CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-400

Chemistry Review(s)

MEMORANDUM to CHEMISTRY REVIEW #2
For NDA 21-400
LEVITRA (vardenafil hydrochloride) Tablets, 5mg, 10mg, and 20mg

Sponsor: Bayer – Pharmaceutical Division, West Haven, CT
Indication: Treatment of erectile dysfunction (ED)

DATE: August 19, 2003

Three minor deficiencies in the product label have been corrected by Bayer in their commitment to revise the Labeling for LEVITRA (submitted 19-AUG-2003).

The deficiencies that were noted in Chemistry Review #2 on p. 33 and p. 34 have been addressed as follows:

1) the Storage Condition statement that lacked the word "see" has been revised to read: "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]"

2) the improper chemical name [redacted]

has been replaced with "piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl, monohydrochloride" and

3) the incorrect term "emboss" (under "Description") has been replaced with "deboss."

LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In their review of the LEVITRA container label and carton, DMETS identified the following areas for possible improvement that should minimize potential user error. These issues were communicated by project management to the sponsor during the 18-AUG-2003 teleconference. The DMETS issues and sponsor's responses (dated 19-AUG-2003) are listed as follows:

A. CONTAINER LABEL (30 TABLETS)

1. Relocate the net quantity statement so that it is not presented in close proximity to the strength. Revise accordingly.
2. Consider using a different background color for either the 2.5 mg tablets or the 20 mg tablets, since the colors are similar. See below.

RESPONSE (dated 19-AUG-2003): The container label for the 30 tablet bottle, the 20 mg strength, has been changed to dark purple. We will also move the number of tablets to the lower right side of the bottle label to facilitate greater separation between the dosage strength and number of tablets in future printing runs.

COMMENT: **ACCEPTABLE**

B. BLISTER LABEL (6 TABLET PACKAGE)

DMETS notes that the sponsor did not qualify the strength on the blister label. Since the strength is based on the active moiety and not the salt, the strength should be qualified (e.g., ...5 mg* or equivalent to 5 mg Vardenafil) on all labels and labeling. Revise accordingly.

RESPONSE (dated 19-AUG-2003): The strength has been qualified by the statement "Equivalent to 10 mg of vardenafil."

COMMENT: **ACCEPTABLE**

C. CARTON LABELING (6 TABLET PACKAGE)

1. The various strengths (i.e., 2.5 mg, 5 mg, 10 mg, and 20 mg) should be differentiated using contrasting color, boxing, etc. Revise accordingly.

RESPONSE (dated 19-AUG-2003): To make the strength more prominent on the commercial packages of 6, we will consider different placements and changing the color of the 20 mg dose text.

COMMENT: **ACCEPTABLE**

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2. Consider using a different background color and contrasting font for easier legibility. The current presentation (i.e., orange on purple and vice versa) is difficult to read. Revise accordingly.

RESPONSE (dated 19-AUG-2003): The purple and orange color scheme are already used worldwide and must remain aligned with our global branding

COMMENT: **ACCEPTABLE**

These revisions to the CMC content of the LEVITRA product label (for container/carton labels and Package Insert) are acceptable. No remaining chemistry, manufacturing and controls issue require review. NDA 21-400 LEVITRA is approved without conditions.

Review Chemist: Allan Fenselau

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

/s/

Allan Fenselau
8/19/03 03:11:18 PM
CHEMIST

David T. Lin
8/19/03 03:19:27 PM
CHEMIST
I concur.

NDA 21-400

LEVITRA™ Tablets
(vardenafil HCl)

Bayer Corporation

Allan Fenselau, Ph.D.
Division of Reproductive and Urologic Drug Products
(HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-400**

2. **REVIEW # 2**

3. **REVIEW DATE**: 15-JUL-2003

4. **REVIEWER**: Allan Fenselau

5. **PREVIOUS DOCUMENTS**:

Previous Documents	Document Date
Original	24-SEP-2001
Amendment (BM)	28-SEP-2001
Amendment (BC)	07-DEC-2001
Amendment (SU)	23-APR-2002
Amendment (BC)	03-JUN-2002
Amendment (BC)	08-JUL-2002
Amendment (BL)	10-JUL-2002
Action Letter (AE)	23-JUL-2002

6. **SUBMISSIONS BEING REVIEWED:**

Submissions Reviewed	Document Date
Original	24-SEP-2001
Amendment (AZ)	17-FEB-2003
Amendment (BC)	01-APR-2003
Amendment (BC)	29-APR-2003
Amendment (C)	01-MAY-2003
Amendment (BC)	13-MAY-2003
Amendment (SU)	16-MAY-2003

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bayer Corporation; Pharmaceutical Division
Address: 400 Morgan Lane; West Haven, CT 06516-4175
Representative: Mary E. Taylor, M.P.H.; VP Reg.Affairs North America
Telephone: (203) 812-2678

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LEVITRA
b) Non-Proprietary Name (USAN): Vardenafil hydrochloride
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority:
Chem. Type: 1
Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARM. CATEGORY: PDE5 Inhibitor/Treatment of Erectile Dysfunction

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 2.5mg, 5mg, 10mg, and 20mg

13. ROUTE OF ADMINISTRATION: Oral

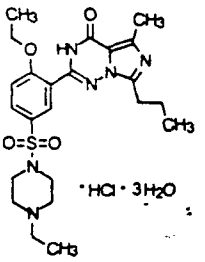
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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:



Molecular formula: $C_{23}H_{32}N_6O_4S \cdot HCl \cdot 3H_2O$
Molecular weight: 579.1
Chemical name: [redacted]

or

Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl-, monohydrochloride

VARDENAFIL HCl CAS-224785-91-5 (as HCl salt); CAS-224785-90-4 (as free base)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Chemistry Review # 1 (no changes)

B. Other Documents: See Chemistry Review # 1 (no changes)

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	See Chem.Review #1		
EES	Acceptable	18-MAR-2003	Office of Compliance
Pharm/Tox	See Chem.Review #1		
Biopharm	See Chem.Review #1		
LNC	See Chem.Review #1		
Methods Validation	To be submitted		Allan Fenselau
OPDRA	See Chem.Review #1		
EA	See Chem.Review #1		
Microbiology	See Chem.Review #1		

Chemistry Review for NDA 21-400

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval of NDA 21-400 can be recommended based on a review of chemistry, manufacturing and control issues that pertain to the drug product LEVITRA (vardenafil HCl) Tablets, 2.5mg, 5mg, 10mg, and 20mg.

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

The sponsor has agreed to re-evaluate, by one year after NDA approval, the acceptance criteria for the drug product degradant content in the 2.5mg, 5mg, 10mg, and 20mg tablets (see Review # 1 and the amendment dated 29-APR-2003).

II. Summary of Chemistry Assessments

A. Description of the Drug Product

During the first review cycle of NDA 21-400 the clinical review team determined that safe use of LEVITRA would be improved by the availability of a 2.5mg dosage strength. The CMC recommendation for adding a new dose strength was that the resubmission should include manufacturing information on three batches of the new dose strength with accompanying stability data in the proposed market container closure system. More stability data might be necessary to establish an acceptable shelf life, if the formulation and manufacturing process differed significantly from the 5mg, 10mg, and 20mg strengths. This concern for possible differences in formulation and manufacturing, however, is not an issue. From early stages in the drug development process, Bayer has focused attention on producing tablets with strengths from 2.5mg to 20mg that would be considered identical with regard to formulation and manufacture.

All vardenafil HCl tablets contain the [redacted] drug substance vardenafil HCl, [redacted] microcrystalline cellulose NF, [redacted], crospovidone NF, [redacted] colloidal silicone dioxide NF, [redacted], and magnesium stearate NF, [redacted] The various components—both the active and inactive drug product ingredients—are identical for all dose strengths; the specifications and test methods are also the same. The percentages of [redacted] have been kept identical in all dose strengths, so that critical properties, such as tablet dissolution, may be displayed similarly.

Vardenafil tablets will be manufactured and tested at Bayer AG (in Leverkusen, Germany). Bayer indicates that the Bayer Corporation, Pharmaceutical Division (in West Haven, CT) will be used as an alternative facility for packaging of blisters and bottles for a period during 2003 and 2004. After this transition period, [redacted] blisters will be packaged only at Leverkusen facility, and [redacted] bottles will only be packaged at the Bayer HealthCare LLC, Animal Health Division, Shawnee, KS facility. All sites have received an acceptable recommendation from the Office of Compliance.

The manufacturing steps for the 2.5mg tablets are essentially the same as those described in the original submission for the 5mg, 10mg, and 20mg tablets. The major difference is the batch formula, which has been appropriately adjusted to manufacture of the (uncoated) 2.5mg tablets.

The in-process control points in the manufacture of all dose strengths with uncoated and coated tablets examine the same attributes and employ the same test methods. The acceptance criteria for weight and hardness differ based on tablet size; however, criteria for disintegration and moisture are the same for all tablet strengths.

The components for use in packaging the 2.5mg tablets are the same as those that were found acceptable in Chemistry Review #1. All relevant DMFs were also reviewed in Chemistry Review #1 and were found to be adequate. Blisters containing 6 tablets are composed of film, film, and unprinted laminated foil. The bottles contain 30 tablets. The packaging processes for the blister packs and bottle containers, including labels and outsert literature, were previously reviewed and considered adequate.

The regulatory specification for the 2.5mg tablets of LEVITRA (vardenafil HCl) includes the following key tests [with the procedures in brackets]: Assay , Degradation Products , Water Content [Karl Fischer Titration], and Dissolution after 15 min [USP <711>, App.2]. In addition, three tests—Disintegration, Hardness, and Color—were performed with the pilot-scale batches at all time points and were determined not to be stability-indicating. Tests performed at release include: Tablet Markings [Visual], Identity and Content Uniformity . Finally, Microbial Purity [Plate/Direct] will be tested at only [Abbreviations used: If re-testing of Dissolution and Content Uniformity is required, additional test conditions and acceptance criteria have been specified. Based on the results to date, the acceptance criteria for the degradant content of the 2.5mg tablets may be too generous. Consequently, one year after NDA approval Bayer has agreed to re-evaluate this matter with the 2.5mg dose strength, along with the other three dose strengths. In any event, the specification for 2.5mg dose strength is in accord with the specifications for the other three dose strengths.

All of the tests are the same as those described in the original submission for the higher dose strengths. To be noted is that — will be used as an alternative analytical method (to for Content Uniformity, but will <u>not</u> be used as an alternative analytical method for Assay. The — method and its validation were evaluated in the present review and found adequate as an alternate method for determining Content Uniformity. In sum, all of the methods appear adequate to provide data for ensuring the quality of the LEVITRA (vardenafil HCl) product at all dose strengths.

The dissolution test deserves special consideration since it provides substantial support for the claim of equivalency of the 2.5mg tablet with the other 3 strengths. The findings using the standard dissolution conditions in 0.1N HCl (employing USP <711> apparatus 2 at 50 rpm) as well as the "worse case" conditions in phosphate buffer at pH 6.8 strongly support the conclusion that dissolution of the 2.5mg tablet is comparable to that for the higher strength tablets. Since all strengths qualify as highly permeable, highly soluble tablets—which is the feature of significance for this product, no additional dissolution testing beyond that already included in the regulatory specification is required.

The stability of the 2.5mg vardenafil HCl tablets was examined in several different ways: bulk vs. packaged tablets and tablets subjected to stress or normal storage conditions. The stress conditions examined stability to light exposure and exposure to elevated storage temperatures. The bulk tablets were stored at 25°C/60% RH and 30°C/70% RH in colorless and ——— sacks/bags placed in tight metal containers. No attribute during the year of testing provided an out-of-specification result; in fact, the results at all time points deviated little from the release results, including results for water content. The 2.5mg tablets subjected to accelerated storage conditions were stored in opened ——— bottles at 40°C/75% RH and were subjected to testing through 26 weeks. All parameters remained within the acceptance criteria for the product stored at lower temperatures, deviating little from the release results. Of significance is the fact that total degradants increased no more than — from the initial levels. The water content increased slightly, meaning that the required trihydrate state of hydration for vardenafil HCl was being maintained. Similar findings of product stability under accelerated storage conditions were also reported for the 5mg, 10mg, and 20mg tablet strengths. The results of the photostability testing of vardenafil HCl tablets showed a slight but insignificant increase (——— in degradation products over the tested irradiation time. All samples complied with the specification. According to these results, no light protection for storage instruction is required.

The long-term stability studies on three pilot-scale (—) batches of all four dosage strengths in both ——— blisters and ———bottles were monitored through 104 weeks at 25°C/60% RH. Worth noting is the fact that the sponsor also performed comparable studies at 30°C/70% RH and 5°C (as well as the studies at 40°C/75% RH for 26 weeks). Of considerable significance is the fact that the Assay results do not significantly change over time for all storage conditions and packaging configurations. Correspondingly, there were slight to no changes in the amount of the known and unknown degradation products, which were found to be below the limit of detection to — %. In all cases, the stability data complied with the current acceptance criteria. These results from the pilot-scale batches are to be accepted as primary stability data in accord with the agreement made during review of the original NDA submission. In compliance with ICH Guidelines for stability of new drug products, the sponsor has committed to providing full long-term and accelerated stability data for the first three commercial batches to be marketed.

In addition, the stability of one commercial-scale [redacted] batch of both the 5mg and 20mg tablets was examined. The storage conditions and test intervals used in these stability study batches included open storage in [redacted] plastic bottles at 25°C/60% RH and 40°C/75% RH and testing at 4 and 13 weeks with an optional time point at 26 weeks. The stability study results obtained with these commercial-scale batches were in excellent agreement with the results reported with the pilot-scale batches. Taken in their totality these findings demonstrate clearly the satisfactory stability of the LEVITRA drug product.

The proposed shelf life for vardenafil HCl tablets is 24 months, which is supported by long-term data through 104 weeks with pilot-scale batches and 26 weeks with commercial-scale batches. The shelf life is applicable to [redacted] bottles and [redacted] blister [redacted] film or equivalent [redacted] blisters with laminated foil backing. This expiration dating period is acceptable for the three tablet strengths previously reviewed as well as the 2.5mg tablet strength described in this submission. The post-approval stability protocol is acceptable in that it complies with guidance recommendations.

The product label was acceptable, except for three minor mistakes (see Review p. 33 and p. 34). These deficiencies will be corrected by the sponsor on the Package Insert for LEVITRA before the product launch and on the Container Labels during the next print after the product launch.

B. Description of Intended Use of the Drug Product

LEVITRA (vardenafil HCl) is indicated for the treatment of erectile dysfunction. The recommended starting dose for LEVITRA Tablets is 10 mg, taken orally 25 to 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20mg or decreased to 2.5mg based on efficacy and tolerability. The recommended dose frequency is a maximum of once per day as desired. LEVITRA Tablets can be taken with or without food. When packaged in [redacted] bottles or [redacted] blister packs and stored at 25°C (77°F), LEVITRA—regardless of tablet strength—has a 24-month expiration dating period.

C. Basis for Approval Recommendation

All product quality issues that relate to the safety and efficacy of this drug product have been adequately addressed to support a recommendation to approve this NDA submission. The drug substance has been satisfactorily characterized by a variety of physicochemical methods. The manufacturing process is adequately controlled to assure consistent production of quality material. The drug substance specification includes attributes with acceptable tests and acceptance criteria to assure the quality of this material (see Chemistry Review #1 for the detailed evaluation of the drug substance).

The four dose strengths—5mg, 10mg, and 20mg dosages (considered in Chemistry Review #1) as well as the 2.5mg dosage (reviewed herein)—employ the same components that are considered safe for use. In all cases, tablet formulation is based on producing a drug product with equivalent properties, which has been demonstrated—particularly with regard to tablet solubility and permeability. Manufacturing operations are well-described with sufficient control to assure consistent production of quality material.

All manufacturing, packaging, and testing sites have undergone inspection and been found to be in compliance with cGMPs. The attributes included in drug product specification—along with their test methods and acceptance criteria—are adequate for assuring drug product quality. Acceptable stability of the product was displayed under stress conditions and normal and accelerated storage conditions, permitting a recommendation of a two-year shelf life for the product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580 ChemistName/Date: Allan Fenselau/09-JUN-2003
HFD-580 ChemistryTeamLeaderName/Date: David Lin/
HFD-580 ProjectManagerName/Date: Eugenia De-Guia/

C. CC Block

HFD-820 Deputy Division Director: Duu-Gong Wu/
HFD-820 Division Director: Eric Duffy/

Redacted 26

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secret and/or

confidential

commercial

information

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/s/

Allan Fenselau
7/30/03 09:18:17 AM
CHEMIST

David T. Lin
7/30/03 09:23:52 AM
CHEMIST
I concur.

NDA 21-400

Levitra (vardenafil HCl) 5, 10, 20 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Bayer Corp.
400 Morgan Lane
West Haven, CT 06516

Indication: Treatment of erectile dysfunction

Presentations:
Bottles of 30: 5 mg, 10 mg, 20 mg
Blister package of 6: 10 mg, 20 mg
Tri-fold package of 6: 10mg , 20 mg

EER Status: Acceptable 13-JUN-2002

Consults: ODS – Tradename: Levitra - acceptable 27-JUN-2002
Statistics – none
EA – no consult - waiver requested – granted

Phase IV Commitments:
The sponsor has committed to re-evaluate the drug product degradation products acceptance criteria at one year after approval (see the amendment of June 3, 2002, the teleconference of June 19, 2002, and the amendment of July 8, 2002).

The original NDA was received 24-SEP-2001

The **drug substance** is manufactured by:

Bayer AG
Geschaftsbereich Pharma
Wuppertal-Elberfeld, GM

Bayer AG
Leverkusen, GM

The synthetic process is [redacted] beginning from [redacted] This was accepted as starting

material with good controls over impurities and a change control protocol in place. The drug substance is the [redacted] which is the most stable polymorph. The [redacted]

The manufacturing process is well defined and in-process controls are adequate.

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. Impurities and degradation products were well studies and are adequately controlled. A re-test period of — months is supported by submitted stability data. The stability testing protocol is considered adequate.

Conclusion
Drug substance is acceptable.

The **drug product** is film coated 5, 10 20 mg tablets.

Manufacturer:

Bayer AG
Leverkusen, GM

Packaging:
Bayer Corp.
West Haven, CT

The manufacturing method is [redacted] process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable except for degradation products – a commitment has been made to further study these impurities and revise the acceptance criteria if appropriate. The dissolution test and acceptance criteria were found acceptable by OCPB – see review dated 8-Jul-2002. The — months of submitted stability data support the proposed — month expiry. The stability testing protocol is considered adequate. No labeling comments in this review cycle.

No deficiencies have been cited for the 5, 10,l 20 mg strengths – all were resolved in the course of the review.

The overall Compliance recommendation is acceptable as of 13-JUN-2002.

All associated DMFs are acceptable.

Overall Conclusion
Since it has been determined that a 2.5 mg stenth is clinically needed information for this strength will need to be submitted. From a CMC perspective the application is approvable.

Needed for Approval (Deficiency Comment)
Since the FDA believes that the 2.5mg dosage strength will be needed, you must submit chemistry, manufacturing and controls information to support approval of the 2.5 mg strength. This should include manufacturing information on three (3) batches with accompanying stability data in the proposed market container closure system. This information may be submitted with 3 months accelerated and room temperature data with a commitment to update the stability data with an additional three (3) months of data when available. However, if the formulation and manufacturing process differs significantly from the 5, 10, and 20 mg strengths more stability data will be necessary to establish an acceptable shelf life.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
7/22/02 05:06:43 PM
CHEMIST

NDA # 21-400

Levitra Tablets
(Vardenafil HCl)

Bayer Corporation

Jila H. Boal, Ph.D.

Division of Reproductive and Urologic Drug Products
(HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. **NDA #** 21-400
2. **REVIEW #:** 1
3. **REVIEW DATE:** 10-June-2002 (Revised 16-July, 2002)
4. **REVIEWER:** Jila H. Boal
5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	24-SEP-2001
Amendment (BM)	28-SEP-2001
Amendment (BC)	07-DEC-2001
Amendment (SU)	23-APR-2002
Amendment (BC)	03-JUN-2002
Amendment (BC)	08-JUL-2002
Amendment (BL)	10-JUL-2002

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bayer Corporation, Pharmaceutical Division
Address: 400 Morgan Lane, West Haven, CT 06516
Representative: Gautam Shah, Ph.D., Deputy Director
Telephone: (203) 812-3051

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) **Proprietary Name:** Levitra
b) **Non-Proprietary Name (USAN):** Vardenafil hydrochloride
c) **Code Name/# (ONDC only):** NA
d) **Chem. Type/Submission Priority (ONDC only):**
- **Chem. Type:** 1
- **Submission Priority:** S

9. **LEGAL BASIS FOR SUBMISSION:** Not applicable

10. **PHARMACOL. CATEGORY:** PDE 5 inhibitor / Treatment of Erectile Dysfunction

11. **DOSAGE FORM:** Tablets

12. **STRENGTH/POTENCY:** 5 mg, 10 mg, and 20 mg

13. **ROUTE OF ADMINISTRATION:** Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note16]:

_____SPOTS product–Form Completed

__X__Not a SPOTS product

In the formulation, only magnesium stearate is identified as substance with possible —— origin: Magnesium stearate used in the production of vardenafil HCl tablets is of ›rigin only (see document T.03.61 Magnesium stearate).
Consequently, there is no TSE risk for vardenafil HCl tablets (all dosages).

All substances in the vardenafil HCl —— production process were checked of their origin (see T.09.05). No raw material of . origin was identified. Therefore vardenafil HCl —— drug substance must be free of spongiform encephalophathy (SE) contaminants.

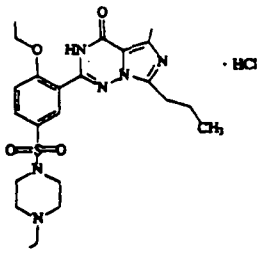
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:

or

Piperazine, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-*f*][1,2,4]triazin-2-yl)-4-ethoxyphenyl]-4-ethyl-, monohydrochloride

Structural formula:



Molecular formula:
$C_{23}H_{32}N_6O_4S \cdot HCl$

Molecular weight:
——

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	III			3	Adequate	27-SEP-2000	Reviewed by Dr. D. N. Klein (DMF ——
	III			3	Adequate	24-JUL-1999	Reviewed by Dr. James D. Vidra
	III			1	Adequate	10-APR-2002	Reviewed by Dr. Jila H. Boal
	III			3	Adequate	14-MAR-2001	Reviewed by Dr. S. Prasad Peri
	III			1	Adequate	28-May-2002	Reviewed by Dr. Jila H. Boal
	III			3	Adequate	07-SEP-2001	Reviewed by Dr. D. N. Klein (DMF ——
	III			1	Adequate	05-APR-2002	Reviewed by Dr. Jila H. Boal
	III			1	Adequate	22-MAR-2002	Reviewed by Dr. Jila. H. Boal
	III			1	Adequate	04-APR-2002	Reviewed by Dr. Jila. H. Boal

[redacted]

[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 #	[redacted]	Original active IND
Patent	4,278,673	Titled: Pharmacologically Active Compounds
Patent	6,362,178	Drug substance, drug product, method of use of vardenafil

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	NA		
EES	Acceptable	13-JUN-02	S. Adams
Pharm/Tox	NA		
Biopharm	Dissolution specification acceptable	8-JUL-02	Dr. D. J. Chatterjee
LNC	NA		
Methods Validation	Pending Will be submitted to the FDA Laboratory	01-JUL-02	Dr. Jila H. Boal
OPDRA	Acceptable	27-JUN-02	Denise P. Toyer, Pharm.D.
EA	Categorical Exclusion Granted.	23-MAR-02	Dr. Jila H. Boal
Microbiology	NA		

The Chemistry Review for NDA # 21-400

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be approved with respect to chemistry, manufacturing and controls (CMC). However, final labeling recommendations are pending (see labeling section of this review).

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

The sponsor has committed to re-evaluate the drug product degradation products acceptance criteria at one year after approval (see the amendment of June 3, 2002, the teleconference of June 19, 2002, and the amendment of July 8, 2002).

II. Summary of Chemistry Assessments

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

Drug Product:

Vardenafil HCl tablets are immediate release, film-coated tablets with dosage strengths of 5 mg, 10 mg and 20 mg. The tablets are orange, round, and are debossed with the Bayer cross on one side and the dosage strength on the other side. The diameter of the 5 mg, 10 mg, and 20 mg tablet is , respectively.

Vardenafil HCl tablets contain drug substance (vardenafil HCl , microcrystalline cellulose, NF , crospovidone, NF , colloidal silicone dioxide, NF and magnesium stearate, NF . The qualitative composition, as well as the percentage of are identical for all dosage strengths.

The coating contains hydroxypropyl methylcellulose, USP , polyethylene glycol , NF , and ferric oxide, NF (yellow), ferric oxide, NF (red) and titanium dioxide, USP as pigments.

The manufacturing process uses conventional pharmaceutical methods and equipment, with process, and assures that the drug substance in the tablet is present as the which is the well-defined morphic form of the drug substance.

Scale-up to commercial production was performed with **batches** of vardenafil HCl premix and **three batches** of each dose strength of vardenafil HCl

tablets (——). The scale-up included variation of the batch size, variation of the particle size of the drug substance, and investigation of hold-times of the ready-to-press mix (up to 8 weeks). The premix contains all of the drug substance

in order to achieve acceptable tablet size /strength.

The premix is QC-tested for 1) appearance; 2) identity by (—— and 3) blend uniformity by (—— The proposed retest period of —— **months** for the premix when stored in stainless steel containers in the climatic zone of I and II as proposed in document T.04.01 is considered appropriate.

Tablets for phase III clinical trials and for primary stability studies were manufactured on pilot scale (—— of uncoated tablets). During scale-up from pilot scale to commercial production scale (—— of uncoated tablets), debossed tablet markings were introduced.

The data provided suggests that the scale change and debossing have no impact on the quality of the drug product. The dissolution rate similarity factor between the pilot scale and commercial scale batches demonstrates that the dissolution rate remains unchanged (see the discussion on the dissolution similarity factor in the review).

The final product quality is controlled by the following specifications: 1) Identity by —— 2) assay and content uniformity by —— —— method; 3) degradation products by —— 4) dissolution in 0.1N HCl at 50 rpm.

Vardenafil HCl tablets will be manufactured by Bayer AG at the Leverkusen, Germany site. Bulk tablets are stored in a —— bag in a metal drum and then shipped to West Haven, CT for packaging into 30-count —— bottles (45 cc white, —— bottles with child resistant screw caps), or into 6-count blisters with laminated foil backing. In addition, final packaging can be performed at the Leverkusen, Germany facility.

Primary stability results are submitted for three pilot-scale batches per dose strength in both —— bottles and —— foil blisters. The tablets were manufactured at a representative scale of —— (corresponding to —— tablets, depending on the dose strength). At all time-points, the tablets were tested for 1) appearance, 2) dissolution at 15 minutes, 3) water content, 4) assay, and 5) degradation products. In addition, tablet hardness and color were monitored during early time-points of stability testing.

Additional tests were carried to assess thermal and hydrolytic stability at accelerated temperature of 40°C/75% RH with open storage on —— tablet batch of each dose strength. The presented data confirm the excellent stability of the drug substance in the formulation.

Based on the data presented, the drug product has an —— month expiry when stored at 25°C/60% RH.

Drug Substance:

Vardenafil is a new member of the class of PDE5 inhibitors to be used for the treatment of erectile dysfunction. This compound was selected for development by Bayer because of its greater potency and selectivity for PDE5 inhibition compared with sildenafil (Viagra), and its favorable toxicity profile based on sponsor's pre-clinical pharmacology / toxicology assessment.

Vardenafil HCl is a new molecular entity. The form is a white to slightly colored solid, which is very slightly soluble in water, soluble in 0.1N HCl and ethanol, and freely soluble in DMSO. Therefore, the water soluble hydrochloride salt of vardenafil is used.

The structural backbone of vardenafil is very similar to sildenafil (approved as Viagra). The difference between the two molecule is **1)** the presence of an ethylpiperazine ring in vardenafil vs. a methylpiperazine ring in sildenafil, **2)** the presence of methyl imidazol ring in vardenafil vs. methyl pyrazol ring in sildenafil.

The structure of vardenafil has been confirmed through NMR and x-ray with further confirmation from , and through elemental analysis.

Vardenafil HCl was examined for polymorphism and pseudopolymorphism. At ambient temperature and humidity, vardenafil HCl always which is the thermodynamically stable pseudopolymorphic form. The four anhydrous, strongly hygroscopic modifications convert to the when exposed to ambient humidity.

Vardenafil HCl used for clinical trials, stability studies and bioavailability studies, batch size , was synthesized by Bayer AG, at the facility in Wuppertal, Germany and at the Bayer AG facility in Leverkusen, Germany. **batches** were manufactured for Pre-clinical studies and **batches** were manufactured for clinical studies . Commercial drug substance will be synthesized and at the same facilities.

Vardenafil HCl is packaged in sealed , foil bags inside drums.

The structure of the starting material, , represents an important structural element of the vardenafil HCl. The class of their synthesis, structure, and chemical and physical properties are well described in the literature.

However, is not a commercially available starting material and is synthesized by the sponsor at Wuppertal, Germany. The compound is thoroughly analyzed and the synthetic route is discussed in the NDA. In addition, the impurity profile is well determined.

Procedures to assure consistent quality of the starting material, in case of potential

future changes of the synthesis or manufacturer, have been defined in a "Qualification Protocol for Starting Material after Change of Synthesis or Vendor."

The specification for vardenafil HCl — is adequate to assure the strength, quality, identity and purity of the drug substance. The tests consist of 1) appearance; 2) identity (—, chloride); 3) water; 4) residual solvents; 5) heavy metals; 6) sulfate; 7) sulfated ash; 8) solution (clarity and color); 9) microbial purity; 10) assay —; 11) organic impurities —.

Long term stability results for — months storage are available for 4 pilot-scale batches of vardenafil HCl — packaged in — foil bags inside drums. All stability indicating parameters (appearance, clarity, color of solution, water content, assay and organic impurities) were tested during long-term storage and accelerated conditions. The results from these studies show that the drug substance is chemically and physically stable, and conform to all acceptance criteria.

A retest period of — months at 25°C/60 % RH with no special light protection is acceptable.

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

The recommended starting dose for vardenafil HCl Tablets is 10 mg, taken orally 25 to 60 minutes before sexual activity. The dose may be increased to a maximum recommended dose of 20 mg or decreased to 5 mg based on efficacy and tolerability. The recommended dose frequency is a maximum of once per day as desired. Vardenafil HCl Tablets can be taken with or without food.

When packaged in — bottles and clear blister packs, the product has an — month expiry, when stored at 25°C (77°F).

C. Basis for Approvability or Not-Approval Recommendation

There were twenty-one CMC deficiencies that were conveyed to the sponsor through a CMC discipline letter dated May 15, 2002. The June 3, 2002 amendment is the sponsor's response to the deficiencies. The sponsor has satisfactorily answered the questions and has agreed on all of the changes that were requested in the letter. Therefore, from a CMC point of view, the data in this application supports the approval of the NDA.

The following are the major CMC issues that were resolved during the review process:

- With regard to the drug substance specifications, based on the stability data provided to the NDA, the level of impurities in the drug substance should be tightened. The CMC discipline letter dated May 15, 2002 conveyed this information to the sponsor. The sponsor has agreed to tightened the acceptance criteria for the impurities and degradation products. The sponsor submitted this agreement in the amendment of June 3, 2002.

- The proposed acceptance criteria for assay and dissolution are acceptable. However, based on the batch analysis the proposed acceptance criteria for impurities at release and stability should be modified (tightened) and this was conveyed to the sponsor through a discipline letter dated May 15, 2002. The amendment of June 3, 2002

contains the sponsor's response. Basically the sponsor has satisfactorily revised the acceptance criteria and agreed to a commitment to re-evaluate the acceptance criteria (see the discussions on (i) the teleconference of June 19, 2002 and (ii) the relevant section in the review, and (iii) amendment of July 8, 2002).

- Sponsor requested a shelf life of — at USP controlled room temperature that was not granted. However, an expiry date of — months could be granted. The shelf life of the tablets is evaluated based on the available stability batch records (see the comments made in the review). The expiry date of — months was conveyed to the sponsor in the discipline letter dated May 15, 2002. The sponsor initially did not agree to the FDA recommended — month expiry (see amendment of June 3, 2002). After further discussions the sponsor has agreed to the — month expiry (see the teleconference of June 19, 2002, and the amendment of July 8, 2002).

- OPDRA did not accept the proposed trade name "NUVIVA". Therefore, the sponsor proposed the new trade name, "Levitra". This proprietary name was determined to be acceptable by OPDRA (see the DMETS review of the Proprietary Name "Levitra" by Denise P. Toyer, Pharm.D., dated June 27, 2002).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/JBoal/DLin/EDe-Guia/Date: July 18, 2002

C. CC Block

HFD-820/EDuffy/DWu

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

/s/

Jila Boal
7/18/02 05:37:17 PM
CHEMIST

David T. Lin
7/19/02 09:32:18 AM
CHEMIST
I concur.

Categorical Exclusion granted. See Chemistry Review # 1.

ENVIRONMENTAL

Date: August 29, 2001

Name of Applicant/Petitioner: Bayer Corporation
Pharmaceutical Division

Address: 400 Morgan Lane
West Haven, CT 06516

The submission of an environmental assessment for the proposed action to distribute Vardenafil tablets is not required.

As a result of our expected marketing and sales volumes, the concentration of Vardenafil to enter the environment in the 5th year of marketing and sales will be below 1 part per billion. Thus, as per 21 CFR section 25.31(b), the submission of an environmental assessment is not required for this Vardenafil NDA.

As calculated by the formula in CDER's document, "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Application and Supplements," the concentration of Vardenafil entering the aquatic environment from the sale of Vardenafil, in the fifth year of marketing and sales, will only be [redacted] ppb.

Since the manufacture and distribution of Vardenafil fits the requirements of 21 CFR 25.31(b) categorical exclusion, an environmental assessment is not being submitted.

/S/

Signature of Responsible Official
Gary Toczylowski
Director of Health, Environment
And Safety

Microbiology Review Not Applicable

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21400/000
Stamp: 24-SEP-2001
Regulatory Due: 24-JUL-2002
Applicant: BAYER
400 MORGAN LANE
WEST HAVEN, CT 065164175
Priority: 1S
Org Code: 580

Action Goal:
District Goal: 25-MAY-2002
Brand Name: NUVIVA(VARDENAFIL HCL)5/10/20MG TABLETS
Estab. Name:
Generic Name: VARDENAFIL HCL

Dosage Form: (TABLET)
Strength: 5, 10, AND 20 MG

Application Comment:
FDA Contacts: J. BOAL (HFD-580) 301-827-4259 , Review Chemist
D. LIN (HFD-580) 301-827-4230 , Team Leader

Overall Recommendation: ACCEPTABLE on 13-JUN-2002 by S. ADAMS (HFD-324) 301-594-0095

Establishment: 9610135
BAYER AG
LEVERKUSEN, , GM
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: CRU OAI Status: NONE
Estab. Comment: DRUG SUBSTANCE [redacted] SITE.
TABLET MANUFACTURING SITE ALSO.
DRUG PRODUCT PACKAGING SITE.
RELEASE TESTING OF THE BULK TABLETS. (on 30-OCT-2001 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2001				BOALJ
SUBMITTED TO DO	21-NOV-2001	GMP			GARCIAM
ASSIGNED INSPECTION	29-NOV-2001	GMP			GARCIAM
INSPECTION SCHEDULED	25-FEB-2002		20-MAR-2002		IRIVERA
INSPECTION PERFORMED	03-APR-2002		20-MAR-2002		IRIVERA
DO RECOMMENDATION	13-JUN-2002			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	13-JUN-2002			INSPECTION ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2001				BOALJ
SUBMITTED TO DO	21-NOV-2001	GMP			GARCIAM
ASSIGNED INSPECTION	29-NOV-2001	GMP			GARCIAM
INSPECTION SCHEDULED	25-FEB-2002		20-MAR-2002		IRIVERA
INSPECTION PERFORMED	03-APR-2002		20-MAR-2002		IRIVERA
DO RECOMMENDATION	13-JUN-2002			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	13-JUN-2002			INSPECTION ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment: 9610496
BAYER AG
GESCHAFTSBEREICH PHARMA
WUPPERTAL-ELBERFELD, , GM D-42096
DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER
INTERMEDIATE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE MANUFACTURES THE DRUG SUBSTANCE AND THE INTERMEDIATES OF THE DRUG SUBSTANCE.IT ALSO PERFORMS THE STABILITY STUDIES OF THE DRUG SUBSTANCE. (on 22-JAN-2002 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2001				BOALJ
SUBMITTED TO DO	21-NOV-2001	10D			GARCIAM
DO RECOMMENDATION	29-NOV-2001			ACCEPTABLE BASED ON FILE REVIEW	GARCIAM
4/13/00					
OC RECOMMENDATION	29-NOV-2001			ACCEPTABLE DISTRICT RECOMMENDATION	GARCIAM

Establishment: 1216486
BAYER CORP
400 MORGAN LANE
WEST HAVEN, CT 065164175

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-MAR-2002				FERGUSONS
OC RECOMMENDATION	26-MAR-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Profile: TCM OAI Status: NONE

Estab. Comment: DRUG PRODUCT PACKAGING.
DRUG PRODUCT STABILITY TEST. (on 30-OCT-2001 by J. BOAL (HFD-580) 301-827-4259)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2001				BOALJ
OC RECOMMENDATION	21-NOV-2001			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Methods validation has not yet been requested.

APPEARS THIS WAY
ON ORIGINAL

DMF Number: [redacted] DMF Type: III

TITLE: [redacted]

1. CHEM REVIEW No. 1 2. REVIEW DATE: April 5, 2002

3. ITEM REVIEWED

A. IDENTIFICATION: [redacted]

B. LOCATION IN DMF:

Type of Submission	Date of Submission	Location of Information
Amendment	May 25, 2000	Vol.4.1
Amendment	August 8, 2001	Vol.4.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location
Full Supplement	September 29, 1995	Vol.4.1
Chemistry Review # 1	December 5, 1995	Vol.3.1
Chemistry Review # 2	October 23, 1997	Vol.3.1
Chemistry Review # 3	August 13, 1999	Vol.4.1

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE:

TELEPHONE NUMBER:
FAX

6. DMF REFERENCED FOR:

NDA:	21-400	
APPLICANT NAME:	Bayer Corporation, Pharmaceutical Division	
LOA DATE:	August 9, 2001	
DRUG PRODUCT NAME:	Vardenafil HCl	
DOSAGE FORM:	Tablet	CODE: 500
STRENGTH:	5, 10, and 20 mg	
ROUTE OF ADMINISTRATION:	Oral	CODE: 001
SUPPORTING DOCUMENTS:	None	

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: August 8, 2001
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: August 8, 2001

9. **CONSULTS:**
None

10. **COMMENTS:**
The DMF is reviewed for [redacted]

11. **CONCLUSION:**
This DMF is adequate to support the use of [redacted] in NDA 21-400.

/S/ 4/25/02
Jila. Boal, Ph. D.
Review Chemist, HFD-580

/S/ 4/25/02
David T. Lin, Ph. D.
Chemistry Team Leader, HFD-580

cc:
DMF #[redacted] (2 copies)
HFD-580/NDA 21-400 Division File
HFD-580/JBoal
HFD-580/DLin
HFD-580/EDe-Guia
File name: DMF[redacted] Review

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DMF Number: [redacted] DMF Type: III
TITLE: [redacted]

1. CHEM REVIEW No. 1 2. REVIEW DATE: March 22, 2002

3. ITEM REVIEWED
A. IDENTIFICATION: [redacted]

B. LOCATION IN DMF:

Type of Submission	Date of Submission	Location of Information
Amendment 104	September 3, 1999	Vol.10.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location
Information Letter	June 22, 1999	Vol.10.1
Amendment 104	May 18, 1999	Vol.10.1

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):
NAME: [redacted]
ADDRESS: [redacted]

REPRESENTATIVE or U.S. AGENT (if applicable): NA
NAME:
ADDRESS:

CONTACT PERSON'S NAME, TITLE, DEPARTMENT: [redacted]

TELEPHONE NUMBER: [redacted]

6. DMF REFERENCED FOR:

NDA:	21-400	
APPLICANT NAME:	Bayer Corporation, Pharmaceutical Division	
LOA DATE:	August 9, 2001	
DRUG PRODUCT NAME:	Vardenafil HCl	
DOSAGE FORM:	Tablet	CODE: 500
STRENGTH:	5, 10, and 20 mg	
ROUTE OF ADMINISTRATION:	Oral	CODE: 001
SUPPORTING DOCUMENTS:	None	

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: NA

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: NA

9. **CONSULTS:**
None

10. **COMMENTS:**
The DMF is reviewed for [redacted] and is found to be adequate.

11. **CONCLUSION:**
This DMF is adequate to support the use of [redacted] in NDA 21-400.

/S/ 4/26/02
Jill. Boal, Ph. D.
Review Chemist, HFD-580

/S/ 4/26/02
David T. Lin, Ph. D.
Chemistry Team Leader, HFD-580

cc:
DMF # [redacted] 2 copies)
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HFD-580/JBoal
HFD-580/DLin
HFD-580/EDe-Guia
File name: DMF [redacted] Review

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DMF Number: [redacted] DMF Type: III
TITLE: [redacted]

1. CHEM REVIEW No. 1 2. REVIEW DATE: April 25, 2002

3. ITEM REVIEWED

A. IDENTIFICATION:
Tradename: [redacted]
Manufacturer's Code: [redacted]

B. LOCATION IN DMF:

Type of Submission	Date of Submission	Location of Information
Amendment	June 15, 1993	Vol.1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location
None		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):
NAME:
ADDRESS: [redacted]

REPRESENTATIVE or U.S. AGENT (if applicable): NA
NAME:
ADDRESS:

CONTACT PERSON'S NAME, TITLE, DEPARTMENT: [redacted]

TELEPHONE NUMBER: [redacted]

6. DMF REFERENCED FOR:
NDA: DMF [redacted]
APPLICANT NAME: [redacted]
LOA DATE: April 4, 1997
DRUG PRODUCT NAME: [redacted]
DOSAGE FORM:
STRENGTH:

ROUTE OF ADMINISTRATION:
SUPPORTING DOCUMENTS: None

8. **CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF: January 18, 2001
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: NA

9. **CONSULTS:**
None

10. **COMMENTS:**
The DMF is reviewed in support of DMF[redacted]

11. **CONCLUSION:**
This DMF is adequate to support the use of[redacted] as described in DMF[redacted]

/S/ 4/26/02
Jila. Boal, Ph. D.
Review Chemist, HFD-580

/S/ 4/26/02
David T. Lin, Ph. D.
Chemistry Team Leader, HFD-580

cc:
DMF #[redacted] 2 copies)
HFD-580/NDA 21-400 Division File
HFD-580/JBoal
HFD-580/DLin
HFD-580/EDe-Guia
File name: DMF[redacted] Review

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DMF Number: [redacted] DMF Type: III

TITLE: [redacted]

1. CHEM REVIEW No. 1 2. REVIEW DATE: April 4, 2002

3. ITEM REVIEWED

A. IDENTIFICATION: [redacted]

B. LOCATION IN DMF:

Type of Submission	Date of Submission	Location of Information
Amendment 123	January 6, 2000	Vol.11.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location
NA		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME: [redacted]

ADDRESS: [redacted]

REPRESENTATIVE or U.S. AGENT (if applicable): NA

NAME:

ADDRESS:

CONTACT PERSON'S NAME, TITLE, DEPARTMENT: [redacted]

TELEPHONE NUMBER: [redacted]

6. DMF REFERENCED FOR:

NDA:	21-400	
APPLICANT NAME:	Bayer Corporation, Pharmaceutical Division	
LOA DATE:	August 9, 2001	
DRUG PRODUCT NAME:	Vardenafil HCl	
DOSAGE FORM:	Tablets	CODE: 500
STRENGTH:	5, 10, and 20 mg	
ROUTE OF ADMINISTRATION:	Oral	CODE: 001
SUPPORTING DOCUMENTS:	None	

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: NA

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN

PROVIDED: NA

9. **CONSULTS:**
None

10. **COMMENTS:**
The DMF is reviewed for [redacted] and is found adequate.

11. **CONCLUSION:**
This DMF is adequate to support the [redacted] and its use in NDA 21-400.

/S/ 4/26/02
Vila. Boal, Ph. D.
Review Chemist, HFD-580

/S/ 4/26/02
David T. Lin, Ph. D.
Chemistry Team Leader, HFD-580

cc:
DMF # [redacted] (2 copies)
HFD-580/NDA 21-400 Division File
HFD-580/JBoal
HFD-580/DLin
HFD-580/EDe-Guia
File name: DMF [redacted] Review

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