CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202276Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 17, 2012

TO: NDA 202-276 CMC Review # 1

FROM: Hamid R. Shafiei, Ph.D., CMC Reviewer
(ONDQA/Division II/Branch IV)

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief
(ONDQA/Division II/Branch IV)

SUBJECT: Final CMC Recommendation

In review # 1 of NDA 202-276, this NDA was not recommended for approval from the CMC perspective due to the following reasons:

1) The executed batch record provided in the NDA was from a small scale manufacturing process that did not adequately reflect the proposed set points for critical process parameters that were identified and recommended for commercial manufacturing of avanafil tablets
2) CMC related label/labeling issues were not resolved
3) An overall recommendation of "Acceptable" from the Office of Compliance regarding the facilities involved in this NDA was not yet issued

The applicant has submitted an amendment on March 19, 2012 that includes a master batch record that fully reflects the proposed set points for the critical process parameters identified and recommended for the large scale commercial manufacturing of the avanafil tablets.

The CMC label/labeling issues have been resolved via the amendments dated March 13, 2012 and April 11, 2012. This drug product is intended for marketing in the United States under the trade name "Stendra" (see the **Attachment -2**).

The Office of Compliance has also made an overall recommendation of "Acceptable" for the facilities involved in this NDA on April 17, 2012 (see the **Attachment-1**).

Therefore, this NDA is now recommended for **approval** from the ONDQA perspective.

Appendix

Attachement-1

EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202276/000	**Action Goal:**	
Stamp Date:	29-JUN-2011	**District Goal:**	
Regulatory:	29-APR-2012		
Applicant:	VIVUS	**Brand Name:**	(b) (4) AVANAFIL)
	1172 CASTRO ST	**Estab. Name:**	
	MOUNTAIN VIEW, CA 94040	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	580	001; TABLET; AVANAFIL; 50MG 002; TABLET; AVANAFIL; 100MG 003; TABLET; AVANAFIL; 200MG	
Application Comment:			

FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	H. SHAFIEI	Review Chemist	3017962326
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 17-APR-2012	by D. SMITH	(HFD-323)	3017969643
	PENDING	on 15-JUL-2011	by EES_PROD		

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) (b) (4) FEI: (b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING INTO BLISTER CARDS, BOTTLES, LABELING (on 11-JUL-2011 by R. MCKNIGHT () 3017961765)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
OC RECOMMENDATION	15-JUL-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Establishment Comment: (b) (4)
(on 13-JUL-2011 by D. CHRISTNER () 3017961341)
MANUFACTURING, IN-PROCESS TESTING, BULK TABLET TESTING AND PACKAGING SITE (on 11-JUL-2011 by R. MCKNIGHT () 3017961765)
Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
SUBMITTED TO DO	15-JUL-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-JUL-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	30-SEP-2011		28-OCT-2011		IRIVERA
INSPECTION PERFORMED	28-OCT-2011		28-OCT-2011		IRIVERA
UNDER REVIEW	09-JAN-2012				STOCKM
NOT YET ASSIGNED TO CSO YET; IN QUEUE FOR REVIEW					
DO RECOMMENDATION	09-APR-2012			ACCEPTABLE	STOCKM
PAI ENDING ON 10/28/2011 WAS CLASSIFIED VAI.				INSPECTION	
OC RECOMMENDATION	09-APR-2012			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Establishment Comment: (b) (4)
(b) (4)
Profile: **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
SUBMITTED TO DO	15-JUL-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	15-JUL-2011	GMP Inspection			PHILPYE
INSPECTION SCHEDULED	30-SEP-2011		03-NOV-2011		IRIVERA
INSPECTION PERFORMED	03-NOV-2011		03-NOV-2011		RUSSELL.RILEY

I conducted this inspection of a finished drug product and API manufacturer per FACTS ID 7149648. It was a pre-approval inspection for NDA 202276 (b) (4) Avanafil) tablets for Erectile Dysfunction that was initiated by CDER (HFD-325) and DFFI. This facility intends to manufacture the API for the NDA sponsor, VIVUS, Inc. of Mountain View, CA, as described under DMF (b) (4)

The inspection was comprehensive in scope. Although the facility manufactures sterile injectable drugs, capsules, tablets, granules, and powders, only one of the APIs it manufactures (b) (4) is currently exported to the US - (b) (4) During my inspection I followed Compliance Programs 7346.832 (Pre-Approval Inspections) and 7356.002F (Active Pharmaceutical Ingredients). My coverage of the latter included the Quality, Laboratory, Production, and Facilities and Equipment systems, plus the Materials system to a limited extent. I did not cover the Packaging and Labeling system.

On 10/31/2011 I showed my credentials to (b) (4) because he is the most responsible person at this facility.

The previous inspection of this facility occurred (b) (4) and was a pre-approval inspection regarding changes to the facility's production of (b) (4) The inspection did not result in an FDA-483 but one concern was discussed: (b) (4) (b) (4) Although I did not find anything objectionable in the current inspection about the firm's (b) (4) I did discuss with the firm its (b) (4) (b) (4) The classification of the previous inspection was not available.

My inspection of this facility resulted in an FDA-483 with four observations:
- Data of failing the assay specification during stability testing for a lot of Avanafil API was not recorded anywh

UNDER REVIEW	09-JAN-2012				STOCKM
CSO NOT YET ASSIGNED; EIR IS IN QUEUE FOR REVIEW					
DO RECOMMENDATION	16-APR-2012			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	17-APR-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SMITHDE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING INTO BLISTER CARDS, LABELING (on 11-JUL-2011 by R. MCKNIGHT () 3017961765)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
OC RECOMMENDATION	15-JUL-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Establishment Comment: PACKAGING INTO BOTTLES, LABELING (on 11-JUL-2011 by R. MCKNIGHT () 3017961765)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
OC RECOMMENDATION	15-JUL-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** [redacted] **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Establishment Comment:

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

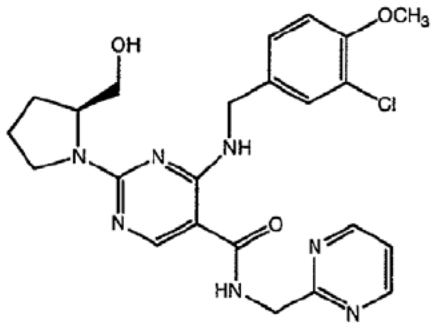
Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	15-JUL-2011				MCKNIGHTR
SUBMITTED TO DO	15-JUL-2011	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	18-JUL-2011	Product Specific			WMILLAR
INSPECTION SCHEDULED	26-JUL-2011				WMILLAR
INSPECTION PERFORMED	18-AUG-2011		18-AUG-2011		WMILLAR
3-ITEM 483: NOT FOLLOWING SOP, LACK OF ACCESS LIMITATION AND AUDIT TRAIL FOR HPLC SOFTWARE, AND TRAINING NOT PROVIDED FOR CONTRACTOR.					
DO RECOMMENDATION	22-AUG-2011			ACCEPTABLE	WMILLAR
PAI ACCEPTABLE. 3-ITEM 483 FOR GMP; NOT FOLLOWING SOP, LACK OF ACCESS LIMITATION AND AUDIT TRAIL FOR HPLC SOFTWARE, TRAINING NOT PROVIDED FOR CONTRACTOR.				INSPECTION	
OC RECOMMENDATION	24-AUG-2011			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

Attachment-2

1) Final labeling (Description and How Supplied sections)
The applicant has submitted an interim labeling on March 13, 2012 addressing all CMC labeling issues that were documented in CMC review #1 of this NDA.

DESCRIPTION

STENDRA is a selective inhibitor of cGMP specific PDE5. (b) (4) is designated chemically as (S)-4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide and has the following structural formula:



Avanafil occurs as white crystalline powder, molecular formula $C_{23}H_{26}ClN_7O_3$ and molecular weight of 483.95 and is slightly soluble in ethanol, practically insoluble in water, soluble in 0.1 mol/L hydrochloric acid. STENDRA, for oral administration, is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with dosage strengths. In addition to the active ingredient, avanafil, each tablet contains the following inactive ingredients: mannitol, fumaric acid, hydroxypropylcellulose, low substituted hydroxypropylcellulose, calcium carbonate, magnesium stearate, and ferric oxide yellow.

How Supplied

STENDRA (avanafil) is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with strengths.

	50 mg	100 mg	200 mg
Bottle of 30	NDC 62541-301-30	NDC 62541-302-30	NDC 62541-303-30
Bottle of 100	NDC 62541-301-01	NDC 62541-302-01	NDC 62541-303-01

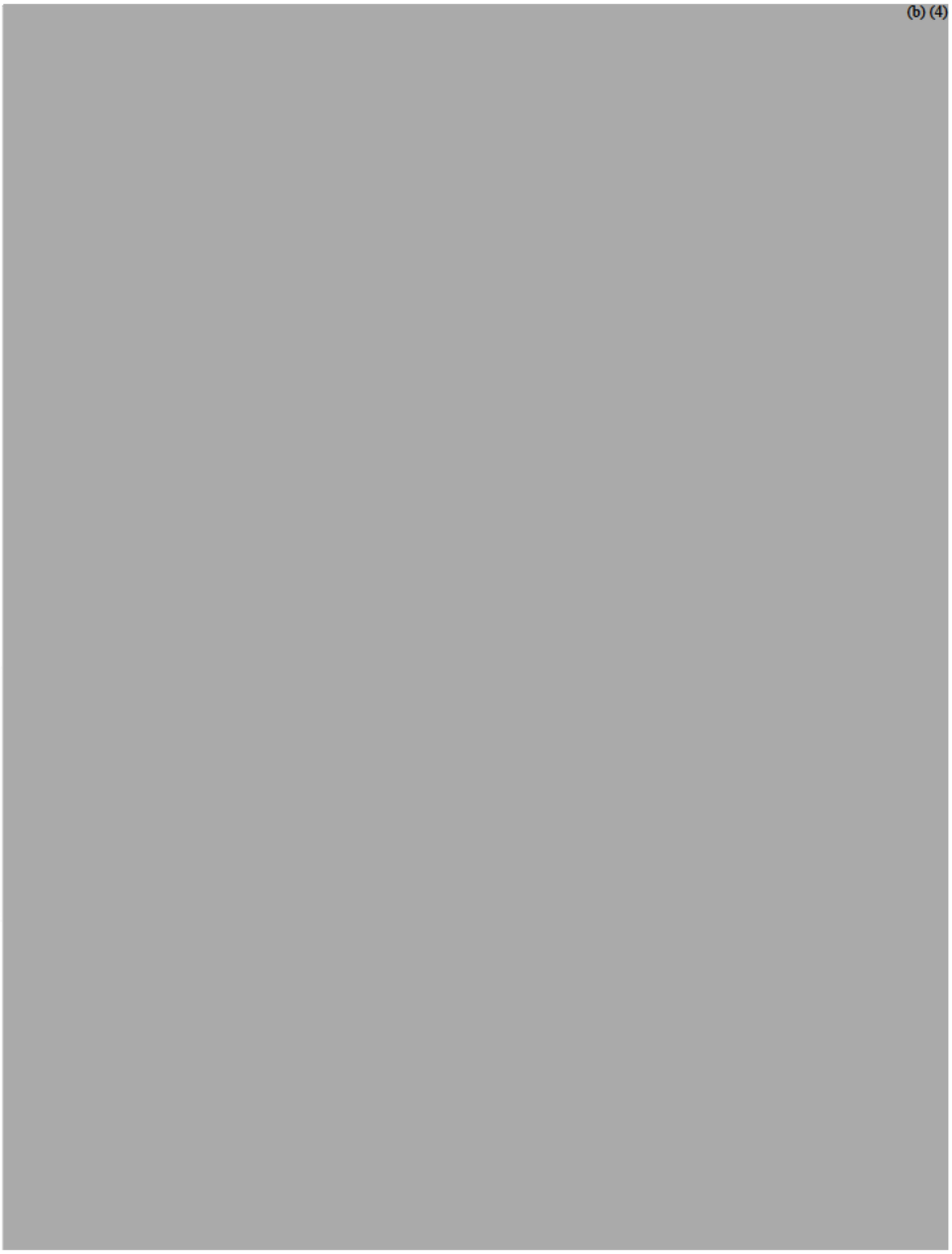
Recommended Storage: Store at 20-25°C (68-77°F); excursions permitted to 30°C (86°F) [see USP Controlled Room Temperature].

Protect from light [see USP Controlled Room Temperature].

2) Final immediate container label
The applicant has provided a labeling amendment on April 11, 2012 that provides the container labels for all strengths and packaging configurations for Stendra (avanafil) tablets

The figure below is the immediate container label for the 100-tablet packaging configuration for the 100 mg strength of Stendra (avanafil) tablets. Although labels for all other strengths and packaging configurations of Stendra tablets are provided in the amendment, for brevity are not copied below.

Figures below show immediate container and external carton labels for the 3-tablet blister cards intended for use as physician samples, respectively.



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/s/

HAMID R SHAFIEI
04/17/2012

MOO JHONG RHEE
04/17/2012
Chief, Branch IV

MEMORANDUM

Date: April 17, 2012

To: NDA 202-276

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

Subject: Tertiary review of ONDQA recommendation for Approval of NDA 202-276, avanafil 50 mg, 100 mg and 200 mg tablet.

I have assessed the ONDQA reviews of NDA 202-276 by Hamid Shafiei, Ph.D. entered into DARRTS March 1, 2012 and April 17, 2012. The initial CMC review (March 1, 2012) recommend a Complete Response for this NDA due to the lack of an Executed Batch Record as required by 21 CFR 314.50(d)(1)(ii)(b), outstanding labeling issues and a lack of Overall Recommendation from the Office of Compliance. The follow-up CMC memorandum (April 17, 2012) states that the approvability issues identified in the initial CMC review, status of the manufacturing and testing sites, was resolved on April 17, 2012 when the Office of Compliance issued an Overall Recommendation of Acceptable for the listed manufacturing and testing sites. No other CMC issues remain unresolved.

The Drug Master File (DMF) (b) (4) for the drug substances were reviewed by Dr. Shafiei and found to be ADEQUATE to support this NDA on February 2, 2012.

No post marketing commitments are proposed by ONDQA.

Avanafil 50 mg, 100 mg and 200 mg tablets are designed for immediate release. The tablets are all pale yellow, oval shaped and debossed with dosage strength. They differ by size and markings. The proposed commercial configuration of the drug product is tablets presented in two packaging configurations of 30 tablets and/or 100 tablets in a white HPDE bottle enclosed with a child-resistant cap. Avanafil tablets are also packaged, as physician samples, in blister cards containing 3 tablets. Avanafil tablets are recommended to be stored at room temperature. A 24 month expiry period is recommended based on the submitted stability data. The drug product is manufactured by (b) (4) and will be marketed in the U.S. by Vivus, Inc.

All manufacturing and testing facilities have acceptable site recommendations as of April 17, 2012, based on the Overall Recommendation made on April 17, 2012.

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

Secondary review of the CMC review was performed by Moo-Jhong Rhee, Ph.D.

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/s/

TERRANCE W OCHELTREE
04/17/2012

NDA 202-276

Trade Name (avanafil) tablets
50mg, 100mg, 200mg

Vivus, Inc.

Hamid Shafiei, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC REVIEW
For the Division of Reproductive and Urologic Drug Products

Table of Contents

Deleted:

CMC Review Data Sheet

1. NDA 202-276

2. REVIEW #: 1

3. REVIEW DATE: 03/01/2012

4. REVIEWER: Hamid Shafiei, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	06/30/2011
Correspondence (C)	
Amendment (BC)	09/30/2011
Amendment (BC)	02/21/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Vivus, Inc.
Address:	1172 Castro Street, Mountain View, CA 94040
Representative:	Malcolm McKay, Ph.D.
Telephone:	(650) 934-5288

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Pending
b) Non-Proprietary Name: Avanafil
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of Erectile Dysfunction

11. DOSAGE FORM: Tablet

CMC Review Data Sheet

12. STRENGTH/POTENCY: 50mg, 100mg, and 200mg

13. ROUTE OF ADMINISTRATION: Oral

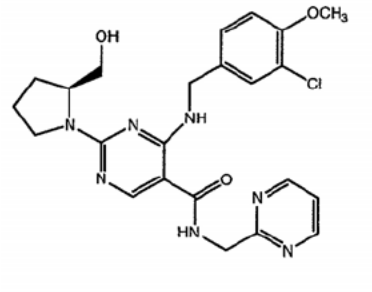
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Avanafil

(b) (4)

Empirical Formula:	$C_{23}H_{26}ClN_7O_3$
Molecular Weight:	483.95
CAS Number:	330784-47-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	2	(b) (4)	Drug Substance	1	Adequate	02/22/2012	Reviewed by Hamid Shafiei, Ph.D.
	3		(b) (4)	4			
	3			4			
	3			4			
	3			4			
	3			4			
	3			4			

[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	N/A	
NDA	N/A	

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	N/A		
EA	Categorical exclusion is acceptable (see P. 79)	11/28/2011	Ron A. Bloom, Ph.D.
Microbiology	N/A		

The CMC Review for NDA 202-276

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has ***not*** provided sufficient information to assure identity, strength, purity, and quality of the drug product, TRADENAME (avanafil) tablets.

However, the Office of Compliance has ***not*** made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.

Also label/labeling issues identified have ***not*** been satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval in its present form, per 21 CFR 314.125(b)(1),(6) & (13).

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

Not applicable.

II. Summary of CMC Assessments

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

(1) Drug Substance

Avanafil is a potent and highly specific type 5 phosphodiesterase (PDE5) inhibitor and is intended for the treatment of erectile dysfunction. Avanafil is a (b) (4) (b) (4) white crystalline powder and is manufactured by (b) (4) Detailed description for the manufacturing, control of raw material, control of manufacturing critical steps, specification, justification for specification, packaging, storage condition, stability, and retest period for this drug substance is provided in DMF # (b) (4). The proposed specification for avanafil release and stability testing is provided both in DMF # (b) (4) and this NDA application. The proposed testing and acceptance criteria in the drug substance specification are considered adequate to assure its identity, strength, purity, and quality of the API. There have been no CMC changes or amendments since the submission of the original DMF # (b) (4) This DMF has been reviewed and found adequate to support this NDA.

(2) Drug Product

TRADENAME (avanafil) tablets are indicated for the treatment of erectile dysfunction. Avanafil tablets are oval-shaped pale yellow debossed on one side with the strength and are formulated as immediate release tablets. Avanafil tablets are produced at 50mg, 100mg, and 200mg strengths. Each strength of avanafil tablets is presented in two packaging configurations of 30 tablets and/or 100 tablets in a white HPDE bottle enclosed with a child-resistant cap. Avanafil tablets are also packaged in blister cards containing 3 tablets as physician samples. This product is manufactured by [redacted] (b) (4) and will be marketed in the U.S. by Vivus, Inc.

The manufacturing process for this drug product is deemed well controlled and supported by adequate pharmaceutical and manufacturing development studies. Avanafil tablets are produced through a [redacted] (b) (4)

Avanafil tablets contain [redacted] (b) (4) avanafil API as the active ingredient, and mannitol [redacted] (b) (4) fumaric acid [redacted] (b) (4) hydroxypropylcellulose [redacted] (b) (4) low substituted hydroxypropylcellulose [redacted] (b) (4) [redacted] (b) (4) calcium carbonate [redacted] (b) (4) magnesium stearate [redacted] (b) (4) and yellow ferric oxide [redacted] (b) (4) as the excipients. The product composition for the 3 strengths (50mg, 100mg, and 200mg) of the avanafil tablets are [redacted] (b) (4)

(b) (4) All excipients used in the manufacture of this drug product are compendial excipients.

The release specification for TRADENAME (avanafil) tablets includes tests and acceptance criteria for description, identification, assay, impurities (mainly degradation products since the process related impurities are controlled during the drug substance release), content uniformity of dosage unit, dissolution, microbial limits, and specified micro-organisms. The acceptance limits in the product release specification are consistent with relevant current USP requirements and current ICH Q6B. The proposed specification for the release and stability testing of TRADENAME (avanafil) tablets is deemed acceptable.

All strengths of avanafil tablets are packaged as 30 tablets or 100 tablets in white HDPE bottles enclosed with white child-resistant screw caps. Avanafil tablets are also packaged in 3-tablet blister cards. The blister card packaging configuration is intended only for use as physician samples.

All strengths of the drug products, 3 batches each, packaged in HDPE have been proven to be stable for up to 18 months under long-term and 12 months under both intermediate and accelerated conditions. Long-term stability data from 4 batches of drug product (one 50mg batch, one 100mg batch, and two 200mg batches) packaged in blister cards also show that this product is stable for 24 months. Based on the results of the 18-month long-term and 12-month accelerated stability from 3 batches of each strength of the drug product, the proposed 24-month expiration dating period is granted.

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

TRADENAME (avanafil) tablets are oval-shaped pale yellow immediate release tablets for once-a-day oral administration and are indicated for the treatment of erectile dysfunction. Avanafil tablets are produce in 3 different tablet strengths containing 50mg, 100mg, and 200mg of avanafil API. Avanafil tablets are debossed on one side with the strength and are packaged as 30-tablet unit or 100-tablet unit in white HDPE bottles with child-resistant caps. Avanafil tablets are also provided as physician samples in 3-tablet blister cards.

C. Basis for Not-Approval Recommendation

21 CFR 314.125 (b)(1)

- The Executed Batch Record as required by 21 CFR 314.50(d)(1)(ii)(b) is missing.

21 CFR 314.125 (b)(6)

- Label/labeling issues has not been resolved (see the List of Deficiencies, p. 78).

21 CFR 314.125 (b)(13)

- The final "Acceptable" recommendation from the Office of Compliance is still "Pending".

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Hamid Shafiei, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch IV, ONDQA

C. CC Block: entered electronically in DFS

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/s/

HAMID R SHAFIEI
03/01/2012

MOO JHONG RHEE
03/01/2012
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Hamid Shafiei, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Hamid.Shafiei@fda.hhs.gov
Phone: (301)-796-2326
Fax: (301)-796-9745

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202-276

Name of Product (b) (4) (avanafil)tablets, 50 mg, 100 mg, and 200 mg

Applicant: VIVUS, Inc.

Applicant's Contact Person: Malcom McKay, Ph.D.

Address: 1172 Castro Street, Mountain View, CA 94040

Telephone: 650-934-5288 Fax: 650-934-5209

Date Methods Validation Consult Request Form Received by DPA: 8/15/2011

Date Methods Validation Package Received by DPA: 8/15/2011

Date Samples Received by DPA: 10/18/2011

Date Analytical Completed by DPA: 1/23/2012

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☐
2. Methods are acceptable with modifications (as stated in accompanying report). ☒
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

Cover memo and comments are attached

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3813
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Date: January 23, 2012

To: Hamid Shafiei, Methods Validation Requestor,

Through: Benjamin Westenberger, Deputy Director, Division of Pharmaceutical Analysis (HFD-920)

From: Michael L. Trehy, Ph.D., Division of Pharmaceutical Analysis (HFD-920)

Subject: Evaluation of NDA 202-276 (b) (4) (avanafil) 50 mg tablets

The methods in Table 1 were evaluated and are acceptable for quality control and regulatory purposes. Minor changes are suggested for the drug substance and drug product purity methods.

Table 1. Methods evaluated for NDA 202-276 (b) (4) (avanafil) tablets

Method ID	Method Title	Volume/Page
TM-001	Assay HPLC Analysis for TA-1790 Tablets and TA-1790 Active Ingredient	NDA 202-276 Mod 3.2.R.2
AVAP/2-3/HR	ANALYTICAL PROCEDURES (AVANAFIL API, (b) (4) Purity (b) (4)	DMF (b) (4) Mod 3.2.S.4.2
AVAP/2-3/HR	ANALYTICAL PROCEDURES (AVANAFIL API, (b) (4) Assay (HPLC)	DMF (b) (4) Mod 3.2.S.4.2

The methods in Table 2 were evaluated and will be acceptable for quality control and regulatory purposes with modifications. The modifications are given in the Comments section below.

Table 2. Methods evaluated for NDA 202-276 [redacted] (avanafil) tablets

Method ID	Method Title	Volume/Page
TA1790 HPJ-03/IM-2	Testing method for Purity (Related Substances) of TA-1790HP Tablets	NDA 202-276 Mod 3.2.P.5.2
AVAP/2-3/HR	ANALYTICAL PROCEDURES (AVANAFIL API, [redacted] Purity (Process Related Impurities and Potential Degradation Products; HPLC)	DMF [redacted] Mod 3.2.S.4.2

DPA has the following comments concerning the methods and specifications:

TA1790 HPJ-03/IM-2

Specifications listed for "Testing method for Purity (Related Substances) of TA-1790HP Tablets (TA1790 HPJ-03/IM-2)" did not seem to be complete. [redacted]

The method, TA1790HPJ-03/IMM-2 Testing method for Purity (Related Substances) of TA-1790HP Tablets, specifies reporting the results to 2 decimal places from 0.10% and greater and that concentrations less than 0.10% are not reported. [redacted]

The method does not indicate [redacted]

TA1790 HPJ-03/IM-2 and AVAP/2-3/HR

Preparation of solutions of [redacted] impurities or giving the relative retention time ranges for each impurity is necessary to match their retention times to peaks in the chromatograms.

Drug Product

Method-Result	Limit
TM-001.00 Assay HPLC for TA-1790 Tablets and TA-1790 Active Ingredient	
Identification Pass Δ = 0.0 min Assay 100.0%, 99.5% avg(2) = 99.7%	Identification R.T (std) – R.T. (sample) = Δ < 0.3 min Assay 95.0% - 105.0%
TA1790HPJ-03/IMM-2 Testing method for Purity (Related Substances) of TA-1790HP Tablets	
(b) (4)	

Drug Substance

DMF (b) (4) AVAP/2-3/HR ANALYTICAL PROCEDURES (AVANAFIL API, (b) (4)) **Assay (HPLC)**	
Identification Pass Δ = 0.0 min Assay 99.0%	Identification R.T (std) – R.T. (sample) = Δ < 0.3 min Assay 98.0% - 102.0%
DMF (b) (4) ANALYTICAL PROCEDURES (AVANAFIL API, (b) (4)) **Purity (Process Related Impurities and Potential Degradation Products; HPLC)**	
(b) (4)	
DMF (b) (4) ANALYTICAL PROCEDURES (AVANAFIL API, (b) (4) **Purity ((b) (4)**	
(b) (4)	(b) (4)

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

/s/

JAMES F ALLGIRE
01/23/2012

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	Division of Reproductive and Urologic Products
NDA:	202-276
Applicant:	Vivus
Stamp Date:	30-Jun-2011
PDUFA Date:	30-Apr-2012
Trademark:	(b) (4)
Established Name:	Avanafil
Dosage Form:	Tablets (50 mg, 100 mg, 200 mg)
Route of Administration:	Oral
Indication:	Erectile Dysfunction
CMC Lead:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	X	☐

Summary and Critical Issues:

A. Summary

Avanafil tablets are oval, pale yellow, and available in 50 mg, 100 mg and 200 mg dosage strengths. (b) (4) The tablets are differentiated by the dosage strength debossed on the tablets. Tablets are packaged in HDPE bottles with CRC screw caps of 30 or 100 mg tablets/bottle. Physician Samples of three 100 mg tablets are available in blister cards.

B. Critical issues for review

1. *All drug substance information is provided in the cross-referenced DMF, which will require review.*

2. *The sponsor has used a bracketing stability study design. According to the **Guidance for Industry: Q1D Bracketing and Martrixing Designs for Stability Testing of New Drug Substances and Products**, bracketing should be performed on the extremes of certain design factors, which includes container size and/or fill, and that only one attribute should be varied. The guidance also states that if size and fill both vary, it should not be assumed that the smallest and largest sized bottles represent the extremes, but the extremes should be characterized by comparing characteristics that may affect product stability, such as surface area to volume ratio, headspace to volume ratio, etc. (See pages 2 and 3 of the Guidance).*

   The sponsor has performed their stability studies using only the smallest bottle sizes (30 cc and 45 cc) and a fill of 30 tablets, but seeks to additionally market their product in both a larger bottle size (60 cc and 90 cc) and fill of 100 tablets. From a strict reading of

the guidance, only the 30-tablet/30cc bottles (50 mg and 100 mg) and the 30-tablet/45 cc bottles (200 mg) could be justified, and the sponsor would need to either remove the larger fill/bottle size from consideration or the application could potentially be Refuse-to-File. At this point in time, neither pathway is recommended, but the following alternative is put forward to address this as a review issue:

- *The sponsor should provide justification why the larger bottle and fill sizes were not included on stability. Since the tablets are manufactured* (b) (4)
- *The sponsor states that avanafil is very stable, with little or no change on stability. Review of the stability data on the bulk and packaged product may indicate that there is little risk in allowing a larger bottle/fill.*
- *Post-approval stability studies could be performed in the larger bottle/fill to confirm.*
- *If review of the data are not compelling, the sponsor could withdraw the 60cc and 90cc bottles of 100 fill during the review cycle, and submit these configurations in a post-approval supplement.*

C. Comments for 74-Day Letter

Submit a copy of the drug substance specification to the NDA so that they can be documented within the NDA review.

*According to the **Guidance for Industry: Q1D Bracketing and Martrixing Designs for Stability Testing of New Drug Substances and Products**, bracketing should be performed on the extremes of certain design factors, which includes container size and/or fill, and that only one attribute should be varied. The guidance also states that if size and fill both vary, it should not be assumed that the smallest and largest sized bottles represent the extremes, but the extremes should be characterized by comparing characteristics that may affect product stability, such as surface area to volume ratio, headspace to volume ratio, etc. (See pages 2 and 3 of the Guidance). Provide justification on why the 60 cc and 90 cc bottles and 100-tablet fills were not included on stability. Provide a comparison of the characteristics of the container closure system that may affect the product stability as outlined in the Guidance.*

Include a bar code on the container labels and indicate its placement.

D. Recommendation:

This NDA is fileable from a CMC perspective. Hamid Shafiei, Ph.D. has been assigned as the primary CMC reviewer. As outlined in draft IQP 5101.01, this application qualifies for dissolution to be reviewed by the CMC reviewer. Concurrence was received on 22-Jul-2011. As per the IQP, any decisions concerning dissolution will need to be concurred with by the BioPharmaceutics Supervisor/Team Leader prior to any correspondence with the sponsor, and the 5 month draft review and 8 month primary review needs concurrence and sign-off in DARRTS from the Biopharmeceutics Supervisor/Team Leader as well.

REGULATORY BRIEFING RECOMMENDATION: As an NME, this is recommended for an Office-level Briefing.

Donna F. Christner, Ph.D.

NDA Number: 202276 **Type: 1** **Established/Proper Name: avanafil**

Applicant: Vivus **Letter Date: 30-Jun-2011** **Stamp Date: 30-Jun-2011**

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?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		See attachment to 356h
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** (b) (4) **API.**		X	N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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)	X		See attachment to 356h
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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)	X		See attachment to 356h

9.	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: • 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)	X		See attachment to 356h
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		See attachment to 356h

* 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?	X		Exemption requested. EIC calculation provided in Module 1.12.14.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Information provided via cross-reference to DMF (b) (4) DMF is electronic.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Information provided via cross-reference to DMF (b) (4) DMF is electronic.
14.	Does the section contain information regarding the characterization of the DS?	X		Information provided via cross-reference to DMF (b) (4) DMF is electronic.
15.	Does the section contain controls for the DS?	X		Information provided via cross-reference to DMF (b) (4). DMF is electronic.
16.	Has stability data and analysis been provided for the drug substance?	X		Information provided via cross-reference to DMF (b) (4) DMF is electronic.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

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?	X		
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?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Formulation change from early development to Phase 2/3 studies bridged via BE study TA-020
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		24 months expiry requested
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		As per IQP 5105, a Method Validation request will be initiated for this NME.

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

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?	X		See below

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Avanafil API	12-Mar-2011	Will need review
	III		(b) (4)	26-Jan-2011	See reviews dated 31-Aug-1999 (45cc bottle), 09-May-1996 (30cc bottle) See ONDC Policies on Bottles and Blisters*
	III			31-Jan-2011	See review dated 26-Jul-2004 See ONDC Policies on Bottles and Blisters*
	III			25-Jan-2011	See review dated 21-Jan-2011 by G. Lunn
	III			14-Feb-2011	See review dated 09-Jun-2009 by B. Wu
	III			21-Jan-2011	No review found

(b) (4)	III	(b) (4)	(b) (4)	04-Nov-2010	No review found

**Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001*
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		The sponsor does not plan to use cartons. The container labels do not have a bar code. The sponsor should indicate placement.

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
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.		X	N/A
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See comments to the sponsor in Section C.

{See appended electronic signature page}

Donna F. Christner, Ph.D. Date
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D. Date
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No___x___ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____ _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble **(**e.g., gold nanoparticle**)** in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

REVIEW NOTES

Clinical studies were performed under IND 51,235. The following CMC-related documents are available in DARRTS. The primary reviewer should check DARRTS for a full overview of the regulatory history of the IND. Copies of correspondences are also provided in Module 1.6, 1.8 and 1.12 in the NDA.

- **PreIND meeting held 07-Nov-2001 by J. Salemme and D. Lin:** CMC stated the data were sufficient to open the IND. FDA recommended that information on the 200 mg drug product dose be provided, along with proof of structure for the drug substance, the impurity profile of DS used in the preclinical studies, clarification for use of a titration assay method, and a request for information of starting materials not commercially available. A reference to the Phase 1 IND Guidance was provided.
- **Initial IND review dated 12-Dec-2001 by S. Tran.**
    - A number of CMC comments were conveyed for the Phase 1 IND study. The IND was found relatively safe-to-proceed from the CMC standpoint.
- **Review dated 10-Jan-2009 evaluating SDN 86, 88, 89 and 93 by D. Christner.** Reviewed in conjunction with a Special Protocol Amendment for a proposed (b) (4) stability study design for Avanafil 50 mg, 100 mg and 200 mg Formulation II tablets. (b) (4)
    - FDA did not agree with (b) (4) design and suggested that a bracketing design may be more appropriate. Recommended a Bioequivalence study be performed to bridge the major changes in formulation between Formulations I and II.
    - FDA agreed that the additional stability data could be submitted up to Month 5 of the NDA review cycle.
    - FDA agreed that the proposed tests appeared to be adequate, but noted that the adequacy of the acceptance criteria is a NDA review issues. FDA also recommended that impurities be tested for on stability during development and that microbial limits should be included in the specification.
- **Review dated 23-Jan-2009 evaluating SDN 79 and 80** for identification of starting material for (b) (4) of the drug substance by D. Christner. Meeting request was denied, but written advice was provided.
    - FDA agreed that the (b) (4) could be designated as starting materials provided that:
        - Full information of the (b) (4) for each starting material was provided in the NDA or DMF
        - A commitment was provided that any change in the manufacturers of the starting materials would be provided in a Prior Approval Supplement
        - Specifications for the starting materials be established and related substances of the starting materials be listed a process impurities in the drug substance specifications, unless they are less than the detection limits

- **Letter dated 02-Nov-2009 with Special Protocol Agreement (Stability).** Questions included a scale-up and site change for the tablets and a change in site for one of the API starting materials, stability package for drug product packaged in blisters and bottles.
    - Concerning the tablet scale-up/site change and manufacturing site change for an API staring material:

        - FDA concurred with the sponsor's plan and requested comparative dissolution profiles in the application media for drug product manufactured at two different sites.
        - FDA also recommended that as part of their Post-Approval Stability Commitment that two additional (b) (4) lots should be manufactured and used to produce one lot of each dosage strength and the drug product s place on stability using the bracketing design.
        - FDA reminded the sponsor that if a bracketing design is used and either the lower or higher strength is not used for commercialization, that stability would still need to be continued to support the bracket for the intermediate strength.
    - Concerning the stability package for both the blisters and bottles, the FDA concurred that the data package should be sufficient to set an expiry during the NDA review cycle.
- **NAI to General Correspondence dated 13-Jan-2010**: The sponsor acknowledged and agreed to the CMC comments in the SPA dated 02-Nov-2009.
- **NAI to General Correspondence dated 13-Mar-2010:** The sponsor acknowledged our agreement with their 10-Oct-2008 and 14-Dec-2009 submissions.
- **preNDA meeting held on 20-Oct-2010:** The following CMC recommendations were made:
    - Provide a complete list of all manufacturing facilities as an attachment to the 356h
    - The sponsor requested that any changes in the starting material manufacturers be submitted as a CBE-30 instead of a PAS. FDA recommended that a PAS be submitted, but stated that the supplement could be submitted as a CBE and the final determination of the supplement level would be made upon evaluation of the supplement.
    - The FDA agreed that the acceptance criteria for the starting material appeared adequate at this time, but final evaluation was an NDA review issue
    - FDA agreed that the proposed API specifications appeared adequate at the time, with the following additional comments that the (b) (4) limit for Total Impurities appeared generous and may need to be tightened, the limit for the (b) (4) may need to be tightened, and the Residual Solvents should be reported in ppm. The sponsor was also reminded that final determination is an NDA review issue.
    - The FDA agreed that the acceptance criteria for the drug product appeared adequate at this time, but final evaluation was an NDA review issue
    - The FDA concurred that post-approval completion of concurrent validation plan for the tablets was acceptable
    - The sponsor was reminded that if the blisters were available for commercial distribution, that they would need to comply with 16 CFR 1700.14(a)(10) for child resistance.
- **Email dated 16-May-2011:** Sponsor proposed (b) (4) CMC concurred pending final NDA review and concurrence from DMEPA.

During development, the sponsor made a formulation change. As requested, sponsor performed a BE study. See Appendix 1 of this document for Clinical Studies performed and Formulations used for those studies.

DRUG SUBSTANCE

No information is provided in the NDA on the drug substance. All information is provided via cross-reference to DMF (b) (4) **The DMF is electronic and can be found in the EDR.** The following table on the manufacturing site is provided as an attachment to the 356h. The structure is taken from the Physician's Insert.

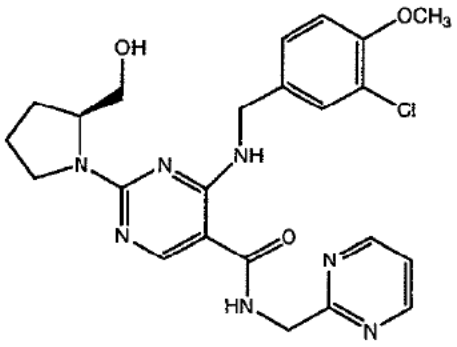


Table 1 Avanafil API Manufacturing and Testing Site

(b) (4)

Comment: *Information is provided on the drug substance manufacturing site. EES was submitted on 15-Jul-2011 by Becky McKnight. As of 21-Jul-2011, the site status is Assigned Inspection.*

The sponsor will be requested to submit a copy of the drug substance specification to the NDA so that they can be documented within the NDA review.

The DMF is all electronic. No review has been performed, so a full review will be necessary.

DRUG PRODUCT

Avanafil tablets are oval, pale yellow, and available in 50 mg, 100 mg and 200 mg dosage strengths. The tablets are differentiated by the dosage strength debossed on the tablets. Tablets are packaged in HDPE bottles with CRC screw caps of 30 or 100 mg tablets/bottles. Physician Samples of three 100 mg tablets are available in blister cards.

The formulation is shown below. Tablets are dose proportional. All excipients are compendial and are controlled by adherence to compendial methods.

Table 1 Composition of Avanafil Tablets

			50 mg Tablets		100 mg Tablets		200 mg Tablets	
Component	**Reference to Quality Standard**	**Function**	**mg**	**%**	**mg**	**%**	**mg**	**%**
Avanafil	In-house Standard	Active Ingredient						(b) (4)
Mannitol	USP							(b) (4)
Fumaric Acid	NF							
Hydroxypropylcellulose	NF							
Low substituted Hydroxypropylcellulose	NF							
(b) (4) Calcium Carbonate	USP							
Magnesium Stearate	NF							
Yellow Ferric Oxide	NF							
Total Mass (mg/tablet)	--							

(b) (4)

Comment: *Information is adequate to allow review.*

Manufacturing

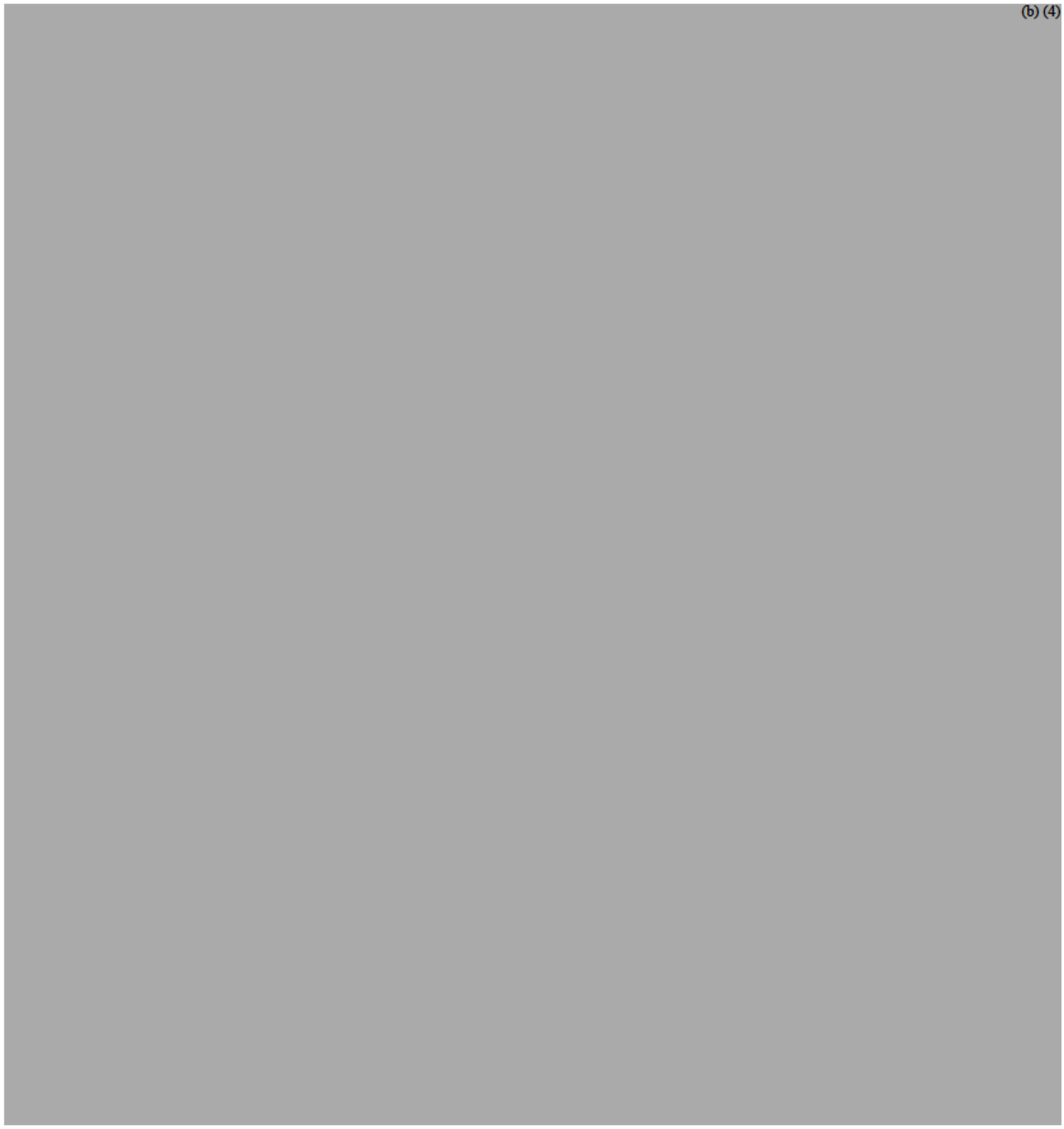
The following facilities have manufacturing responsibilities for the drug product:

Table 3 Overview of Commercial Product Manufacturing and Testing Sites

Establishment	Function	Address
(b) (4)		
VIVUS, Inc.	• Bulk tablet release • Import of bulk tablets into US • Finished Drug Product release	VIVUS Inc. 1172 Castro Street Mountain View, CA 94040
(b) (4)		

Comment: *Information is provided on the drug product manufacturing sites. A more detailed table with full information on contacts is provided as an attachment on the 356h and is not reproduced in the IQA. The sponsor was contacted on 11-Jul-2011 by Becky McKnight to clarify the roleof the VIVUS, Inc facility. The sponsor confirmed that VIVUS does not perform any testing for release, but only evaluates the data generated at* (b) (4) *EES was submitted on 15-Jul-2011 by Becky McKnight. As of 21-Jul-2011, packaging sites are Acceptable and the manufacturing and testing sites are Assigned Inspection.*

The sponsor has provided the following flow chart of the manufacturing process. Narratives are provided as well.



Comment: *Information is adequate to allow review.*

Specification:

The quality of the drug product is controlled by adherence to the following specification:

Table 1 Proposed Specifications for Commercial Bulk Avanafil Tablets

Test	Method[a]	Acceptance Criteria
Description (Appearance)	Visual	Pale yellow oval tablets embossed with dose strength (50 or 100 or 200)
Identification [b]	HPLC	(b) (4)
Assay	HPLC	
Purity (Potential Degradation Products)	HPLC	
Uniformity of Dosage Unit [b]	USP<905> Weight Variation Method	
Dissolution	USP <711> Apparatus 2	
Microbial Limits	USP<61>	
Specified Organisms [b]	USP<62>	

[a] See Table 1 in Section 3.2.P.5.2

(b) (4)

The sponsor states the following concerning the specification for potential degradation products:

> No degradation products have been specified in Table 1 because no degradation products have been observed in ongoing stability studies with Avanafil Tablets (see Section 3.2.P.8.1) conducted under long term (25°C/60%RH), intermediate (30°C/65%RH), and accelerated stability conditions (40°C/75%RH), and no degradation products were detected in 3-month stress tests (50°C, 40°C/75% RH open storage, and light exposure with up to 1.2 million lux hours) with the drug product (Section 3.2.P.5.5). Avanafil API process related impurities (b) (4) are not degradation products, and they are controlled at the level of the drug substance.

Methods and validation are provided for all tests. As per IQP 5101, a Method Validation Request will be submitted.

Comment: *The specification appear typical for IR tablets. It should be noted that the sponsor performs Uniformity of Dosage Units via Weight Variation instead of Content Uniformity. Since the API comprises (b) (4) of the tablet weight, this is acceptable as per USP<905>.*

As per DRAFT IQP 5101.01 Biopharmaceutics Review Procedures in ONDQA, the dissolution information for an immediate release dosage form can be assigned to the primary CMC reviewer upon concurrence of the Biopharmaceutics Review Supervisor/Team Leader (BRS/TL). The IQP states the the CMC Lead or Reviewer should obtain concurrence to review this information from

the BRS/TL and document this decision in the IQA. If the dissolution data is reviewed by the primary CMC reviewer, concurrence on the regulatory decision must be obtained from the BRS/TL before the information is finalize and before any communication with the sponsor/applicant is made. The draft CMC review at Month 5 must also be forwarded to the BRS/TL for secondary review and when the CMC review is finalized at month 8, the BRS/TL should be added to the signers list in DARRTS for this review. In discussion with Dr. Moo-Jhong Rhee, it was determined that this application qualifies for dissolution to be reviewed by the primary CMC reviewer. Concurrence was requested on 20-Jul-2011 and was given on22x-Jul-2011. See attached email.

The acceptance criteria for Microbial Limits should be checked to see if they agree with USP standards; if not, OPS Microbiology should be consulted for evaluation.

Container Closure and Stability

The sponsor has provided the following information on the container closure system for commercial distribution:

> **3.2.P.1.3 Container Closure**
>
> Individual dosage strengths of Avanafil Tablets are supplied in the following package types:
>
> - 30 cc and/or 60 cc HDPE bottle (containing thirty (30) 50 mg or 100 mg tablets)
> - 45 cc and/or 60 cc HDPE bottle (containing thirty (30) 200 mg tablets)
> - 45 cc HDPE bottle (containing one hundred (100) 50 mg tablets)
> - 60 cc HDPE bottle (containing one hundred (100) 100 mg tablets)
> - 90 cc HDPE bottle (containing one hundred (100) 200 mg tablets)
> - blisters containing three 100 mg tablets (for physician samples only)
>
> The HDPE bottles used for packaging Avanafil Tablets are closed with a screw-cap containing (b) (4) foil liner and the bottles contain a (b) (4) Further details are provided in Section 3.2.P.7.
>
> Physician samples are provided in blisters, and blister cards contain three 100 mg tablets. The blister materials are (b) (4) push-through foil and (b) (4) (b) (4) Further details are provided in Section 3.2.P.7.

The sponsor has provided the following information on the stability package to support their requested 24-month expiry. Stability studies on the 50mg and 100mg tablets were performed on 30 tablets packaged in 30cc bottles and the 200mg tablets were packaged as 30 tablets in a 45 cc bottle. The sponsor is seeking to market drug product packaged in these bottle sizes as well as 60 cc and 90 cc bottle sizes.

> Stability studies were conducted on materials and packaging configurations matching or simulating those of the proposed commercial Avanafil Tablets. Avanafil Tablets will be packaged in two configurations—HDPE bottles and (b) (4) foil blisters (physician samples only). Registration stability batches were packaged in the proposed commercial primary container closures, HDPE bottles and (b) (4) foil blisters as described below.
>
> **Bottled product**: The commercial packaging for Avanafil Tablets is a child-resistant screw-capped, foil-sealed, HDPE bottle containing 30, or 100 tablets.
>
> **Blister-packed product**: Blisters are proposed for use as physician samples only. They are comprised of foil-backed (b) (4) blisters and are sealed between a card designed to hold three tablets.
>
> This NDA includes at least 12 months of primary stability data for registration stability batches packaged in bottles and blisters. As agreed with the Agency (FDA correspondence dated 16 January 2009), VIVUS will provide a 5-month post-NDA submission stability update with additional results for the registration stability batches packaged in bottles and blisters.
>
> This NDA also provides 24 months of real-time and 6 months of accelerated stability data on Avanafil Tables stored in the bulk container closure system used during development (b) (4) (b) (4)

Comment: *According to the* ***Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products****, bracketing should be performed on the extremes of certain design factors, which includes container size and/or fill, and that only one attribute should be varied. The guidance also states that if size and fill both vary, it should not be assumed that the smallest and largest sized bottles represent the extremes, but the extremes should be characterized by comparing characteristics that may affect product stability, such as surface area to volume ratio, headspace to volume ratio, etc. (See pages 2 and 3 of the Guidance).*

The sponsor has performed their stability studies using only the smallest bottle sizes (30 cc and 45 cc) and a fill of 30 tablets, but seeks to additionally market their product in both a larger bottle size (60 cc and 90 cc) and fill of 100 tablets. From a strict reading of the guidance, only the 30-tablet/30cc bottles (50 mg and 100 mg) and the 30-tablet/45 cc bottles (200 mg) could be justified, and the sponsor would need to either remove the larger fill/bottle size from consideration or the application could potentially be Refuse-to-File. At this point in time, neither pathway is recommended, but the following alternative is put forward to address this as a review issue:

- *The sponsor should provide justification why the larger bottle and fill sizes were not included on stability. Since the tablets are manufactured* (b) (4)
- *The sponsor states that avanafil is very stable, with little or no change on stability. Review of the stability data on the bulk and packaged product may indicate that there is little risk in allowing a larger bottle/fill.*
- *Post-approval stability studies could be performed in the larger bottle/fill to confirm.*
- *If review of the data are not compelling, the sponsor could withdraw the 60cc and 90cc bottles of 100 fill during the review cycle, and submit these configurations in a post-approval supplement.*

The following comment should be conveyed to the sponsor in the 74-day letter:

According to the ***Guidance for Industry: Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products****, bracketing should be performed on the extremes of certain design factors, which includes container size and/or fill, and that only one attribute should be varied. The guidance also states that if size and fill both vary, it should not be assumed that the smallest and largest sized bottles represent the extremes, but the extremes should be characterized by comparing characteristics that may affect product stability, such as surface area to volume ratio, headspace to volume ratio, etc. (See pages 2 and 3 of the Guidance). Provide justification on why the 60 cc and 90 cc bottles and 100-tablet fills were not included on stability. Provide a comparison of the characteristics of the container closure system that may affect the product stability as outlined in the Guidance.*

Labeling

Adequate container labels are provided for review. (b) (4)
However, there is no bar code on the labels. Sponsor should indicate placement.
Comment: *Include a bar code on the container labels and indicate placement.*

Appendix 1

Table 6 Dosage Strengths and Formulations Used in Clinical Studies

Study ID	Type of Study	Phase	Avanafil Tablet Formulation[a] / Strength	Packaged Lot Number[b]
HP-01	PK, tolerability	1	Formulation I / 12.5 mg Formulation I / 50 mg Formulation I / 100 mg Placebo (Form I) / 12.5 mg Placebo (Form I) / 50 mg Placebo (Form I) / 100 mg	00021 and 00043 00020 and 00042 00035 00023 and 00045 00022 and 00044 00036
TA-02	PK, safety single, multi dose	1	Formulation I / 50 mg Formulation I / 100 mg Placebo (Form I) / 50 mg Placebo (Form I) / 100 mg	20042 20043 20045 20046
TA-04	Drug-drug interaction (nitrate)	1	Formulation I / 100 mg Placebo (Form I) / 100 mg	20043 20046
TA-07	PK, BID dosing	1	Formulation I / 100 mg	20043[c]
TA-011	Drug-drug interaction (ritonavir, erythromycin, ketoconazole)	1	Formulation II / 50 mg Formulation II / 100 mg	17TA90080021 17TA90080022
TA-012	Drug-disease interaction (hepatic)	1	Formulation II / 200 mg	17TA90090020
TA-013	Drug-disease interaction (renal)	1	Formulation II / 200 mg	17TA90090020
TA-014	Elderly vs. young PK, Semen PK	1	Formulation II / 200 mg	17TA90080024
TA-015	Drug-drug interaction (alcohol)	1	Formulation II / 200 mg Placebo (Form II) / 200 mg	17TA90090020 17TA90090027
TA-016	Drug-drug interaction (warfarin)	1	Formulation II / 200 mg Placebo (Form II) / 200 mg	17TA90090020 17TA90090027
TA-017	Drug-drug interaction (alpha blockers)	1	Formulation II / 200 mg Placebo (Form II) / 200 mg	17TA90090020 17TA90090027
TA-018	Drug-drug interaction (omeprazole, desipramine, and rosiglitazone)	1	Formulation II / 200 mg	17TA90090020
TA-019	Drug-drug interaction (enalapril, amlodipine)	1	Formulation II / 200 mg Placebo (Form II) / 200 mg	17TA90090020 17TA90090027
TA-020	Food effect, relative bioavailability, dose proportionality	1	Formulation II / 100 mg Formulation II / 50 mg Formulation I / 100 mg	17TA90090022 17TA90090021 20043[c]
TA-021	Sperm function	1	Formulation II / 200 mg Placebo (Form II) / 200 mg	17TA90090020 17TA90090027
TA-140	TQT	1	Formulation II / 100 mg Placebo (Form II) / 100 mg	17TA90080022 17TA90080026
TA-01	Visual stimulation	2	Formulation I Tablet / 50 mg Formulation I Tablet / 100 mg Placebo (Form I) / 50 mg Placebo (Form I) / 100 mg	10017 10018 10013 10014
TA-03	Home administration	2	Formulation I / 100 mg	20044
TA-05	Safety, efficacy	2	Formulation I / 12.5 mg[e] Formulation I / 50 mg[e] Formulation I / 100 mg[e] Capsules filled with Avicel®	30027 20042 20043, 20044 NA
TA-301	Safety, efficacy in generalized ED	3	Formulation II / 50 mg Placebo (Form II) / 50 mg	17TA90080021 17TA90080025
TA-302	Safety, efficacy in diabetics	3	Formulation II / 100 mg Placebo (Form II) / 100 mg	17TA90080022 17TA90080026

(b) (4)

(b) (4) [c]This study is ongoing, and is not part of the original NDA submission. [e]In these Clinical Study Reports, Lot 200430 was misidentified as Lot 40118. Study files and chain of custody documents trace this lot correctly.

Table 6 Dosage Strengths and Formulations Used in Clinical Studies (continued)

Study ID	Type of Study	Phase	Avanafil Tablet Formulation[a] / Strength	Lot Number[b]
TA-303[d]	Safety, efficacy in pts with prostatectomy	3	Formulation II / 100 mg Placebo (Form II) / 100 mg	17TA90080022 17TA90080026
TA-314	Long term follow up (rollover from TA-301 and TA-302)	3	Formulation II / 50 mg Formulation II / 100 mg Formulation II / 200 mg Formulation II / 200 mg	17TA90080021 17TA90080022 17TA90080023 17TA90080024

(b) (4)

(b) (4) [d]This study is ongoing, and is not part of the original NDA submission. [e]In these Clinical Study Reports, Lot 200430 was misidentified as Lot 40118. Study files and chain of custody documents trace this lot correctly.

A clinical bioequivalence study was also performed to compare Formulation I and Formulation II Avanafil Tablets (see Clinical Study Report TA-020; Section 5.3.1.2.1). The statistical comparisons of avanafil C_{max}, AUC_{0-t} and AUC_{0-inf} for Formulation II versus Formulation I showed that the 90% CIs of the geometric LS Means ratios were within 80% to 125%, suggesting that Formulations I and II are bioequivalent.

Table 3 Avanafil Tablets Formulation I

Components	Composition (mg / tablet)				% Composition
	12.5 mg	25 mg	50 mg	100 mg	
Avanafil API	12.5	25.0	50.0	100.0	(b) (4)
Mannitol	(b) (4)				
Fumaric acid					
Hydroxypropylcellulose					
Low substituted hydroxypropylcellulose					
(b) (4) calcium carbonate					
Magnesium stearate					
Total mass (mg / tablet)					

Table 4 Avanafil Tablets Formulation II

Components	Composition (mg / tablet)			% Composition
	50 mg	100 mg	200 mg	
Avanafil API	50.0	100.0	200.0	(b) (4)
Mannitol	(b) (4)			
Fumaric acid				
Hydroxypropylcellulose				
Low substituted hydroxypropylcellulose				
(b) (4) calcium carbonate				
Magnesium stearate				
Yellow ferric oxide*				
Total mass (mg / tablet)				

* Not included in total mass

Email correspondence concerning dissolution review:

From: Marroum, Patrick J
Sent: Friday, July 22, 2011 08:57 AM
To: Christner, Donna
Cc: Dorantes, Angelica
Subject: RE: NDA 202276 Dissolution evaluation

Donna:

A cmc reviewer can handle the dissolution method.

Patrick

From: Christner, Donna
Sent: Thursday, July 21, 2011 7:51 PM
To: Marroum, Patrick J
Cc: Dorantes, Angelica
Subject: Re: NDA 202276 Dissolution evaluation

Hi Patrick,

Given the information below, should the CMC reviewer evaluate the dissolution method, or will you assign a BioPharm reviewer for the application?

Thanks,

Donna

From: Marroum, Patrick J
Sent: Thursday, July 21, 2011 09:09 AM
To: Christner, Donna
Cc: Dorantes, Angelica
Subject: RE: NDA 202276 Dissolution evaluation

Donna:

Yes, Thank you.

Patrick

From: Christner, Donna
Sent: Wednesday, July 20, 2011 7:50 PM
To: Marroum, Patrick J
Cc: Dorantes, Angelica
Subject: RE: NDA 202276 Dissolution evaluation

Hi Patrick,

As far as your question about a biowaiver, here is something from the discussion at the preNDA meeting held in Oct 2010.

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This is the study design for the BE study. 200 mg tablets were not used:

<< OLE Object: Picture (Enhanced Metafile) >>

Is this the kind of information you need?

Thanks,

Donna

From: Christner, Donna
Sent: Wednesday, July 20, 2011 12:40 PM
To: Marroum, Patrick J
Cc: Dorantes, Angelica
Subject: RE: NDA 202276 Dissolution evaluation

Hi Patrick,

There was a formulation change during development and they performed a BE study to bridge the two formulations.

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Dissolution was performed in four different media (pH 1.2, 4.0, 6.8 and water) using the 50 mg tablets. The NDA is for 50 mg, 100 mg and 200 mg strength. Tablets are from a (b) (4)

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As far as the dissolution method goes, they are using Apparatus 2 @ 50 RPM, simulated gastric fluid w/o pepsin, and a spec of Q= (b) (4) at 15 minutes.

I am attaching my draft IQA which contains a list of the clinical studies performed and a comparison of the formulation change at the end of the document. I was fairly silent on dissolution since I assumed that ONDQA BioPharm would evaluate it. It was after discussion with Moo-Jhong that it was determined that this may fall under the IQP.

Thanks,

Donna

<< File: IQA 202276_avanafil .doc >>

From: Marroum, Patrick J
Sent: Wednesday, July 20, 2011 11:50 AM
To: Christner, Donna
Cc: Dorantes, Angelica
Subject: RE: NDA 202276 Dissolution evaluation

is there any biowaiver request within the NDA or any other biopharmaceutics issues?

Patrick

From: Christner, Donna
Sent: Wednesday, July 20, 2011 7:02 AM
To: Marroum, Patrick J; Dorantes, Angelica
Subject: NDA 202276 Dissolution evaluation

Good morning Patrick and Angelica,

We have a new NDA for an IR tablet for an NME. In discussions with Moo-Jhong, it was determined that the dissolution information in this application could be reviewed by the primary CMC reviewer. What information (if any) do you need to provide concurrence?

Thanks in advance,

Donna

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

/s/

DONNA F CHRISTNER
07/28/2011

MOO JHONG RHEE
07/28/2011
Chief, Branch IV