CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022526Orig1s000

CHEMISTRY REVIEW(S)

NDA 22526

Addyi (flibanserin) Tablets, 100 mg

Sprout Pharmaceuticals Inc

Zhengfang Ge, Ph.D.

Branch V, Division of New Drug Quality Assessment II

For

Division of Bone, Reproductive and Urologic Products

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Chemistry Review Data Sheet

1. NDA 22526

2. REVIEW #3

3. REVIEW DATE: 8-June-2015

4. REVIEWERS: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	June 23, 2010
Review #2	Sep 10, 2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (#0062)	Feb 12, 2015
Amendment (#0069)	May 4, 2015
Amendment (#0070)	May 6, 2015
Amendment (#0072)	May 29, 2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Sprout Pharmaceuticals, Inc.
Address:	4608 Six Forks Rd Suite 1010 Raleigh, NC 27609
Representative:	Richard A. Davan, Director of Regulatory Affairs
Telephone:	919-882-0850

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Addyi
b) Non-Proprietary Name (USAN): Flibanserin
CAS Registery #: 167933-07-5

Internal Code: BIMT 17 BS
Chem. Type/Submission Priority (ONDP only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Premenopausal hypoactive sexual desire disorder (HSDD)

11. DOSAGE FORM: Immediate release tablets

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

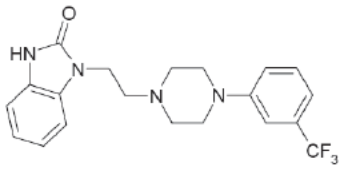
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

CAS Name:
2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl) phenyl-]-1-piperazinyl]ethyl]-

Structure:



Molecular Formula: $C_{20}H_{21}F_3N_4O$
Molecular Weight: 390.41 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III		(b) (4)	3	Adequate	23-Sep-2005 by D. Klein	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	18-Mar-2009 by B. Kurtyka	
	III			3	Adequate	05-April-2002 by J. Boal	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	23-Jan-2008 by B. Kurtyka	
	III			3	Adequate	21-May-2008 by A. Schroeder	

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

None

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

Chemistry Review Data Sheet

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections		pending	
Pharm/Tox				See Review #1
Biopharm	Dissolution		Acceptable	See Biopharm review by Dr. V. R. Kolhatkar dated 19-May-2015
DMEPA	N/A			
Methods Validation				See Review #1
EA				See Review #1
Microbiology	N/A			

The Chemistry Review for NDA 22526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure identity, strength, purity, and quality of the drug.

Overall "Acceptable" recommendation has been issued for the facilities involved.

The labels/labeling are satisfactorily resolved.

Therefore from the CMC perspective, this NDA is recommended for a***pproval*** with an expiration dating period of 48 months.

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

None

II. Summary of Chemistry Assessment

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

The NDA was recommended for "Approval" from CMC perspective in the Review #1 and #2. In this resubmission, the applicant proposed to change the drug product manufacturer from BI to [redacted] (b) (4). The applicant also proposed to change the 30 count tablet [redacted] (b) (4) HDPE bottles to 30 cc bottles. [redacted] (b) (4) The new manufacturer uses a comparable manufacturing process [redacted] (b) (4) controls. Same test methods are provided in the drug product specification except that the alternative [redacted] (b) (4) method for content uniformity will not be used in the new facility. The analytical methods have been transferred from BI to [redacted] (b) (4). Information for the method transfer is provided in the resubmission and adequate. Stability data including 9 month at long term storage condition and 6 months at accelerated storage condition are provided for one batch of the drug product packaged in 30 cc HDPE bottles and manufactured at [redacted] (b) (4). The tests conducted for the stability study met the specification and are comparable to the previous batches manufactured at BI. The applicant updated stability data for the primary drug product batches to 36 months. Since no signification changes have happened under the accelerated condition, the proposed 48 months expiration dating period is granted per ICH Q1E

Biopharm reviewer has reached an "Approval" recommendation.

Division of Inspection and Facility in OPF has reached an overall "Approval" recommendation for the facilities involved.

Labels and labeling have required information from the CMC perspective.

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

The proposed drug is a 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist and it is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women

The dose is 100 mg taken once daily at bedtime with or without food

C. Basis for Approvability or Not-Approval Recommendation

The raw materials are well controlled and processes and controls are deemed satisfactory for manufacturing the same quality of the drug product consistently. The proposed specifications for the drug substance and drug product are also deemed adequate to assure the statutory requirements for the drug substance and the drug product.
Stability data indicate that the drug product will provide, during the expiration dating period of 48 months, the same efficacy and safety profile as demonstrated by the clinical batches used in the pivotal clinical studies.

Facilities are in compliance with cGMP.

Labels and labeling have required information from the CMC perspective.

III. Administrative

A. Reviewer's Signature

Zhengfang Ge -S

Digitally signed by Zhengfang Ge -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhengfang Ge -S, 0.9.2342.19200300.100.1.1=1300225581
Date: 2015.07.16 12:26:11 -04'00'

Chemistry Reviewer: Zhengfang Ge, Ph.D.

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Moojhong Rhee -S, 0.9.2342.19200300.100.1.1=1300041261
Date: 2015.07.16 12:34:07 -04'00'

Branch Chief: Moo-Jhong Rhee, Ph.D.

B. Endorsement Block

Chemistry Reviewer: Zhengfang Ge, Ph.D.
Branch Chief: Moo-Jhong Rhee, Ph.D.

C. CC Block

CMC Lead: Mark Seggle, Ph.D.
Project Manager: Jennifer L. Mercier

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S. DRUG SUBSTANCE

S.2.1 Manufacturers

No changes were made for the drug substance. The names and addresses of the drug substance manufacturing sites remain the same.

Company Name & Address (CFN/FEI Number)	Operation(s) Performed
[redacted] (b) (4)	Manufacturing, labeling, testing, and stability testing
	[redacted] (b) (4) packaging

Evaluation: Adequate
The manufacturing facilities are acceptable.

P. DRUG PRODUCT [Flibanserin Tablets, 100 mg]

This is the 3rd review of the product. Complete responses were issued for the NDA on Aug 10, 2010 and Sep 23, 2013. No CMC related deficiencies were found during the previous review circles. Therefore, only new information in this resubmission is reviewed.

P.1 Description and Composition of the Drug Product

In the previous submission, the applicant changed the ownership from BI to Sprout, and changed the [redacted] (b) (4) to a symbol of 'f100' debossed on one side of the tablet. The coating color was changed [redacted] (b) (4) to [redacted] (b) (4) pink [redacted] (b) (4). This information has been recaptured in this resubmission. Therefore, no change has actually been made since review #2 for the components/composition.

The proposed market package presentation for flibanserin tablets, 100 mg, is 30 cc HDPE plastic bottles, which is changed from previous [redacted] (b) (4)

Evaluation: ***Adequate.***
No change has been made since review #2 for the components/composition of the product. The proposed container/closure system has been changed [redacted] (b) (4) to 30 cc bottles. [redacted] (b) (4)

P.3 Manufacture [Flibanserin Tablets, 100 mg]

P.3.1 Manufacturers

Boehringer Ingelheim Roxane Inc. at Columbus, OH was previous manufacturer. The applicant proposed to change the manufacturer from BI to [redacted] (b) (4). [redacted] (b) (4) was also the manufacturer for the product used in clinical trials SPR-14-01 and SPR-14-06

Table 1 Commercial Manufacturer(s)

Company Name & Address (CFN/FEI Number)	Operation(s) Performed
[redacted] (b) (4)	Manufacturing, packaging, labeling, testing, stability
	Excipients testing

Evaluation: Adequate
The manufacturing facilities are acceptable.

P.3.2 Batch Formula

Table 1 Batch Formula for Flibanserin Film-coated Tablets, 100 mg

Ingredient	per Batch (kg) (Approx. (b) (4) Tablets)
	(b) (4)
Flibanserin	
Lactose monohydrate	(b) (4)
Microcrystalline cellulose	
Hypromellose	(b) (4)
Croscarmellose sodium	
Magnesium stearate	
	(b) (4)
(b) (4) Pink	(b) (4)
	(b) (4)
Total theoretical weight of coated tablets batch	
	(b) (4)

Evaluation:
The batch formula provided in this section of the submission is the same as the batch formula that was manufactured at BI. However, as information provided in the technology transfer report and the Master Batch Report for the product to be manufactured at (b) (4) the batch scales are (b) (4). Although the batch size is different, the quantitative composition of the batch formula is proportional. The applicant needs to clarify what the exact batch size will be manufactured for the commercial batches at the new site.

Information Request:

- *You have provided batch sizes of (b) (4) for the core tablets in (b) (4) technology transfer report, but (b) (4) in section 3.2.P.3.2. Please clarify the commercial batch size for the drug product to be manufactured at (b) (4) and update the information in section 3.2.P.3.2*

Response provided in the amendment dated 6-May-2015
The applicant confirms that the commercial batch size is (b) (4) for the uncoated cores. The updated batch formula is provided below:

Table 1 Batch Formula for Flibanserin Film-coated Tablets, 100 mg

Ingredient	per Batch (kg) (Approx. (b) (4) Tablets)
	(b) (4)
Flibanserin	(b) (4)
Lactose monohydrate	(b) (4)
Microcrystalline cellulose	
Hypromellose	(b) (4)
Croscarmellose sodium	
Magnesium stearate	
	(b) (4)
(b) (4) Pink	(b) (4)
	(b) (4)
Total theoretical weight of coated tablets batch	
	(b) (4)

Evaluation: Adequate

P.3.3 Description of Manufacturing Process and Process Controls

Details of the manufacturing transfer and comparative manufacturing process of two sites are provided in this section. A flow diagram of the process to be used in (b) (4) is provided below:

Figure 1: Manufacturing Process Flowchart

(b) (4)

provided in (b) (4) Master Batch Record-Manufacturer. After (b) (4), the following in-process tests are conducted with the limits shown in the Table, as provided in (b) (4) Master Batch Record-(b) (4)

II. QUALITY ASSURANCE SPECIFICATIONS

(b) (4)

Test	Limits	Results	Approved By/Date	Approved By/Date
A. Organoleptic	White, oval-shaped tablets, debossed "f100" on one side			
B. Average Weight Variation	(b) (4)			
Individual Weight Variation				
C. Hardness				
D. Thickness				
E. Friability				
F. Disintegration (b) (4)				

Evaluation:

The manufacturing process at BI used (b) (4)

Individual Weight Variation	
BI	(b) (4)

(b) (4)

Information Request:

- *According to the Quality Assurance Specification provided in* (b) (4) *Master Batch Record-* (b) (4) *Please clarify what the* (b) (4) *control will be used for commercial product at* (b) (4) *and justify for the difference from the one used at BI.*

Response provided in the amendment dated 6-May-2015

The applicant agreed that (b) (4) *will amend their procedures to reflect the BI* (b) (4)

(b) (4)

Evaluation: Adequate

P.5 Control of Drug Product [Flibanserin Tablets, 100 mg]

P.5.3 Validation of Analytical Procedures

Same test methods are provided in the drug product specification. The analytical methods for Assay, Degradation Products, Uniformity of Dosage Units, Identification and Dissolution using HPLC were transferred from BI to (b) (4). Method transfer protocol and acceptance criteria were provided in the submission. The results from (b) (4) were compared to the results listed on the BI Certificate of Analysis (COA) and the experimental results meet the established pre-approved acceptance criteria.

Evaluation: *The protocol and test results of method transfer from BI to (b) (4) were provided for HPLC methods used in Assay, Degradation Products, Uniformity of Dosage Units, Identification and Dissolution. The protocol includes the details of the experiment design, acceptance criteria and verification of system suitability. Test results of the method transfer are reviewed and acceptable. However, no method transfer for (b) (4) content uniformity, which is an alternative method in drug product specification, is provided in the method transfer. The applicant needs to provide the method transfer for the (b) (4) content uniformity or delete this method in the specification if it is not intended to be used in the new site*

Information Request:

- *Please provide an updated drug product specification with the test methods that have been transferred from BI to (b) (4).*

Response provided in the amendment dated 6-May-2015

The applicant provided the following updated specification with (b) (4) document for the methods

Test	Analytical Procedure	Acceptance Criteria
Description	FPSPMF1189A	Pink, oval, biconvex, film-coated tablets, one side debossed with "f 100"
Identification A (HPLC)	FPSPMF1189A	The retention time of the flibanserin peak of the Sample Preparation corresponds to that of the Standard Preparation
Identification B (UV-PDA)	FPSPMF1189A	The UV spectrum of the flibanserin peak of the Sample Preparation corresponds to that of the Standard Preparation
Assay: Flibanserin	FPSPMF1189A	90.0 % – 110.0 % of label claim
Any Unspecified Degradation Product:	FPSPMF1189A	Not more than (b) (4)%
Total Degradation Products:	FPSPMF1189A	Not more than %[a]
Content Uniformity: Flibanserin	FPSPMF1189A	Meets USP <905> requirements[a]
Dissolution: Flibanserin	FPSPMF1189A	Meets USP requirements (S1, S2, S3): Q = (b) (4)% of label claim at 30 minutes
Microbial Limits[b]	FPSPMF1189A – MICROBIAL LIMITS	Total Aerobic Microbial Count: Not more than (b) (4) Total Yeasts and Molds Count: Not more than (b) (4) E. coli: Absent

[a] USP <905> LIMITS for Content Uniformity are as follows: SI: AV ≤15.0; SII: AV ≤15.0, no dosage units less than 0.75M nor more than 1.25M.

[b] Microbial Limits – If the first three production batches are within acceptance criteria, this test is not required for further batches.

Evaluation: Adequate

The applicant provided the above updated specification. At the Agency's request, the applicant provided document for the analytical procedure FPSPMF1189A as shown in the above Table. The test methods are the same as the ones submitted in the original submission. (b) (4) method as an alternative method for the content uniformity in the original submission will not be used in this new facility.

P.7 Container Closure System [Flibanserin Tablets, 100 mg]

The Container Closure System has been changed (b) (4) to 30 cc. bottle with a plastic (b) (4) and an induction foil seal liner. The surfaces in direct contact with the product are HDPE

and the induction foil seal liner. A description of the container closure components and the materials of construction are provided in the following Table:

Table 1 Primary Packaging Components

Component		Material of Construction	
Description	Supplier & DMF No.	Description	Supplier
Bottle: White, high density polyethylene (HDPE), 30 cc, (b) (4) (b) (4)	(b) (4)	HDPE (b) (4 (b) (4	(b) (4)
Cap: (b) (4)			

Evaluation: ***Adequate***

The bottle has been changed (b) (4). The materials in contact with the drug product are the same as the ones that were previously reviewed and therefore are acceptable.

P.8 Stability [Flibanserin Tablets, 100 mg]

P.8.1 Stability Summary and Conclusions

The applicant updated the stability data that have been collected since original submission. Stability results including 36 month at long-term condition (25°C/60% RH) and 6 months at accelerated condition (40°C/75% RH) are provided for the primary stability batches packaged in 30 count (b) (4) HDPE bottles (b) (4) . Stability results including 24 month at long-term conditions and 6 months at accelerated condition are provided for the product using (b) (4) Pink (b) (4). In addition, the applicant initiated an additional stability study for one batch of the product packaged in 30 cc bottles that were manufactured at (b) (4) 9 month stability data at 25°C/60RH and 30°C/75RH, 6 months at 40 C/75RH for this batch were available at the time of submission. The updated stability studies covering all the changes since the original NDA submission are summarized in the following Tables:

Table 1 Tabulated Summary of Completed Stability Studies

Type of Stability Study	Storage Condition	Packaging	(b) (4)	100 mg	Maximum Storage Period	Results
				nes		
Stress stability	(b) (4)			1	12 months	No change over time
	25°C/60% r.h.	Open storage		1	12 months	No change over time
	30°C/75% r.h.	Open storage		1	12 months	No change over time
	40°C/75% r.h.	Open storage		1	6 months	No change over time
	(b) (4)			1	14 hours	No change
Primary accelerated and long-term stability				3	36 months	No change over time
				3	6 months	No change over time
				3	36 months	No change over time
				3	6 months	No change over time

* According to ICH Guideline Q1B.

Table 2 Tabulated Summary of On-going Stability Studies for Flibanserin Film-coated Tablets, 100 mg

Type of Stability Study	Storage Condition	Packaging	No. of Batches on Stability	Latest Available Data	Results
Colorant change stability					(b) (4)
Additional primary accelerated and long-term stability	(b) (4) 25°C/60% r.h.	30 cc HDPE bottle	1	9 months	No change over time
	30°C/75% r.h.	30 cc HDPE bottle	1	9 months	No change over time
	40°C/75% r.h.	30 cc HDPE bottle	1	6 months	No change over time

No changes were observed for any of the test parameters at any of the storage conditions investigated. No degradation products more than the reporting threshold were detected. All results meet the specifications.

Based on 1) 36 months real time stability data for 3 primary batches of the drug product packaged in (b) (4) HDPE bottles (b) (4), 2) 24 months stability data for the equivalent product using the new (b) (4) film-coating colorant (see review #2), 3) 9 month stability data for one batch of the product packaged in the 30 cc HDPE bottles, (b) (4) the applicant proposed 48 months expiration dating period for the drug product packaged in 30 counts 30 cc HDPE bottles at the controlled temperature.

Evaluation: Adequate

The applicant provided sufficient stability data to demonstrate the stability of the drug product in 36 months. No signification changes will be expected according to the statistical analysis. The proposed 48 months expiration dating period is acceptable according to ICH Q1A. See review in section P.8.3. Stability Data

P.8.2 Post Approval Stability Protocol and Stability Commitment

The following stability commitments are provided:

1) Testing will continue to be performed on the colorant stability batch of 100 mg tablets in the (b) (4) HDPE bottle according to the protocol.
2) Testing will continue to be performed on the additional primary stability batch of 100 mg tablets in the 30 cc HDPE bottle according to the protocol
3) Sprout Pharmaceuticals commits to stability testing the first 3 routine production batches manufactured and packaged according to the commercialized manufacturing process. The stability studies once initiated will be performed at the long-term storage condition according to the protocol shown in Table 3 (shown below). The stability studies will continue for a total period of 48 months.

Table 3 **Storage Conditions, Time-points and Test Parameters for Stability Testing of the First Three Routine (b) (4) Production Batches (Flibanserin Tablets, 100 mg with (b) (4) Film-coat (b) (4)**

Storage Condition (Batch)	Time (Months)									
	0	1	3	6	9	12	18	24	36	48
25°C/60% r.h. (1)	A			B	B	B	B	B	B	B
25°C/60% r.h. (2)	A		B		B	B		B	B	B
25°C/60% r.h. (3)	A		B	B		B	B		B	B

Key to Test Parameters:

A = Description
Dissolution
Assay for Flibanserin
Degradation Products:
Any Unspecified Degradation Product
Total Degradation Products
Microbial Limits:
Total Aerobic Microbial Count
Total Yeasts and Molds Count
E. Coli

B = Description
Dissolution
Assay for Flibanserin
Degradation Products:
Any Unspecified Degradation Product
Total Degradation Products

4) Long-term stability testing at 25°C/60% RH will be carried out on at least one (1) commercial batch produced during each year of manufacture, if at least one (1) batch is produced. The batches will be tested according to the protocol through the shelf life.
5) The results of the stability studies on the commercial batches will be reported to the FDA in the Annual Report. In accord with 21 CFR 314.70(d)(5), the shelf life for the drug product may be extended in the Annual Report based on acceptable stability data from these studies.
6) Any batch found to fall outside the approved specification for the drug product will be withdrawn from the market. If there is evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the drug product, the deviation will be immediately discussed with the FDA Division and justification will be provided for the continued distribution of that batch. The change or deterioration in the distributed drug product will be reported to the FDA.

Evaluation: Adequate

The post stability protocol and commitment have been updated to 48 months real time stability study. The tests included in the stability studies remain unchanged. The updated information is adequate.

P.8.3 Stability Data

Stability results for the primary stability batches and colorant change batch continue to meet the specification for 48 months and 24 months respectively. Stability data including 9 month at 25°C/60% RH and 30°C/75% RH and 6 months 40°C/75% RH are provided for one batch of the drug product packaged in 30 cc HDPE bottles and manufactured at (b) (4). Stability data for description, assay, dissolution and degradation products are provided in the resubmission.

Physical Testing
All physical test results for description meet the product specification limits through the 9-month time-point for both long-term (25°C/60% RH and 30°C/75% RH) and 6-month time-point for the accelerated (40°C/75% RH) storage conditions. No change in the product was observed.

Chemical Testing
All chemical tests results for dissolution, assay for Flibanserin, any unspecified degradation product, and total degradation product meet product specification limits through the 9-month time-point for both long-term (25°C/60% RH and 30°C/75% RH) and 6-month time-point for the accelerated (40°C/75% RH) storage conditions. No change in the product was observed.

Evaluation: Adequate
Stability results are reviewed. The stability results for the product packaged in 30 cc bottle are in agreement with the previously generated primary and on-going colorant stability data for 9 months under long-term conditions (both at 25°C/60% RH and 30°C/75% RH) and 6 months under accelerated conditions (40°C/75% r.h.). Since the head space of a 30 cc bottle (b) (4) *to a 30 cc bottle should not adversely affect the product stability. Therefore, the expiration dating period proposed in P.8.1 based on the primary stability batches is acceptable.*

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The applicant provided in the Labeling section the proposed labeling text, samples of carton label and container label.

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

DRUG (flibanserin) Tablets

Evaluation: **Satisfactory**

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Proprietary name: ADDYI Established name: flibanserin **Satisfactory**
Dosage form, route of administration	Tablets **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	Tablets: 100 mg **Satisfactory**
Whether the drug product is scored	N/A

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

DRUG tablets are available as 100 mg, oval, pink film-coated tablets debossed on one side with "f100" and blank on the other side.

Evaluation: Satisfactory

Item	Comments on the Information Provided in NDA
Available dosage forms and	Tablet, 100 mg

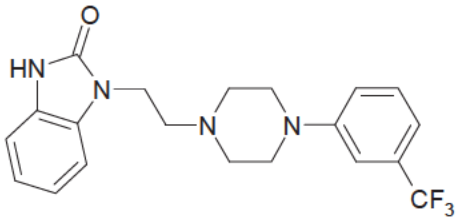
strengths: in metric system	**Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	oval, pink film-coated tablets debossed on one side with "f100" and blank on the other side **Satisfactory**

#11. Description

(b) (4)

The chemical name of flibanserin is 2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]-. Its empirical formula is $C_{20}H_{21}F_3N_4O$ and its molecular weight is 390.41.

The structural formula is:



Flibanserin is a white to off-white powder, insoluble in water, sparingly soluble in methanol, ethanol, acetonitrile, and toluene, soluble in acetone, freely soluble in chloroform, and very soluble in methylene chloride.

Each ADDYI tablet contains 100 mg of flibanserin. Inactive ingredients consist of lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, (b) (4), and the coloring agents, titanium dioxide and iron oxide.

Evaluation: minor edit needed during labeling review

Item	Comments on the Information Provided in NDA
Proprietary name and established name	Proprietary name is indicated. Established name is provided as flibanserin. The full name that is1st appeared in this section has been changed to "ADDYI (flibanserin)" during team labeling review **Satisfactory**
Dosage form and route of administration	Tablets **Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	N/A

Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	Inactive ingredients are provided **Satisfactory.**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist **Satisfactory.**
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Solubility information is provided

#16. How Supplied/Storage and Handling

ADDYI is available as 100 mg oval, pink, film-coated tablets debossed on one side with "f100" and blank on the other side. Available in bottles of 30 tablets. (NDC 0000-0000-00)
Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

Evaluation: Satisfactory

Item	Comments on the Information Provided in NDA
Strength of dosage form	100 mg **Satisfactory**
Available units (e.g., bottles of 100 tablets)	bottles of 30 tablets **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	provided **Satisfactory.**
Special handling (e.g., protect from light)	N/A
Storage conditions	provided **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	This is provided at the end of labeling Distributed by: Sprout Pharmaceuticals, Inc. Raleigh, NC 27609 USA **Satisfactory.**

#17. Patient Labeling

The following information is provided in the patient labeling

DRUG (flibanserin) Tablets

How should I store ADDYI?

- Store ADDYI at room temperature between (b) (4) °F (b) (4) °F ((b) (4) °C).
- Keep ADDYI and all medications out of the reach of children.

What are the ingredients in DRUG (b) (4)?

- Active Ingredient: flibanserin
- Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, (b) (4), and the coloring agents titanium dioxide and iron oxide

Distributed by:
Sprout Pharmaceuticals, Inc.
Raleigh, NC 27609 USA

Product and trademark licensed from:
Sprout Pharmaceuticals, Inc.

2. **Immediate container label**

(b) (4)

Evaluation: Satisfactory

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	addyi (flibanserin) tablets 100 mg ***Satisfactory***
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	100 mg. **Satisfactory**
Net contents (21 CFR 201.51(a))	30 tablets **Satisfactory**
"Rx only" displayed prominently on the main panel	Provided **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	Provided **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Provided **Satisfactory**
Storage conditions	Stored at 25°C (77°F) (see insert) **Satisfactory**

Bar code (21CFR 201.25)	Not Provided **Acceptable for the** (b) (4) **bottle**
Name of manufacturer/distributor	Provided **Satisfactory**
And others, if space is available	Keep out of reach of Children (b) (4) ***Satisfactory***

3. Carton label

(b) (4)

Evaluation: Satisfactory

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	addyi (flibanserin) tablets, 100 mg **Satisfactory**
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	100 mg **Satisfactory**
Net quantity of dosage form (21 CFR 201.51(a))	30 tablets **Satisfactory**
"Rx only" displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed, but need to move to prominent place (see DMEPA review) **Satisfactory**
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Provided **Satisfactory**
Storage conditions	Provided.

	Satisfactory
Bar code (21CFR 201.25)	Provided. **Satisfactory**
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	Provided. **Satisfactory**
Manufacturer/distributor's name 21CFR201.1(a)	Provided **Satisfactory**
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	N/A **Satisfactory**
Statement of being sterile (if applicable)	N/A
(b) (4))	(b) (4) **Satisfactory**
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	Provided **Satisfactory**
Route of Administration (21 CFR 201.100(b)	Tablets **Satisfactory**

III. List Of Deficiencies

None

IV. Attachments

Overall recommendation from the Office of Compliance

NDA 022526-Orig1-Resubmission/Class 2(64) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary | Task Details | Issues | Updates | More

Overview | Facility Inspection - Overall Application Recommendation

Edit Custom Form

Custom Form
Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation

Facility Inspection - Overall Application Recommendation
Approve

Facility Inspection - Overall Application Re-evaluation Date
6/29/15

Navigation Links

Form Link
http://panorama.fda.gov/task/view?ID=54e5a03700039b083bfd66785fd52bd5&activeTab=content-dashboard__5418eab10003b6cd5f0c5f929c4fa823

Assigned To
Donald Lech
Edit Assignment
This was done on
Jun 3, 2015
(Yesterday)
Status
Complete
This task is waiting on
2 Tasks
Last Update
Jun 3, 2015
Submitted On
Feb 19, 2015
Reference Number
3955434

Memorandum

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

Date: **September 10, 2013**

From: **Zhengfang Ge, Ph.D.**
CMC Reviewer, Branch IV
New Drug Quality Assessment Division II
ONDQA

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
New Drug Quality Assessment Division II
ONDQA

To: **CMC Review #2 of NDA 22526**

Subject: **Final Recommendation**

The CMC Review #2 dated 28-Aug-2013 had noted the following two pending issues:

1. 21CFR 314.125(b)(13)
   - Inspection of the manufacturing is pending overall recommendation from the Office of Compliance on the site acceptability.

2. 21 CFR 314.125(b)(6)
   - Deficiencies of the labels in the resubmission have not been resolved.

And because of these deficiencies, in the CMC Review #2, this NDA was not recommended for approval from the ONDQA perspective.

On September 10, 2013, the Office of Compliance **issued an overall "*Acceptable*"** recommendation for the inspections of the manufacturing facilities (see the **Attachment**).

However, label/labeling issues have ***not*** been finalized.

Final Recommendation:

From the ONDQA perspective, this NDA is ***not*** recommended for ***approval*** in its present form based on the following:

21 FR 314.125(b)(6)
- Deficiencies of the labels in the resubmission have not been resolved.

Attachment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22526/000	**Sponsor:**	SPROUT PHARMS
Org. Code:	580		4208-6 FORKS RD STE 1016
Priority:	1		RALEIGH, NC 27609
Stamp Date:	27-OCT-2009	**Brand Name:**	FLIBANSERIN
PDUFA Date:	29-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	FLIBANSERIN
District Goal:	31-JUL-2013	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; TABLET; FLIBANSERIN; 100MG	

FDA Contacts:	Z. GE	Prod Qual Reviewer	3017961358
	K. JENNINGS	Product Quality PM	3017962919
	Z. WILLIAMSON	Regulatory Project Mgr	3017961025
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 10-SEP-2013	by T. SHARP	()	3017963208
	ACCEPTABLE	on 21-JUN-2010	by STOCKM		

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-APR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE (b) (4) DRUG SUBSTANCE PACKAGER		
Profile:	(b) (4)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	10-SEP-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	CFN: FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE (b) (4) DRUG SUBSTANCE PACKAGER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-APR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

ZHENGFANG GE
09/10/2013

MOO JHONG RHEE
09/10/2013
Chief, Branch IV

NDA 22526

Addyi (flibanserin) Tablets, 100 mg

Sprout Pharmaceuticals Inc

Zhengfang Ge, Ph.D.

Branch IV, Division of New Drug Quality Assessment II

For

Division of Bone, Reproductive and Urologic Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22526

2. REVIEW #2

3. REVIEW DATE: 28-Aug-2013

4. REVIEWERS: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	June 23, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (#0039)	March 28, 2013
Amendment (#0046)	June 14, 2013
Amendment (#0048)	July 18, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Sprout Pharmaceuticals, Inc.
Address:	4608 Six Forks Rd Suite 1010 Raleigh, NC 27609
Representative:	Richard A. Davan, Director of Regulatory Affairs
Telephone:	919-882-0850

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Addyi
b) Non-Proprietary Name (USAN): Flibanserin
CAS Registery #: 167933-07-5
Internal Code: BIMT 17 BS
Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Premenopausal hypoactive sexual desire disorder (HSDD)

11. DOSAGE FORM: Immediate release tablets

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

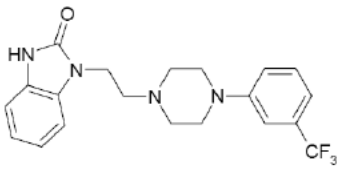
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

CAS Name:
2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl) phenyl-]-1-piperazinyl]ethyl]-

Structure:



Molecular Formula: $C_{20}H_{21}F_3N_4O$
Molecular Weight: 390.41 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III		(b) (4)	3	Adequate	23-Sep-2005 by D. Klein	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	18-Mar-2009 by B. Kurtyka	
	III			3	Adequate	05-April-2002 by J. Boal	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	23-Jan-2008 by B. Kurtyka	
	III			3	Adequate	21-May-2008 by A. Schroeder	

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

None

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	(b) (4)	BI	Original IND

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULT	CMC Related Reviews	Recommendation	Dates	Reviewer
Biometrics	N/A			
EES	Site inspections	pending		
Pharm/Tox	Genotoxic impurity	Acceptable	10-Mar-2010	Dr. A. Alexander (see review #1)
Biopharm	Dissolution	Acceptable	7-Aug-2013	Dr. H. Mahayni
DMEPA	N/A			
Methods Validation	N/A			
EA	Environmental Assessment	Acceptable	12-Feb-2010	Dr. E. McVey (see review #1)
Microbiology	N/A			

The Chemistry Review for NDA 22526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure identity, strength, purity, and quality of the drug.

Labeling issues are still pending (see the List of Deficiencies at the end of this review).

Facilities involved are also pending overall "Acceptable" recommendation from the Office of Compliance.

Therefore from the CMC perspective, this NDA is ***not*** ready for a***pproval*** in its present form per 21 CFR 314.125(b)(6),(13) until all pending issues are resolved

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

None

II. Summary of Chemistry Assessment

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

The NDA was recommended for "Approval" from CMC perspective in Review #1 dated 23-June-2010. In this resubmission, the ownership of the NDA has been changed from BI to Sprout. Therefore, the [redacted] (b) (4) on one side of the tablets has been removed. In the original submission, the proposed commercial drug products were packaged in HDPE bottle containing 30 tablets [redacted] (b) (4) [redacted]. In this resubmission, the applicant proposed to market 30 tablets in HDPE bottles [redacted] (b) (4) [redacted]

A change to the coating film from [redacted] (b) (4) to [redacted] (b) (4) Pink [redacted] (b) (4) has been implemented in the resubmission. The new [redacted] (b) (4) Pink [redacted] (b) (4) is sourced from the same vendor. The two [redacted] (b) (4) pink are qualitatively and quantitatively similar. The applicant provided three months stability data (one batch [redacted] (b) (4) bottle package) for the drug products composed of the new [redacted] (b) (4) Pink. The tests conducted for the stability study include description, assay, dissolution and impurities and met the specification. The applicant also provided comparative dissolution profiles, and according to Biopharm's Review dated 8/7/13, the proposed change in the composition of [redacted] (b) (4) Pink for the coating film is acceptable.

Inspection of the manufacturing facilities has been requested through EES for the resubmission and is pending overall recommendation from the Office of Compliance on the site acceptability.

Deficiencies of the labels in the resubmission have been identified and will be conveyed to the applicant during team labeling review (see section III List of Deficiencies on page 25).

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

The proposed drug is a 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist and it is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women

The dose is 100 mg taken once daily at bedtime with or without food

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(13)

- Inspection of the manufacturing is pending overall recommendation from the Office of Compliance on the site acceptability.

21 CFR 314.125(b)(6)

- Deficiencies of the labels in the resubmission have not been resolved.

  (see section III **List of Deficiencies** on page 25).

III. Administrative

A. Reviewer's Signature

Electronic signature in DFS

B. Endorsement Block

Chemistry Reviewer: Zhengfang Ge, Ph.D.
Branch Chief: Moo Jhong Rhee, Ph.D.

C. CC Block

CMC Lead: Donna Christner, Ph.D.
Project Manager: Charlene Williamson

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S DRUG SUBSTANCE

S.2.1 Manufacturers

The NDA was transferred from BI to Sprout Pharmaceuticals, Inc. in Dec 2012. No changes were made for the drug substance in this resubmission. The names and addresses of the drug substance manufacturing sites remain the same. Inspections of the following manufacturing facilities have been requested through EES:

Company Name & Address (CFN/FEI Number)	Operation(s) Performed
(b) (4)	Manufacturing, labeling, testing, and stability testing
	(b) (4) packaging

Evaluation:
The manufacturing facilities are pending overall recommendation from the Office of Compliance.

P. DRUG PRODUCT [Flibanserin Tablets, 100 mg]

A complete response was issued for the original NDA on Aug 10, 2010. No CMC related deficiencies were found during the 1st review circle. Therefore, only new information in this resubmission is reviewed.

P.1 Description and Composition of the Drug Product

Since the change of the ownership from BI to Sprout, the (b) (4) on one side of the tablets has been removed. The description of the drug products, flibanserin film-coated tablets, 100 mg, are pink, oval, biconvex, film-coated tablets, with one side debossed with 'f100' and the

other side blank. The coating color has been changed from (b) (4) to (b) (4) pink (b) (4). The component and composition of two coatings are similar (see Tables below). The new color coating is sourced from the same vendor. In the original submission, the proposed commercial drug products are packaged in HDPE bottle containing 30 tablets (b) (4). In this resubmission, the applicant proposed tha (b) (4) packaging presentations will be made available as market package presentations including 30 tablets in HDPE bottles (b) (4)

Components/composition of the product is provided in the following Tables.

Table 1 Qualitative and quantitative composition of flibanserin film-coated tablets, 100 mg

Ingredient	mg per Tablet	Function	Reference to Standards
Flibanserin	100.000	Active ingredient	Company Standard
Lactose monohydrate (b) (4)	(b) (4)		NF/Ph. Eur./JP
Microcrystalline cellulose			NF/Ph. Eur./JP
Hypromellose (b) (4 (b) (4)			USP/Ph. Eur./JP
Croscarmellose sodium			NF/Ph. Eur./JP
Magnesium stearate (b) (4			NF/Ph. Eur./JP
			USP/Ph .Eur./JP
(b) (4) Pink (b) (4			Company Standard
Total	**347.0**		(b) (4)

Table 1 Qualitative and Quantitative Composition of Flibanserin Tablets, 100 mg

Ingredient	mg per Tablet	Function	Reference to Standards
Flibanserin	100.000	Active ingredient	Company standard
Lactose monohydrate (b) (4)	(b) (4)		NF/Ph. Eur./JP
Microcrystalline cellulose			NF/Ph. Eur./JP
Hypromellose (b) (4) (b) (4)			USP/Ph. Eur./JP
Croscarmellose sodium			NF/Ph. Eur./JP
Magnesium stearate (b) (4			NF/Ph. Eur./JP
			USP/Ph. Eur./JP
(b) (4) Pink (b) (4)			Company standard
Total	**347.0**		(b) (4)

Table 3 Comparison of Qualitative and Quantitative Composition of (b) (4) Pink (b) (4) and (b) (4) Pink (b) (4)

Ingredient	(b) (4)		Function
	mg per Tablet	mg per Tablet	
(b) (4)			(b) (4)
Titanium dioxide			
(b) (4)			
Iron oxide			
(b) (4)			
Total			

Evaluation: ***Adequate.***

The composition/components of the drug product remain mostly unchanged except that the coating color has been changed from (b) (4) to (b) (4) pink (b) (4). The above Table (Table 3) provided quantitative comparison for two coating agents. The new (b) (4) Pink (b) (4) is sourced from the same vendor and is qualitatively and quantitatively similar to the (b) (4) except (b) (4) is used in the new (b) (4) pink. The information provided in this section is adequate.

The applicant's proposal to market drug products in (b) (4) HDPE bottles (b) (4) acceptable since (b) (4) packaging presentations were reviewed and deemed acceptable in review #1. The applicant has provided sufficient stability data for (b) (4) packaging systems, see review in section P.8.

P.3 Manufacture [Flibanserin Tablets, 100 mg]

P.3.1 Manufacturers

Sprout contracts BI as manufacturer of the drug product. The manufacturing and testing facilities of the drug product remain unchanged. Inspection of the following manufacturing sites has been requested through EES.

Company Name & Address (CFN/FEI Number)	Operation(s) Performed
(b) (4)	Manufacturing, packaging, labeling, testing, stability
	Testing
	Excipients testing

Evaluation:
The manufacturing facilities are pending overall recommendation from the Office of Compliance.

P.4 Control of Excipients [Flibanserin Tablets, 100 mg]

P.4.1 Specifications

Specification for (b) (4) pink is provided in the following Table:

1 (b) (4) Pink (b) (4)

Test	Analytical Procedure	Release Acceptance Criteria
Description	Visual	Pink (b) (4)
Identification A	USP <197K>	The IR spectrum of the Sample corresponds to the IR spectrum of the Standard or previously approved lot.
Identification B	20002651-01	(b) (4)
Residue on Ignition (b) (4)	20002651-02	(b) (4)

Evaluation: Adequate.
A change to the coating film from (b) (4)) to (b) (4) Pink (b) (4) was implemented. The new (b) (4) Pink (b) (4) is sourced from the same vendor. The new (b) (4) pink is qualitatively and quantitatively similar to the (b) (4) Pink (b) (4).

Components of (b) (4) *pink are compendial as shown in the components/composition of* (b) (4) *pink provided in section P.1.*

P.8 Stability [Flibanserin Tablets, 100 mg]

P.8.3 Stability Data

To qualify the use of the new (b) (4) Pink (b) (4), one batch (Batch No. 4001397) was manufactured (b) (4) representing (b) (4) the qualified packaging configurations. The (b) (4) batches were placed on stability at both accelerated and long-term storage conditions. Stability data for description, assay, dissolution and degradation products through the 3-month test point from the (b) (4) batches are provided in the resubmission.

Physical Testing
All physical test results for description meet the product specification limits through the 3-month time-point for both the accelerated, 40°C/75% RH, and long-term, 25°C/60% RH, storage conditions. No change in the product was observed.

Chemical Testing
All chemical tests results for dissolution, assay for Flibanserin, any unspecified degradation product, and total degradation product met product specification limits through the 3-month time-point for both the accelerated, 40°C/75% RH, and long-term, 25°C/60% RH, storage conditions. No change in the product was observed.

Evaluation: Not Adequate
The applicant provided stability data for the test results of description, dissolution, assay and impurities. The test results all met the specification through 3 months. However, the applicant needs to provide COA for the release for drug product batches No. (b) (4). The following IR was conveyed to the applicant.

Information Request:

- *Please provide Certificate of Analysis (COA) for drug product batches No.* (b) (4) *including all the tests required in the drug product specification*

Response submitted on 13-June-2013:
The applicant explained that one batch (#4001397) was produced (b) (4) *for stability study. Therefore, only one COA for batch 4001397 including all the test results required in drug product specification is provided in the amendment.*

Evaluation: Adequate
The result provided in the amendment is reviewed and is satisfactory.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

The applicant provided in the Labeling section the proposed labeling text, samples of carton label and container label.

A. Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section

DRUG (flibanserin) Tablets

Evaluation: **Satisfactory**

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	Proprietary name: Trade name is indicated Established name: flibanserin **Satisfactory**
Dosage form, route of administration	Tablets **Satisfactory**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	Tablets: 100 mg **Satisfactory**
Whether the drug product is scored	N/A

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

DRUG tablets are available as 100 mg, oval, pink film-coated tablets debossed on one side with "f100" and blank on the other side.

Evaluation: Satisfactory

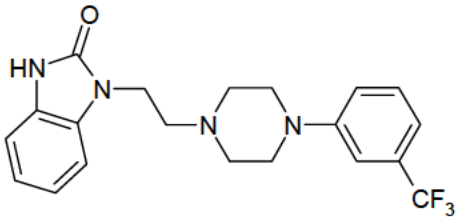
Item	Comments on the Information Provided in NDA

Available dosage forms and strengths: in metric system	Tablet, 100 mg **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	oval, pink film-coated tablets debossed on one side with "f100" and blank on the other side **Satisfactory**

#11. Description

(b) (4) The chemical name of flibanserin is 2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]ethyl]-. Its empirical formula is $C_{20}H_{21}F_3N_4O$ and its molecular weight is 390.41.

The structural formula is:



Flibanserin is a white to off-white powder, insoluble in water, sparingly soluble in methanol, ethanol, acetonitrile, and toluene, soluble in acetone, freely soluble in chloroform, and very soluble in methylene chloride.

(b) (4) contain 100 mg flibanserin. Inactive ingredients consist of lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, (b) (4) and the coloring agents titanium dioxide and iron oxide.

Evaluation: Not Satisfactory

Item	Comments on the Information Provided in NDA
Proprietary name and established name	Proprietary name is indicated. Established name is provided as flibanserin. However, the full name that is1st appeared in this section will be changed to "Drug (flibanserin) tablets" during team labeling review **Not Satisfactory**
Dosage form and route of administration	Tablets **Satisfactory.**
Active moiety expression of strength with equivalence statement (if applicable)	N/A

Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	Inactive ingredients are provided **Satisfactory.**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist **Satisfactory.**
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Solubility information is provided

This section is not satisfactory. The following minor change will be made during team labeling review:

- the full name that is1st appeared in this section will be changed from "(b) (4)" to "Drug (flibanserin) tablets"

#16. How Supplied/Storage and Handling

DRUG tablets (b) (4) available as 100 mg oval, pink, film-coated tablet (b) (4) debossed on one side with "f100" and blank on the other side. Available in (b) (4) bottles of 30 tablets. (NDC 0000-0000-00)

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Evaluation: Not Satisfactory

Item	Comments on the Information Provided in NDA
Strength of dosage form	100 mg **Satisfactory**
Available units (e.g., bottles of 100 tablets)	Available (b) (4) bottles of 30 tablets (b) (4) **Not Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	provided **Satisfactory.**
Special handling (e.g., protect from light)	N/A
Storage conditions	provided

	Satisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	This is provided at the end of labeling Distributed by: Sprout Pharmaceuticals, Inc. Raleigh, NC 27609 USA Product and trademark licensed from: Sprout Pharmaceuticals, Inc. **Satisfactory.**

This section is not satisfactory. The following minor change will be made during team labeling review:

- [redacted] (b) (4)

#17. Patient Labeling

The following information is provided in the patient labeling

DRUG (flibanserin) Tablets

How (b) (4) I store DRUG (b) (4)?

- Store DRUG (b) (4) at room temperature [77°F (25°C)].
- [redacted] (b) (4)
- Keep DRUG (b) (4) and all medications out of reach of children.

What are the ingredients in DRUG (b) (4)?

- Active Ingredient: flibanserin
- Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, (b) (4) and the coloring agents titanium dioxide and iron oxide

Distributed by:
Sprout Pharmaceuticals, Inc.
Raleigh, NC 27609 USA

Product and trademark licensed from:
Sprout Pharmaceuticals, Inc.

This section is satisfactory

2. Immediate container label

Label on Bottle

(b) (4)

[redacted]

Evaluation: Not Satisfactory

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	addyi (flibanserin) 100 mg tablets. ***Not Satisfactory*** *(The dosage form tablets should be moved to follow the established name shown as:* *addyi (flibanserin) tablets, 100mg)*
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	100 mg. **Satisfactory**
Net contents (21 CFR 201.51(a))	30 tablets **Satisfactory**
"Rx only" displayed prominently on the main panel	Provided **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	Provided **Satisfactory**
Lot number and expiration date (21 CFR 201.17)	Space is provided **Satisfactory**
Storage conditions	Stored at 25°C (77°F) (see insert) **Satisfactory**
Bar code (21CFR 201.25)	Provided **Satisfactory**
Name of manufacturer/distributor	Provided **Satisfactory**
And others, if space is available	Keep out of reach of Children (b) (4) [redacted]

Immediate container label for bottle of 30 tablets is not satisfactory:

- *The dosage form tablets should be moved to follow the established name immediately as shown below:*

  Addyi (flibanserin) tablets, 100mg
- *Remove the phrase shown* [redacted] (b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

3. Carton label

Carton label for Bottle Package

(b) (4)

[redacted]

Evaluation: Not Satisfactory

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	addyi (flibanserin, 100 mg) **Not Satisfactory** *The proprietary name, established name, dosage form and strength should be displayed on the main tab of the carton as shown below:* *Addyi (flibanserin) tablets , 100 mg*
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	100 mg **Satisfactory**
Net quantity of dosage form (21 CFR 201.51(a))	Not shown **Not Satisfactory** (b) (4)
"Rx only" displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is displayed. **Satisfactory**
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	Provided **Satisfactory**
Storage conditions	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Not provided **Not Satisfactory**
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	Not Provided **Not Satisfactory**
Manufacturer/distributor's name 21CFR201.1(a)	Provided **Satisfactory**
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	N/A **Satisfactory**
Statement of being sterile (if applicable)	N/A
(b) (4)	The statement of "Dosage: (b) (4) **Satisfactory**
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	Provided **Satisfactory**
Route of Administration (21 CFR 201.100(b)	Tablets **Satisfactory**

Carton Label for bottle package is not satisfactory

- *The proprietary name, established name, dosage form and strength should be displayed on the main tab of the carton as shown below:*

Addyi (flibanserin) tablets, 100 mg

- *Add net quantity, bar code. and NDC number*

(b) (4)

(b) (4)

[redacted]

III. List of Deficiencies

A. Regarding Inspection

- There has been no final recommendation from the Office of Compliance.

B. Regarding Label/Labeling

The following request will be conveyed to the applicant during the team labeling review:

1. The proprietary name, established name, dosage form and strength of the drug products should be displayed as following on carton and container labels:

   Addyi (flibanserin) tablets, 100mg

2. Remove the phrase [redacted] (b) (4)

3. Add net quantity, bar code, and NDC number for the carton label of bottle package.

4. [redacted] (b) (4) .

IV. Attachments

An "Acceptable" site recommendation from the Office of Compliance was made on 21-Jun-2010 for the original submission. However, facilities involved are pending overall recommendation for the current resubmission.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE PACKAGER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-APR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: (b) (4) FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE (b) (4) DRUG SUBSTANCE PACKAGER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-DEC-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	CFN: FEI: (b) (4) (b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE (b) (4) DRUG SUBSTANCE PACKAGER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-APR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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/s/

ZHENGFANG GE
08/30/2013

MOO JHONG RHEE
08/30/2013
Chief, Branch IV

MEMORANDUM

Date: July 23, 2010

To: NDA 22-526

From: Terrance Ocheltree, Ph.D., R. Ph.
Division Director
Division II, ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-526 Girosa (flibanserin) Tablets, 100 mg.

I have assessed the ONDQA review of NDA 22-526 by Zhengfang Ge, Ph.D. The review was finalized on June 23, 2010 with a recommendation for Approval. The Office of Compliance has recommended "Acceptable" for the proposed manufacturing and testing sites, as shown in EES. Sufficient information has been provided to assure identity, strength, purity and quality.

No post marketing commitments are proposed by ONDQA.

NDA 22-526 is for a film coated tablet containing 100 mg of flibanserin. It is indicated for premenopausal hypoactive sexual desire disorder. The proposed commercial packaging is a HDPE bottle, (b) (4) containing 30 tablets. A (b) (4) months expiration period has been proposed and granted when the product is stored at 25°C (77°F) with excursions permitted to 15-30°C.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

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/s/

TERRANCE W OCHELTREE
07/28/2010

NDA 22-526

Girosa (flibanserin) Tablets, 100 mg

Boehringer Ingelheim

Zhengfang Ge, Ph.D.

Branch IV, Division of New Drug Quality Assessment II

For

Division of Reproductive and Urologic Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-526

2. REVIEW #1

3. REVIEW DATE: 23-June-2010

4. REVIEWERS: Zhengfang Ge, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	Oct 27, 2009
Amendment	March 16, 2010
Amendment	April 13, 2010
Amendment	April 26, 2010
Amendment	May 27, 2010
Amendment	June 16, 2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc
Address:	900 Ridgebury Rd PO Box 368 Ridgefield, CT 06877
Representative:	Alexander Rochefort, Director Drug Regulatory Affairs
Telephone:	203-778-7610

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Girosa
b) Non-Proprietary Name (USAN): Flibanserin
CAS Registery #: 167933-07-5
Internal Code: BIMT 17 BS
Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Premenopausal hypoactive sexual desire disorder (HSDD)

11. DOSAGE FORM: Immediate release tablets

12. STRENGTH/POTENCY: 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

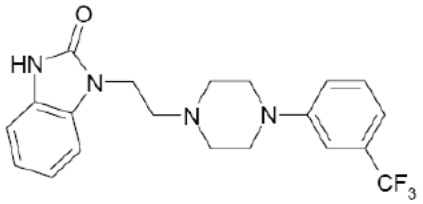
___X__Not a SPOTS product

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

CAS Name:
2H-Benzimidazol-2-one, 1,3-dihydro-1-[2-[4-[3-(trifluoromethyl) phenyl-]-1-piperazinyl]ethyl]-

Structure:

Chemistry Review Data Sheet



Molecular Formula: C20H21F3N4O
Molecular Weight: 390.41 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
(b) (4)	III		(b) (4)	3	Adequate	23-Sep-2005 by D. Klein	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	18-Mar-2009 by B. Kurtyka	
	III			3	Adequate	05-April-2002 by J. Boal	Reviewed previously and additional review not needed per review policy for solid oral dosage forms.
	III			3	Adequate	23-Jan-2008 by B. Kurtyka	
	III			3	Adequate	21-May-2008 by A. Schroeder	

[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)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

None

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	(b) (4)	BI	Original IND

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections		Acceptable	See the Attachment (p.81)
Pharm/Tox	Genotoxic impurity		Acceptable	See section S.3.2.
Biopharm	Dissolution		Revised per review	See section P.5
DMEPA	N/A			
Methods Validation	N/A per ONDQA's policy			
EA	Environmental Assessment		FONSI by Dr. E. McVey	See section II/B
Microbiology	N/A			

The Chemistry Review for NDA 22-526

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient/adequate information to assure the identity, strength, purity, and quality of the drug product.

An "Acceptable" site recommendation from the Office of Compliance has been made.

The labels and labeling (Description and How Supplied sections) have adequate information as required.

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

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

None

II. Summary of Chemistry Assessment

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

Drug Substance

The drug substance, flibanserin, is a new molecular entity. It is a non-hyproscopic, white to off white powder. It has no chiral centers and therefore does not form steroisomers. (b) (4) [redacted]

Flibanserin has good aqueous solubility at acidic pH values but is practically insoluble at neutral and basic pH. The structural identity (b) (4) [redacted].

The commercial manufacturing process for the drug substance is based on (b) (4) [redacted]

Potential process impurities are controlled in accordance with ICH Q3A and are acceptable. Flibanserin is a stable substance and no degradation products were observed during stability study even under the stressed conditions (except excessive UV exposure). The specification also includes testing for appearance, ID, assay, heavy metals, LOD, (b) (4) [redacted], and particle distribution. The acceptance criteria are set based on the batch data and ICH Q6A.

The applicant provided long term stability data up to 60 months and accelerated stability data up to 6 months based on three primary drug substance batches. Stability study was also conducted under stressed conditions. No degradation products are observed upon storage at high temperature, high humidity and the combined effects of humidity and temperature. Flibanserin is only slightly sensitive to photolysis in the solid state. The applicant proposed a retest period of (b) (4) months and is acceptable based on the stability data.

Drug Products

The proposed commercial drug product is film-coated tablet containing 100 mg of flibanserin with clinical indication of premenopausal hypoactive sexual desire disorder. The tablets are packaged in a HDPE bottle (30 tablets) (b) (4) All excipients in the tablets and coating components comply with USP/NF or Ph.Eur/ (b) (4) standards.

A typical process for immediate release tablets is utilized in the manufacturing process. The process involves (b) (4)

The drug product specification includes; description, identification, dissolution, uniformity of dosage unit, assay, degradation products, and microbial limits. The proposed primary test for content uniformity is weight variation which meets the requirement using weight variation according to USP<905>. HPLC and (b) (4) methods for the content uniformity are proposed as the alternative methods and are acceptable. The acceptance limit for dissolution was revised from (b) (4)% at 30 min to (b) (4)% at 30 min by the Agency's request. Due to extremely stable nature of the drug product, no identified degradation products were observed during the stability studies even under stressed conditions, Therefore, only unspecified impurities were controlled at NMT (b) (4)%.

Base on the stability data of 36 months at 25°C/60%RH and 6 months at 40°C/75%RH from the three primary stability batches of the drug products packaged in the proposed container/closure systems, the proposed expiration dating period of (b) (4) months for the drug products when stored at 25°C (77°F) with excursions permitted to 15 – 30°C (59 – 86°F) is granted.

The proposed labels and labeling (Description and How Supplied sections) have adequate information as required from the CMC point of view.

Environmental assessment (EA) indicates that no significant adverse environmental impacts are expected from the approval of the drug product.

An overall "Acceptable" recommendation has been issued from the Office of Compliance on the site acceptability.

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

The proposed drug is a 5-HT_{1A} receptor agonist and a 5-HT_{2A} receptor antagonist and it is indicated for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women

The dose is 100 mg taken once daily at bedtime with or without food

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure the strength, purity, and quality of the drug product during the (b)(4)-month of expiration dating period.

All labels and labeling have adequate information as required.

All facilities have "Acceptable" site recommendations from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

Electronic signature in DFS

B. Endorsement Block

Chemistry Reviewer: Zhengfang Ge, Ph.D.
Branch Chief: Moo Jhong Rhee, Ph.D.

C. CC Block

CMC Lead: Donna Christner, Ph.D.
Project Manager: Charlene Williamson

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

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/s/

ZHENGFANG GE
07/01/2010

MOO JHONG RHEE
07/01/2010
Chief, Branch IV

Memo to File

NDA:	**22-526**
Sequence:	**0031**
Submission Date:	**June 16, 2010**
Type of Submission:	**Response to June 2, 2010 Information Request Letter**
Product name	**Girosa® (Flibanserin)**
Dosage Form:	**Film-Coated Tablets**
Dosage Strengths:	**100 mg**
Sponsor:	**Boehringer Ingelheim Pharmaceuticals, Inc.**

Based on the dissolution data of clinical batches (518670, 415911, and 519259) provided in the Original NDA dated 10/27/2009, it shows that all batches dissolve NLT (b) (4) % in 30 minutes. Therefore, FDA requested on June 2, 2010, the sponsor to adopt the following acceptance criteria: NLT (b) (4) % in 30 minutes instead of the sponsor's proposed acceptance criteria of Q = (b) (4) % of label claim at 30 minutes. On June 16, 2010, the sponsor responded with agreement to FDA's request.
Hence, the following dissolution method and acceptance criteria for flibanserin 100 mg film-coated tablets are acceptable:

<u>Dissolution Method</u>:

Apparatus:	USP Apparatus 2 (Paddle)
Rotation:	50 rpm
Dissolution Medium:	(b) (4) buffer (pH 4.0)
Volume:	900 mL
Temperature:	37° ± 0.5° C
Sampling time:	30 minutes
Acceptance criteria:	NLT (b) (4) % in 30 minutes

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Lead
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22526	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	FLIBANSERIN

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/s/

HOUDA MAHAYNI
06/23/2010

PATRICK J MARROUM
06/23/2010