corus.jnj.com

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) 1-5 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) [TRADE NAME], co-administered with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patient.

/ / / / /

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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Date Signed

Laura A. Donnelly

June 14, 2007

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Laura A. Donnelly

Address

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933

Telephone Number

(732) 524-1729

FAX Number (if available)

(732) 524-2808

E-Mail Address (if available)

jnjuspatent@corus.jnj.com

ldonnel2@corus.jnj.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
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General Information

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- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahm/fdahm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 22-187

SUPPL #

HFD # 530

Trade Name Intelence

Generic Name etravirine

Applicant Name Tibotec, Inc

Approval Date, If Known Jan 17, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

I. 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?

five (5)

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

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

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

YES

NO

If yes, explain:

Name of person completing form: Anne Marie Russell, Ph.D.

Title: Regulatory Project Manager

Date: December 28, 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
1/8/2008 12:46:44 PM
NDA 22-187

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-187 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: July 18, 2007 PDUFA Goal Date: January 18, 2008

HFD 530 Trade and generic names/dosage form: Intelence (etravirine) 100 mg tablets

Applicant: Tibotec, Inc. Therapeutic Class: 7030240 (non-nucleoside reverse transcriptase inhibitor (nrti))

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 (one)

Indication #1: This new drug application provides for the use of Intelence™ (etravirine) 100 mg tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

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.
- XNo: 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 Birth kg mo. yr. Tanner Stage
Max 8 weeks 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: _____

We are waiving submission of pediatric studies in pediatric subjects from birth up to 8 weeks of age because etravirine is being approved for the treatment of HIV-1 in treatment-experienced patients.

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 2 months kg mo. X yr. Tanner Stage
Max 18 years kg mo. yr. X 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
- X Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): Two studies: June 2010 (6yo-18yo) and June 2013(2mos-6yo)

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.

NDA22-187

Page 3

**This page was completed by:
Anne Marie Russell, Ph.D. , Regulatory Project Manager
Division of Antiviral Products**

{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)

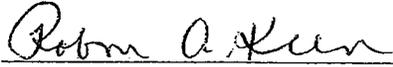
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Anne Marie Russell
1/15/2008 02:34:52 PM

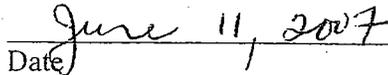
DEBARMENT CERTIFICATION

Tibotec, Inc. certifies that we 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.



Robin A. Keen

Sr. Director, Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-187	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Intelence™ Established Name: etravirine Dosage Form: tablet (100mg)		Applicant: Tibotec, Inc.
RPM: Anne Marie Russell, Ph.D.		Division: HFD-530 Phone # 301-796-2014
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p>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)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>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.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>
❖ User Fee Goal Date ❖ Action Goal Date (if different)		January 18, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> 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)		<input type="checkbox"/> Requested in AP letter <input checked="" type="checkbox"/> Received and reviewed 1/16/2008

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action (Susie Dill 301-443-5382) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action (Chris Kelly 301-827-6252) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Advisory Richard Klein/Office Special Health Issues

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

<p>within the 45-day period).</p> <p><i>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).</i></p> <p><i>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.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Office Director 1/18/08 Division Director 1/18/08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
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 container label
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS <input checked="" type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC <input checked="" type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews: RPM PLR format review <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	RPM Regulatory Filing Review and Memo of Filing Meeting
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> 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. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) • Incoming submission documenting commitment 	Received 1/17/08
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) • Pre-NDA/BLA meeting (<i>indicate date</i>) • EOP2 meeting (<i>indicate date</i>) • Other (e.g., EOP2a, CMC pilot programs) 	Meeting on 12/3/07, no meeting minutes <input type="checkbox"/> No mtg 6/1/07 <input type="checkbox"/> No mtg 6/15/05
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting • 48-hour alert or minutes, if available 	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Products Only Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	1/14/08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	See CMC review 1/14/08 N/A N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) 	Date completed: 1/7/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	1/15/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	Team leader memo 1/17/08 Clin review 1/17/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Included in clin review
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None OSE/hepatotoxicity 1/17/08 DDDP/Stevens-Johnson syndrome case 1/18/08
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 1/16/08
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	See clinical review
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	Included (4 sites)
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/15/08
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Team Leader memo 1/17/08 Pharmacometrics memo 1/18/08 ClinPharm Review 1/17/08

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/

Anne Marie Russell
1/18/2008 03:34:49 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 13, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: NDA 22-187 Clinical Pharmacology Request 9	

Total no. of pages including cover:

Comments: see next page

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 13, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Vikram Arya, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical
Pharmacology 4 (DCP4)
Charu Mullick, M.D., Clinical Reviewer, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Kellie Reynolds, Pharm.D, Deputy Director and Pharmacology Team Leader, DCP4

Subject: NDA 22-187 Clinical Pharmacology etravirine label Request 9

The following comment is being conveyed on behalf of the Dr. Vikram Arya, clinical pharmacology reviewer, and is directed towards your July 18, 2007 submission entitled "New Drug Application." for etravirine. Please provide a response by December 18, 2007.

The results of the drug-drug interaction studies between TMC125 and atazanavir/rtv and TMC125 and lopinavir/ritonavir showed that the mean systemic exposure (AUC) of TMC125 increased by 30 % and 17 % respectively. All subjects in DUET 1 and DUET 2 trials received darunavir/ritonavir as part of the background regimen which has been shown to reduce the mean systemic exposures of TMC125 by approximately 40 %. Hence, the systemic exposures of TMC125 (when co-administered with darunavir/ritonavir) for which safety data is available from the clinical trials are significantly lower than the systemic exposures of TMC125 observed in the drug-drug interaction trials with atazanavir/ritonavir and lopinavir/ritonavir.

Therefore, due to absence of safety data at the TMC125 exposures when co-administered with either atazanavir/ritonavir or lopinavir/ritonavir, the Division proposes the following labeling recommendations:

TMC125 and Atazanavir/Ritonavir:

/ / /

TMC125 and Lopinavir/Ritonavir:

/ / / /

Please inform the Division if additional safety data is available to support the co-administration of TMC125 and atazanavir/ritonavir and/or TMC125 and lopinavir/ritonavir or suggest alternate labeling language.

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 anne.russell@fda.hhs.gov or 301-796-2014 if you have any questions regarding the contents of this transmission.

Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: NDA 22-187 Stats Table 11 Request 8	

Total no. of pages including cover:

Comments: see next page

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 11, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Fraser Smith, Ph.D., Statistical Reviewer, Division of Biometrics IV (DBIV)
Charu Mullick, M.D., Clinical Reviewer, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Greg Soon, Ph.D., Statistical Team Leader, DBIV

Subject: NDA 22-187 Statistical Analysis Table 11 etravirine label Request 8

The following comments are being conveyed on behalf of the Division of Antiviral Products and the Division of Biometrics IV and are directed toward your July 18, 2007 submission entitled "New Drug Application." for etravirine. Please provide a response by December 18, 2007.

Please resolve the following discrepancies in Table 11 of the label entitled "Outcomes of Treatment at Week 24 of the DUET-1 and DUET-2 Trials (Pooled Analysis)" regarding placebo patients.

- a. For placebo subjects who discontinued before Week 24 due to virologic failures:
Discrepancy: Table 11 lists 3 placebo subjects and we identified the following 4 placebo subjects. Please provide the Unique Subject ID, Discontinuation Day and Reason for discontinuation for the placebo subjects who discontinued before Week 24 due to virologic failures, if different than those listed below.

Unique Subject ID	Discontinuation day	Reason for discontinuation
TMC125-C216-0051	150	Subject Reached a Virologic Endpoint
TMC125-C216-0070	129	Subject Reached a Virologic Endpoint
TMC125-C216-0615	143	Subject Reached a Virologic Endpoint
TMC125-C216-0881	153	Subject Reached a Virologic Endpoint

- b. For placebo subjects who discontinued before Week 24 due to other reasons:
 Discrepancy: Table 11 lists 11 placebo subjects and we identified the following 13 placebo subjects. Please provide the Unique Subject ID, Discontinuation Day and Reason for discontinuation for the placebo subjects who discontinued before Week 24 due to other reasons, if different than those listed below.

Unique Subject ID	Discontinuation day	reason for discontinuation
TMC125-C206-0080	91	Subject Withdrew Consent
TMC125-C206-0101	119	Subject Withdrew Consent
TMC125-C206-0193*	37	Subject Non-Compliant
TMC125-C206-0244	114	Subject Withdrew Consent
TMC125-C206-0266	153	Subject Withdrew Consent
TMC125-C206-0307	154	Subject Withdrew Consent
TMC125-C206-1056	137	Sponsor's Decision
TMC125-C216-0026	54	Subject Lost to Follow-up
TMC125-C216-0534	127	Subject Non-Compliant
TMC125-C216-0579	143	Subject Withdrew Consent
TMC125-C216-0862	123	Subject Withdrew Consent
TMC125-C216-0948	72	Subject Withdrew Consent
TMC125-C216-0963	119	Subject Withdrew Consent

*you possibly classified this patient TMC125-C206-0193 as a death.

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Anne Marie Russell, Ph.D.
 Regulatory Project Manager
 Division of Antiviral Products
 Office of Antimicrobial Products



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014

Subject: Trade name Intelence NDA 22-187 Request 7

Total no. of pages including cover:

Comments: see next page

Document to be mailed: NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

Date: December 11, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Charu Mullick, M.D., Clinical Reviewer, DAVP
Mark Seggel, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment/Division of Pre-Marketing Assessment II (ONDQA/DPAII)

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Norman Schmuff, Ph.D., Branch Chief, ONDQA/DPAII

Subject: NDA 22-187 Trade name Intelence Request 7

The following comments are being conveyed on behalf of the Division of Antiviral Products and the Office of New Drug Quality Assessment and are directed toward your July 18, 2007 submission entitled "New Drug Application." for etravirine and your May 7, 2007 submission (SN547) to IND 63,646 entitled "Tradename Consultation" requesting a review of the proposed proprietary name "INTELENCE". Please provide a response by December 18, 2007.

The Division of Drug Marketing, Advertising and Communications (DDMAC) finds the proprietary name, "Intelence" acceptable from a promotional perspective.

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proprietary name, "Intelence". DMETS considers this a final decision. However, if approval of this application is delayed beyond 90 days from the signature date of this review (December 7, 2007), then the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document. DMETS recommends implementation of the label and labeling revisions outlined below to minimize potential errors with the use of this product.

CONTAINER LABEL

1. The established name should be at least ½ the size of the proprietary name per 21 CFR 201.10 (g)(2).

2. Delete the statement "Each tablet contains 100 mg of etravirine", as it is redundant since the strength and established name already appear on the label.
3. At the end of the ALERT statement, add the phrase "... from your healthcare provider", to ensure patients know where to find this essential information.
4. We note there is a rectangle graphic at the bottom of the principle display panel and question what will be printed here and if the graphic will compete or deter from the readability of the proprietary and established names and strength?

PACKAGE INSERT LABELING

5. We do not recommend the use of the abbreviation — We recommend writing out the full word "kilocalorie" throughout the package insert.

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Microbiology labeling comments NDA 22-187 Request 6	

Total no. of pages including cover:

Comments: see next page

Document to be mailed: NO

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 30, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Lisa Naeger, Ph.D., Microbiology Reviewer, DAVP

Concur: Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Kendall Marcus, M.D., Medical Team Leader, DAVP

Subject: NDA 22-187 Microbiology labeling comments Request 6

The following comments are directed toward the microbiology portions of the September 27, 2007 version of the labeling submitted to your July 18, 2007 "New Drug Application." N22-187 for etravirine.

Comments on the Microbiology section of the label are provided below. The revised labeling for the microbiology portion of the label is provided below the comments. Please provide a response by December 18, 2007.

COMMENTS:

4 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH****CLINICAL INSPECTION SUMMARY**

DATE: December 4, 2007

TO: Anne Marie Russell, Regulatory Project Manager
Charu Mullick, 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: 22-187

APPLICANT: Tibotec, Inc.

DRUG: TMC 125 (entravirine) tablets

THERAPEUTIC CLASSIFICATION: Priority Review (6 months)

INDICATION: Treatment - experienced HIV-1 infected subjects.

CONSULTATION REQUEST DATE: June 6, 2007

DIVISION ACTION GOAL DATE: December 28, 2007

PDUFA DATE: January 18, 2008

I. BACKGROUND:

The review division requested inspection of protocols TMC 125-C206/C216: "A phase III randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability and safety of TMC 125 as part of an ART including TMC 114/RTV and an investigator-selected OBR in HIV-1 infected subjects with limited to no treatment options" The sponsor submitted results from the two protocols in support of NDA 22-187. The primary objective of the study was to show the superiority of TMC 125 to placebo as a part of an antiretroviral therapy (ART) containing TMC 125 and an investigator-selected optimized background (OBR), in the proportion of subjects with undetectable plasma viral loads values (< 50 copies/mL) at week

24 in treatment-experienced HIV-1 infected subjects. The inspections targeted four clinical investigators who enrolled a relatively large number of subjects. Two of the sites are foreign sites that conducted the study under protocol TMC 125- C206 (same as C216).

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Site #BR0006	Curitiba, Brazil	C206	9/17/07	11/29/07	NAI
Site# BR000Z/	Rio de Janeiro, Brazil	C206	9/10/07	11/29/07	NAI
Site# US00092	San Diego, CA	C206	8/6/07	8/24/07	VAI
site# US00176	Los Angeles, CA	C216	7/23/07	9/12/07	NAI

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) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol C 206

1. _____

At this site a total of 32 subjects were screened, 15 subjects were reported as screen failures, one subject was discontinued and 17 subjects were randomized. Fifteen (15) subjects were rolled over into the 96 weeks study. All subjects were verified to have signed informed consent prior to entry into the study. The medical records for 10 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events.

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.

2. _____

At this site a total of 71 subjects were screened, 34 subjects were reported as screen failures, subject C206-0993 experienced elevated albumin with Kaposi Sarcoma, received radiotherapy and was discontinued. 36 subjects were randomized and entered the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 12 subjects were reviewed in depth including drug accountability records and compared to case report forms and data listings for primary efficacy endpoint and adverse events. There was no underreporting of adverse events. Subject C206-0712 experienced grade 3 rash was hospitalized and discontinued treatment. Subject C206-0691 experienced convulsion received one dose of phenytoin and continued on the study. 27 of the 36 subjects randomized elected to continue on the extended phase of 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.

3.

At this site a total of 26 subjects were screened, 11 subjects were reported as screen failures, 3 subjects were discontinued, and 15 subjects were randomized. The medical records for 15 subjects were reviewed in depth including drug accountability records and compared to case report forms and data listings for efficacy endpoints and adverse events. The investigation found lack of documentation of the return of used and unused medication bottles for certain visits for subjects 0110, 0136, 0140, 0355, 0370 and 0600. The clinical investigator and staff acknowledged and agreed with the observations. All 15 subjects were verified to have signed informed consents prior to screening and randomization into the study. 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.

At this site a total of 27 subjects were screened, 4 subjects were reported as screen failures, 3 subjects were discontinued, 23 subjects were randomized, 2 subjects were transferred and one subject died due to myeloma. 12 subjects are currently on the study and 5 subjects were rolled over into the extension phase /arm of the study. The records for all subjects were verified to have signed informed consents prior to screening and randomization into the study. The medical records for 8 subjects were reviewed in depth including drug accountability records and compared to case report forms and data listing for primary efficacy endpoint and adverse events. 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 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 Drs. _____ revealed no significant problems that would adversely impact data acceptability. The data submitted from the inspected sites are acceptable in support of the pending application

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

CONCURRENCE:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Antoine El-Hage
12/13/2007 02:32:33 PM
PHARMACOLOGIST

Constance Lewin
12/13/2007 02:38:46 PM
MEDICAL OFFICER



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

FACSIMILE TRANSMITTAL SHEET

DATE: December 7, 2007

To: Wendy Mavroudakis Director, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Johnson and Johnson Pharmaceutical Research and Development, L.L.C.	Division of Antiviral Products
Fax number: (609) 730-2706	Fax number: (301) 796-9883
Phone number: (609) 730-3067	Phone number: (301) 796-2014

Subject: Chemistry Request for Information (Request number 5) NDA 22-187 DMF

Total no. of pages including cover:

Comments: see next page

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Division of Antiviral Products
Food and Drug Administration
Rockville, MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 7, 2007

To: Wendy Mavroudakis
Director, Global Regulatory Affairs

Address: 1125 Trenton-Harbourton Road Titusville, NJ 08560

From: Anne Marie Russell, Ph.D., Regulatory Project Manager

Through: Mark Seggel, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment/Division of Pre-Marketing Assessment II (ONDQA/DPAII)

Concur: Norman Schmuff, Ph.D, Branch Chief, ONDQA/DPAII

Subject: Chemistry Request for Information (Request number 5) DMF Number _____

The following comment is being conveyed on behalf of Dr. Mark Seggel, chemistry reviewer and is directed toward Tibotec's July 18, 2007 submission entitled "New Drug Application." for etravirine (TMC125), Drug Master File number _____ Please provide a response by December 17, 2007.

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 30, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Chemistry Request for Information (Request number 4) NDA 22-187	

Total no. of pages including cover:

Comments: see next page

Document to be mailed: NO

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 30, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager

Through: Sharmista Chatterjee, Ph.D., Chemistry Reviewer, Office of New Drug Quality
Assessment/Division of Pre-Marketing Assessment II (ONDQA/DPAII)

Concur: Norman Schmuff, Ph.D, Branch Chief, ONDQA/DPAII

Subject: NDA 22-187 Chemistry Request for Information (Request number 4)

The following comments are being conveyed on behalf of Dr. Sharmista Chatterjee, chemistry reviewer and are directed toward your July 18, 2007 submission entitled "New Drug Application." Please provide a response by December 14, 2007.

1. 
2.   
3. Account for the variability in values of mean dissolution at 60 minutes for tablets of 7.5 mm thickness between experiments 1 and 2 (refer table 14, section 3.2.P.2.3). For the mean dissolution values listed in this table, provide dissolution values for individual tablets.

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

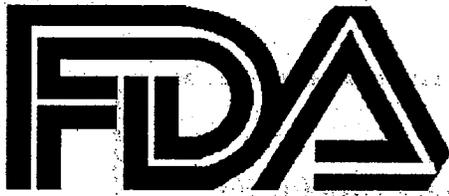
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/s/

Anne Marie Russell
11/30/2007 03:55:57 PM
CSO

fax sent 11/30/07

Norman Schmuff
12/3/2007 08:55:42 AM
CHEMIST



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 26, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Clinical Request for Information (Request number 3) NDA 22-187	

Total no. of pages including cover:

Comments: see next page

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 26, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Charu Mullick, M.D., Medical Officer, DAVP

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

Subject: NDA 22-187 Clinical Request for Information (Request number 3)

The following comment is being conveyed on behalf of Dr. Charu Mullick, clinical reviewer and is directed towards your July 18, 2007 submission entitled "New Drug Application." Please provide a response by November 28, 2007.

1. For patient Subject ID: GB-JNJFOC-20070704917 in TMC125 expanded access program, please provide all available information, specifically including:
 - a. Pathology report for liver biopsy.
 - b. All available clinical and laboratory data.
 - c. Medwatch report (form FDA 3500A).

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

Anne Marie Russell
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CSO

fax and email sent 11/26/07 4:20pm

Kendall Marcus
11/26/2007 04:27:18 PM
MEDICAL OFFICER



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

FACSIMILE TRANSMITTAL SHEET

DATE: November 9, 2007

To: Susan Fiordeliso Manager, Global Regulatory Affairs	From: Anne Marie Russell, Ph.D. Regulatory Project Manager
Company: Tibotec, Inc.	Division of Antiviral Products
Fax number: (609) 730-7501	Fax number: (301) 796-9883
Phone number: (609) 730-7546	Phone number: (301) 796-2014
Subject: Labeling Format NDA 22-187	

Total no. of pages including cover:

Comments: see next page

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MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 9, 2007

To: Susan Fiordeliso
Manager, Global Regulatory Affairs, Tibotec, Inc.

Address: 1020 Stony Hill Road, Suite 300
Yardley, PA 19067

From: Anne Marie Russell, Ph.D., Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Concur: Karen Winestock, Chief, Project Manager Staff, DAVP

Subject: NDA 22-187 Labeling format review

The following comments are directed toward the labeling format of the labeling submitted in your July 17, 2007 submission "New Drug Application."

Highlights:

1. The Highlights must be limited in length to one-half page, in 8 point type, two column format. [See 21 CFR 201.57(d)(8)].
2. The Patient Counseling Information statement must appear in Highlights and must read:
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Contents:

3. A horizontal line must separate the Highlights, Contents and FPI. [See 21 CFR 210.57(d)(2)].
4. The wording of the headings and all sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]. Specifically the following should read as below in both the Contents and FPI:
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
5. The following should read (note capitalization):
[*Sections or subsections omitted from the Full Prescribing Information are not listed]

Full Prescribing Information (FPI):

6. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g. 12.2.1 Central Nervous System). Use headings without numbering (e.g. Central Nervous System).

7. The section headings should be in all cap text, as should FULL PRESCRIBING INFORMATION
8. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance].
9. The section and subsection heading identifying numbers must precede the heading or subheading by at least two square em's (i.e. to squares of the size of the letter "m" in 8 point type).
10. Create a new subsection entitled **12.4 Microbiology** and consolidate all microbiology information in that section.

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Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

Anne Marie Russell
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Anne Marie Russell
11/9/2007 11:52:25 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-187 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: not yet established
Established Name: etravirine
Strengths: 100 mg tablet

Applicant: Tiboetc, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: 07/17/2007
Date of Receipt: 07/18/2007
Date clock started after UN: N/A
Date of Filing Meeting: 08/28/2007
Filing Date: 09/18/2007
Action Goal Date (optional): 01/2/2008 User Fee Goal Date: 01/18/2008

Indication(s) requested: Treatment of HIV infection

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.)

Form 3397 (User Fee Cover Sheet) submitted: 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 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:
- If yes, has OC/DMPQ been notified of the submission? 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/2353fml.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, 5 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-IO

- 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 – 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.

- List referenced IND numbers: 63,646, 75,084 (Expanded access)

- 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) 06/17/2005 (CMC) NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 06/01/2007 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ 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:

- 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? 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? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 08/28/2007

NDA #: 22-187

DRUG NAMES: etravirine (TMC125). Proprietary name not yet established.

APPLICANT: Tibotec, Inc.

BACKGROUND: Etravirine is a new molecular entity (NME) in the class of non-nucleoside reverse transcriptase inhibitors (nnrti) for treatment of HIV infection.

(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: Arya, Vikram; Chatterjee, Sharmista; DeCicco, Anthony W; Ghantous, Hanan; Jadhav, Pravin; Marcus, Kendall; Mullick, Charu; Naeger, Lisa; Nakanishi, Tamiji; O'Rear, Julian; Birnkrant, Debra B; Reynolds, Kellie S; Russell, Anne Marie; Schmuft, Norman R; Seggel, Mark R; Winestock, Karen; Wu, Kuei-Meng; Murray, Jeffrey S; Cox, Edward M; Roeder, David L; Smith, Fraser; Soon, Guoxing

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

Discipline/Organization

Reviewer

Medical:

Charu Mulick

Secondary Medical:

Statistical:

Fraser Smith

Pharmacology:

Kuei-Meng Wu

Statistical Pharmacology:

Chemistry:

Mark Seggel and Sharmista Chatterjee

Environmental Assessment (if needed):

Biopharmaceutical:

Vikram Arya and Pravin Jadhav

Microbiology, sterility:

Microbiology, clinical (for antimicrobial products only):

Lisa Nager

DSI:

Tony El-Hage

OPS:

Regulatory Project Management:

Anne Marie Russell

Other Consults:

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 _____

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 <input type="checkbox"/>	YES <input type="checkbox"/>	NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES			<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
• Sterile product?		YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
If yes, was microbiology consulted for validation of sterilization?		YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments: eCTD, rolling review

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.

Statistics: (not refuse-to-file issues)

1. Please clarify if copies of the laboratory source documents of HIV RNA-Amplicor, HIV RNA-Ultrasensitive and CD4± cell counts for studies TMC125-C206 and TMC125-C216 are available at the sites. If such documents are not available please describe:
 - a. How this information was communicated to the investigators and the sponsor.
 - b. How and where these original source documents are maintained.
2. Please provide the address and phone number of the central laboratory used for studies TMC125-C206 and TMC125-C216.
3. If external vendors were used to generate or manage the treatment allocation codes for studies TMC125-C206 and TMC125-C216, please provide their addresses and telephone numbers. In addition, please disclose to FDA any financial or partnering agreements between Tibotec and the external vendors.
4. Please send the original source documents of the treatment randomization schedules generated for each patient in studies TMC125-C206 and TMC125-C216 to FDA directly. If external vendors were used to generate or manage the treatment allocation codes for studies TMC125-C206 and TMC125-C216, please have the external vendors submit the following information to the FDA
 - a. The treatment allocation codes and information on when the vendors received/generated the original codes.
 - b. Certification that the documents are the original source documents and that the treatment allocation codes were generated/received on the date mentioned in part a (above) prior to study initiation.
5. Please submit all other source documents of treatment allocation codes (e.g., from your Clinical Pharmaceutical Operations or drug packaging group).
6. Please provide your standard operating procedures for randomization treatment code generation, unblinding and release of randomization codes, along with corresponding flow charts.

Anne Marie Russell, Ph.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/

Karen Winestock
10/24/2007 03:37:37 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63, 646

Tibotec, Inc.
Attention: Ms. Susan Fiordeliso,
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Ms. Fiordeliso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC125.

We refer to your March 23, 2007 submission (SN523) requesting a Pre-NDA meeting (Type B). We also refer to your April 27, 2007 submission (SN543) containing meeting background information and questions.

We further refer to our pre-meeting correspondence provided via telephone facsimile on May 18, 2007 which contained our initial responses to the questions submitted in your meeting background package, as well as our post-meeting correspondence provided via telephone facsimile on June 11, 2007 which contained comments as agreed during the meeting.

The purpose of this Type B Pre-NDA meeting was to discuss the proposed content and format of your planned New Drug Application (NDA). The date of this meeting was June 1, 2007.

The official minutes of the meeting are enclosed, including pre and post-meeting communications. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Anne Marie Russell, Ph.D., Regulatory Health Project Manager, at (301) 796-2014.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: June 01, 2007
TIME: 1:00 p.m. – 3:00 p.m. Eastern Daylight Savings Time
APPLICATION: 63,646
DRUG NAME: TMC125 (etravirine)
TYPE OF MEETING: Pre-NDA Type B Meeting: face-to-face

FDA ATTENDEES:

Office of Antimicrobial Products:

Ed Cox, M.D. Director

Office of Antimicrobial Products, Division of Antiviral Products:

Debra Birnkrant, M.D. Director
Jeff Murray, M.D., MPH Deputy Director
Kendall Marcus, M.D. Medical Team Leader
Charu Mullick, M.D. Medical Reviewer
Kimberly Struble, Pharm.D. Medical Team Leader
Kirk Chan-Tack, M.D. Medical Reviewer
Victoria Tyson-Medlock Acting Chief Project Management Staff
Anne Marie Russell, Ph.D. Regulatory Health Project Manager
Kuei-Meng Wu, Ph.D. Pharmacology/Toxicology Reviewer
Jules O'Rear, Ph.D. Microbiology Team Leader
Lisa Naeger, Ph.D. Microbiology Reviewer

Office of Biostatistics, Division of Biometrics IV:

Greg Soon, Ph.D. Statistical Team Leader
Fraser Smith, Ph.D. Statistical Reviewer

Office of Clinical Pharmacology:

Pravin Jadhav, Ph.D. Pharmacometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology 4:

Kellie Reynolds, Pharm.D. Deputy Director
Vikram Arya, Ph.D. Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment, Division of Pre-Marketing Assessment II:

Steve Miller, Ph.D. Pharmaceutical Assessment Lead

EXTERNAL CONSTITUENT ATTENDEES:

Benny Baeten, M.Sc. Vice President, Compound Development
Marie-Pierre de Bethune Vice President, Clinical Virology
Goedele De Smedt Director, Medical
Susan Fiordeliso Manager, Global Regulatory Affairs
Katrien Janssen, M.Sc. Scientist, Biostatistics
Mark Janssens Scientist, Biostatistics

Luc Janssens, Ph.D.	Senior Director, Global Regulatory Affairs
Thomas Kakuda, Pharm.D.	Director, Human Pharmacokinetics
Robin Keen	Senior Director, Global Regulatory Affairs
Jasmine Kestemont, M.Sc.	Assistant Director, Data Management
Ruud Leemans	Senior Director, Global Chemical and Pharmaceutical Dev
Ward Lemaire	Lead data manager DUET trials, Data Management
Diego Miralles, M.D.	Vice President, Medical
Lieve Molenaers	Senior Director, Global Regulatory Affairs
Monika Peeters, M.Sc.	Director, Biostatistics
Araz Raof	Senior Director, Global Preclinical Development
Karin Van Baelen, Pharm.D.	Vice President, Global Regulatory Affairs
Johan Vingerhoets, Ph.D.	Principal Scientist, Clinical Virology
Brian Woodfall, M.D.	Senior Director, Medical

BACKGROUND:

Tibotec requested a Pre-NDA meeting in submission SN523, dated March 23, 2007, received March 26, 2007. The purpose of the meeting was to discuss the format and content of the planned New Drug Application (NDA). The background package was submitted in submission SN543, dated April 27, 2007, received April 30, 2007.

On May 18, 2007, DAVP provided initial responses to all questions via telephone facsimile. The meeting was held on June 1, 2007.

DISCUSSION POINTS:

Agreement was reached by means of pre-meeting communications for most questions. The outstanding issues were discussed during the meeting after a slide presentation by Tibotec.

Below the original questions in the background package are listed, followed by pre-meeting communications and teleconference minutes. For clarity, Tibotec pre-meeting communications are in **bold text** and DAVP pre-meeting communications are in normal text. Meeting minutes are in *italicized text*.

1. **Does the Division agree that the 24-week efficacy analysis of DUET-1 and DUET-2 represent two independent, adequate and well-controlled studies supporting the filing and review of the accelerated approval NDA for TMC125?**

DAVP response: DUET-1 and DUET-2 represent two independent, adequate and well-controlled studies that support the submission of an NDA for TMC125 for review for accelerated approval.

2. **Does the Division agree that the proposed indication, as written in section 1.3 of this document, is supported by the data of DUET-1 and DUET-2?**

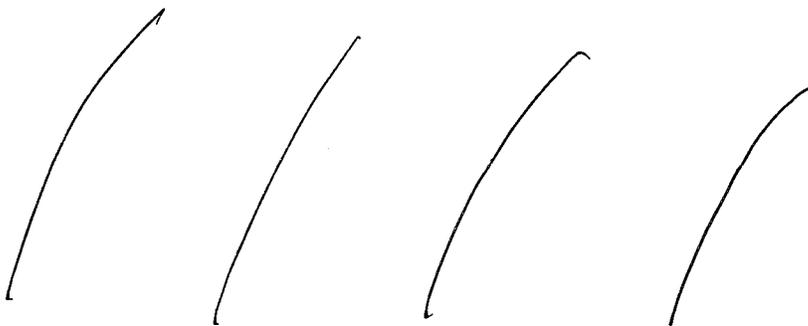
DAVP response: The Division believes that discussions regarding proposed indications are premature. However, please be aware that any proposed indication should accurately reflect the population in which the drug has been evaluated. Please refer to USPIs recently approved for drugs evaluated in treatment-experienced subjects.

Meeting: Tibotec inquired if the Division would consider an indication. The Division replied that the indication must reflect the population studied in DUET-1 and DUET-2 and they would be willing to look at other trial designs to study other populations.

3. **Transmission of drug-resistant HIV leading to suboptimal virologic responses has been documented and there is evidence of increasing rates of drug resistance among newly diagnosed patients both in Europe and the United States. This has led to the recommendation to perform resistance testing before selecting the initial treatment regimen. In view of the efficacy data from our Phase III clinical trials (DUET), specifically in patients with documented NNRTI resistance, TMC125 may represent a viable treatment option. How might the potential role of TMC125 in this setting be reflected in the proposed United States Package Insert (USPI)?**

DAVP response:

- a. The Division does not agree that TMC125 has a role



- b. We would like to remind you that we expect your NDA submission to include a final study report and datasets, including resistance data, for study TMC125-C227.

4. **Does the Division agree that the 24-week pooled safety analysis of DUET-1 and DUET-2 support the filing and review of the accelerated approval NDA for TMC125?**

DAVP response: Please be aware that the Division expects an Integrated Summary of Safety (ISS) to be included in your NDA. The ISS should contain an integrated review of all subjects who received the selected dose (200 mg bid of F060) or a similar dose (800 mg bid of F035), including those subjects enrolled in dose-finding Phase 2 studies.

Meeting: Tibotec indicated agreement with the Division's response and inquired if the selected dose or all doses were of interest. The Division replied that both would be of interest. Tibotec said that the Summary of Clinical Safety portion of the eCTD format will include all components of the ISS.