

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202022Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: April 1, 2011

To: NDA 202-022

From: Terrance Ocheltree, Ph.D., R. Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 202-022, Rilpivirine 25 mg tablet.

I have assessed the ONDQA reviews of NDA 202-022 by Maotang Zhou, Ph.D. and Celia Cruz, Ph.D., and by Tien-Mien Chen, Ph.D. The ONDQA CMC review for this product was finalized on March 28, 2011 and the ONDQA Biopharmaceutics review was completed on March 03, 2011 with an addendum on March 28, 2011. ONDQA recommends **Approval** of this NDA, pending submission of the agreed upon revision to the final labeling.

The March 03, 2011 ONDQA Biopharm review states that the dissolution method was acceptable, but that the dissolution acceptance criteria requires revision. Tibotec submitted the revised dissolution acceptance criteria on March 28 and the ONDQA Biopharm review was amended on March 28, 2011 stating that both the dissolution method and acceptance criteria are acceptable.

The drug substance portion of the NDA was referenced to DMF 23824 (Rilpivirine Hydrochloride) by Janssen Pharmaceutica. This DMF was determined to be Adequate to support this NDA on March 28, 2011.

Rilpivirine 25 mg tablet is an immediate release white, round biconvex, film-coated tablet containing 27.5 mg of rilpivirine hydrochloride (equivalent to 25.0 mg of rilpivirine). The table is film coated for elegance purposes only and is debossed with "25" on one side and "TMC" on the other side. The storage requirements for rilpivirine tablets is "Store at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F). Store in original bottle in order to protect from light". The recommendation to store in original bottle in order to protect from light is also included in the patient information and label text. A 30 month expiry period is recommended based on the submitted stability data and evidence that the potential genotoxic impurity, (b) (4), is adequately controlled in the drug substance synthesis process. A Quality Control Strategy has been developed and is outlined in the Executive Summary of the CMC review.

All manufacturing and testing facilities have acceptable site recommendations as of April 1, 2011, based on the Overall Recommendation made on January 25, 2011.

No post marketing commitments are proposed by ONDQA.

I concur with the "Approval" recommendation from an ONDQA perspective and the absence of ONDQA related post marketing commitments.

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

/s/

TERRANCE W OCHELTREE
04/01/2011

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 202022/000	Sponsor:	TIBOTEC
Code:	530		1125 TRENTON-HARBOURTON RD
Priority:	1		TITUSVILLE, NJ 08580
Stamp Date:	23-JUL-2010	Brand Name:	(b) (4)
PDUFA Date:	23-MAY-2011	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	24-MAR-2011	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; RILPIVIRINE; 25MG
FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	D. MATECKA	Team Leader	301-796-1415

Overall Recommendation: ACCEPTABLE on 25-JAN-2011 by M. STOCK (HFD-320) 301-796-4753

Establishment: CFN: 9614770 FEI: 3003164454
 JANSSEN - CILAG S.P.A.
 4010 BORGO SAN MICHELE
 BORGO SAN MICHELE, LT, ITALY

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-DEC-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9610028 FEI: 3002807336
 JANSSEN PHARMACEUTICA N.V.
 TURNHOUTSEWEG 30
 BEERSE, , BELGIUM

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER
 FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO"
 (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-AUG-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9610034 FEI: 3002807337
JANSSEN PHARMACEUTICA N.V.
JANSSEN PHARMACETICALAAN 3
GEEL, , BELGIUM
DMF No: 23824 **AADA:** I 067699
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-JAN-2011
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9611011 FEI: 3002807361
JANSSEN PHARMACEUTICAL, LTD.
LITTLE ISLAND
CORK, , IRELAND
DMF No: 23824 **AADA:** I 067699
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-AUG-2010
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3003445146
JOHNSON & JOHNSON LIMITED, DBA APDC
HIGI HOUSE OP RALLIWOLF LBS MARG
MUMBAI, MAHARASHTRA, INDIA
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-NOV-2010
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

NDA 202-022

TRADE NAME™, Rilpivirine, 25 mg Tablets

Tibotec, Inc.

Maotang Zhou, Ph.D.

Celia N. Cruz, Ph.D.

Division of New Drug Quality Assessment II

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Chemistry Review Data Sheet

1. NDA 202-022
2. REVIEW #1
3. REVIEW DATE: 28 Mar 2011
4. REVIEWER: Maotang Zhou and Celia N. Cruz
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission Telephone Amendment	23-July-2010
IND 67,699 Advice/Information Request	20-May-2010
IND 67,699 Type C Meeting Minutes	24-Feb-2010
IND 67,699 SN 164 EOP2 Comments	18-Oct-2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission Telephone Amendment	23-July-2010
Quality/Quality Information	25-Aug-2010
Quality/Stability Information	28-Oct-2010
Quality/Response to Information Request	22-Dec-2010
Labeling/Package-Insert Draft/Container-Carton	23-Feb-2010
Quality/Quality Response to Information Request	25-Feb-2010
Quality/Quality Response to Information Request	17-Mar-2011
Quality/Quality Response to Information Request	25-Mar-2011

7. NAME & ADDRESS OF APPLICANT:

Tibotec, Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560
Tel. 609-730-2000
Fax. 609-730-7501

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (USAN): rilpivirine and rilpivirine hydrochloride

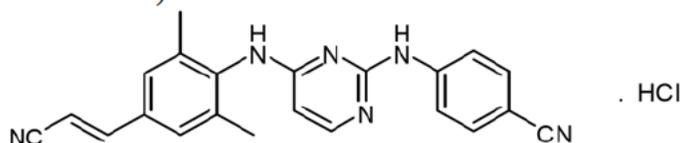
Chemistry Review Data Sheet

c) Code Name/#: N/A

Chem Type/Submission Priority: 1/S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOLOGICAL CATEGORY: Antiretroviral
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 25 mg per tablet
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): N/A
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
4-[[4-[[4-(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2 pyrimidinyl]amino] benzonitrile monohydrochloride
 $C_{22}H_{18}N_6 \cdot HCl$
MW: 402.88 (366.42 + 36.46)



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENT
23824	II	Janssen Pharmaceutica, N.V.	Rilpivirine Hydrochloride (R314585)	1	Adequate	03-28-2010 M. Zhou	N/A
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	10-19-2010 C. Cruz	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	N/A

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67699	Orig-1

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	25 Jan 2011	M. Stock
Pharm/Tox	N/A		
Biopharm	Update specification to Q = ^{(b) (4)} in 45 minutes	02 Mar 2011	T.M. Chen
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	N/A		
Microbiology	N/A		

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW

N/A

The Chemistry Review for NDA 202-022

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The Sponsor has agreed to all CMC labeling changes proposed. Therefore, from the CMC perspective, this NDA is recommended for approval, pending submission of final labeling documenting agreed-upon revisions to the bottle label and package insert.

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

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Substance

TMC278 (rilpivirine, RPV), a diarylpyrimidine derivative, is a potent nonnucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1). TMC278, in combination with other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients.

The drug substance, rilpivirine (TMC278), is a hydrochloride salt and is a white to off-white powder in appearance. It is practically insoluble in water and in many common organic solvents, but soluble in polar non-protic solvents. The molecule does not have stereogenic centers. (b) (4) The (b) (4)

The manufacturing process for rilpivirine drug substance is described in Janssen Pharmaceutica's DMF 23824. A letter of authorization (LOA) is included in the NDA application. The DMF has been reviewed and found adequate as revised.

Executive Summary Section

The manufacturing process consists of [REDACTED] (b) (4)

The structure of rilpivirine was derived from its synthesis and elemental and spectral analyses (UV, IR, NMR and MS), and was confirmed by a single crystal X-ray diffraction data.

The specification includes tests for appearance, identity, assay, impurities, residual solvents, particle size, residue on ignition, water, and heavy metals. As per pre-NDA agreement between the Agency and the sponsor, the genotoxic impurity [REDACTED] (b) (4) is not specified in the drug substance specification, [REDACTED] (b) (4). In order to assure the robustness of the purification process, the DMF holder agrees to test for [REDACTED] (b) (4) as part of the stability monitoring program (i.e., one commercial batch per year, if manufactured).

Rilpivirine drug substance is packaged in closed, [REDACTED] (b) (4) with a secure fitting lid.

The primary stability data for the drug substance stored under the long-term (25 °C/60% RH and 30 °C/75% RH) storage conditions for 36 months and the accelerated (40 °C/ 75%RH) storage condition for 6 months show no trend in degradation and no apparent changes in other test results. However, one specified impurity [REDACTED] (b) (4) is observed at levels of [REDACTED] (b) (4) w/w under the ICH light condition. Based on the evaluation of the stability data, the proposed retest period of [REDACTED] (b) (4) months under the storage condition of “Store in the original container in order to protect from light” is supported.

2) Drug Product

The commercial dosage form is a white, round biconvex, film-coated tablet containing 27.5 mg of rilpivirine hydrochloride, which is equivalent to 25.0 mg of rilpivirine. The tablet is designed for immediate release and the coating is for elegance purposes only. Each tablet is 6.4 mm in diameter and debossed with “25” on Side 1, and “TMC” on Side 2. The packaging configuration available is a month supply, or 30 count, in a 75 ml HDPE bottle with [REDACTED] (b) (4) child resistant closure. The bottle has a foil induction seal.

Each tablet contains the inactive ingredients croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. All core tablet excipients are compendial and within approved quantities for oral dosage. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, PEG 3000, titanium dioxide and triacetin. All the ingredients in the film coat powder mixture are compendial and appropriate for its intended purpose.

The Rilpivirine 25 mg Tablet manufacturing process is [REDACTED] (b) (4)

Executive Summary Section

(b) (4)

The critical processing steps for Rilpivirine 25 mg Tablets are

(b) (4)

The proven acceptable ranges for compression were demonstrated by

(b) (4)

The proposed tablet hardness ranges were confirmed to give acceptable tablet quality, including dissolution profiles, for the range of properties and compression parameters. The data supports the use of tablet hardness, tablet weight, and appearance as critical in-process controls for compression.

The specifications for the Rilpivirine 25 mg Tablets include appearance, identification, assay, chromatographic purity (any unspecified degradation product and total degradation products), uniformity of dosage units (content uniformity), and dissolution. Shelf life specifications include microbiological purity, in addition to the release specifications. The identification method is specific to the rilpivirine hydrochloride form. Finally, the chromatography methods for assay/purity, for content uniformity and for dissolution are satisfactory and appropriately validated.

Based on biopharmaceutical assessment, an updated dissolution specification of $Q =$ at 45 minutes was concluded to be more appropriate and justified by the data. The dissolution method was found acceptable and properly validated.

At time of this review, 24 months of stability data for three full scale batches were submitted at 30 °C/75% RH and 25 °C/60% RH. In addition, 6 months at 40 °C/75% RH and 3 months at 50 °C were submitted as accelerated data. There are no new impurities or degradants in the drug product, other than synthesis impurities. The synthesis impurities are adequately controlled in the drug substance manufacture and do not grow upon storage. In particular, the potential genotoxic impurity has been shown to be adequately controlled in the drug substance process and is shown to not grow significantly upon storage of drug product.

Given that our recommended dissolution specification is $Q =$ at 45 minutes and that there is a statistically significant decrease in dissolution at all conditions with possibility of failures at 30 °C/ 75% RH, we conclude and recommend that the data supports a 30 month shelf life for

Executive Summary Section

Climatic Zones I and II (as supported by the 25 °C/60% RH data) (b) (4)

(b) (4) This is given in context with the currently available stability data and analysis, including the submitted predictions for (b) (4). Therefore, a 30 month expiry is recommended for approval in the US market. (b) (4)

The primary stability study will be continued for 36 months and extension of expiry can be established with additional data and analysis. Finally, a commitment exists to place the first three commercial batches on stability for 36 months at 30 °C/ 75% RH with an additional annual stability program of one commercial lot per year.

The drug substance and drug product are sensitive to light exposure, with synthesis impurities (b) (4) growing slightly under ICH confirmatory light conditions. Overall, under typical indoor lighting, the current package provides sufficient protection against photo degradation. The instruction to “Store in original bottle in order to protect from light” is included in the bottle label and the label text. Also, the evaluation of impurity growth due to light exposure is recommended for future evaluations of primary packaging changes impacting light protection, given that the bottle is the primary source of protection against photo degradation.

The primary container is a 75 ml-HDPE bottle with a (b) (4) child resistant closure and a foil induction seal. There is no secondary packaging. The bottle properties have been qualified and include a maximum light transmission specification to assure protection against photo degradation under typical storage conditions. The package has been shown to be suitable for protection of the drug product for long term storage.

The label storage instructions states “Store at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F). Store in original bottle in order to protect from light”. This labeling storage instruction is justified by the stability data and primary packaging information presented in the application.

3) Quality Control Strategy

The overall control strategy to assure quality for Rilpivirine Tablets 25 mg is comprised of the following elements:

- a. Control of drug substance quality attributes by
 - i. The use of critical process parameters ranges and in process testing specifications (see DMF 23824).
 - ii. Release testing of drug substance lots for appearance, identity, assay, impurities, residual solvents, particle size, residue on ignition, and heavy metals.
 - iii. Inclusion of water content for drug substance in the stability monitoring program (see DMF 23824).

Executive Summary Section

- iv. Inclusion of “Store in original container to protect form light” in the drug substance container label (see DMF 23824).
- b. Control of drug product critical quality attributes by
 - i. The use of (b) (4) critical process parameters (b) (4) and critical in-process tests (b) (4) tablet hardness, tablet appearance and tablet weight).
 - ii. Release testing of drug product batches for appearance, identity, assay, chromatographic purity, dose uniformity, and dissolution.
 - iii. Inclusion of microbial purity testing for drug product in the marketed stability monitoring program.
 - iv. Inclusion of “store in original bottle to protect from light” in the drug product container label.
 - c. Control of the genotoxic impurity (b) (4) by
 - i. Monitoring as part of the specification (b) (4) Refer to DMF 23824.
 - ii. Inclusion of (b) (4) testing at the initial time point as part of the drug substance stability monitoring program
 - iii. Inclusion of (b) (4) in drug product marketed stability protocol for the first three commercial batches.
 - iv. A commitment that any future changes to primary packaging which could significantly reduce the protection from light, will include testing for (b) (4) levels in photo stability studies following ICH Q2B.

B. Description of How the Drug Product is Intended to be Used

The recommended dose of Rilpivirine is one 25 mg tablet taken once daily, with a meal.

Currently, the storage requirements state “Store at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F). Store in original bottle in order to protect from light”. The recommendation to store in original bottle in order to protect from light is also included in the patient information and label text. It is expected that the dispensing environments will be retail and hospital pharmacy, with use environments in patient’s home or inpatient care.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw materials controls, specifications, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. As of March 25, 2011, the applicant agreed to all CMC-related changes to the labeling and will submit a final bottle label and insert prior to approval.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block****C. CC Block**

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/s/

CELIA CRUZ
03/28/2011

MAOTANG ZHOU
03/28/2011

STEPHEN P MILLER
03/28/2011

I concur - this NDA is recommended for approval from the CMC perspective, pending submission of final agreed-upon labeling

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

Filing Checklist

NDA Number: 202-022 Supplement Number and Type: Established/Proper Name: *To be established** (rilpivirine tablets), 25 mg

Applicant: Tibotec Letter Date: 23-Jul-2010 Stamp Date: 23-Jul-2010

* Two proprietary names have been proposed via 25-Aug-2010 amendment: (b) (4) as an alternate name

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	✓		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	✓		
3.	Are all the pages in the CMC section legible?	✓		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	✓		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	✓		Updated list submitted via amendment dated 25-Aug-2010
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR NDA/BLA or Supplement

7.	<p>Are drug substances manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Updated info submitted via amendment dated 25-Aug-2010</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		<p>Updated info submitted via amendment dated 25-Aug-2010</p>

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	✓		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	✓		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	✓		

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?			For all CMC drug substance information cross-reference is provided to DMF Type II 023824.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			See above
14.	Does the section contain information regarding the characterization of the DS?	✓		See above
15.	Does the section contain controls for the DS?	✓		See above
16.	Has stability data and analysis been provided for the drug substance?			See above
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			See above
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			See above

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	✓		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	✓		
21.	Is there a batch production record and a proposed master batch record?	✓		Per agreement at the 20-Jan-2010 meeting, executed production records for one registration stability batch are provided.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	✓		
23.	Have any biowaivers been requested?		✓	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	✓		
25.	Does the section contain controls of the final drug product?	✓		
26.	Has stability data and analysis been provided to support the requested expiration date?	✓		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			DOE experiments in the formulation and manufacturing process development
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	✓		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	✓		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
023824	II	Janssen Pharmaceutica, N.V.	TMC278 Drug Substance	19-Jul-2010	Electronic submission
(b) (4)	III	(b) (4)	(b) (4)	09-Jun-2010	
	III			16-Sep-2010	
	III			16-Sep-2010	
	III			16-Sep-2010	
	III			17-Sep-2010	
	III			16-Sep-2010	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	✓		
33.	Have the immediate container and carton labels been provided?	✓		Bottle labels provided; use of carton is not proposed.

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	✓		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	✓		
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		✓	Not yet identified.

{See appended electronic signature page}

Dorota Matecka
Acting CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Stephen Miller
Acting Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-202022	ORIG-1	TIBOTEC INC	TMC278

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

/s/

DOROTA M MATECKA
08/29/2010

STEPHEN P MILLER
08/30/2010