CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-368

CHEMISTRY REVIEW(S)

NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTs

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-368
2. REVIEW #: 3
3. REVIEW DATE: 20-NOV-2003
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	28-JUN-2001
Amendment	18-SEP-2001
Amendment	25-SEP-2001
Amendment	22-OCT-2001
Amendment	23-JAN-2002
Amendment	01-FEB-2002
Amendment	26-FEB-2002
Amendment	06-MAR-2002
Amendment	22-MAR-2002
Amendment	25-MAR-2002
Amendment	25-MAR-2002
Amendment	04-APR-2002
Amendment	05-APR-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	27-MAY-2003
Amendment	24-JUN-2003
Amendment	11-SEP-2003
Amendment	09-OCT-2003
Amendment	15-OCT-2003
Amendment	20-OCT-2003
Amendment	24-OCT-2003
Amendment	05-NOV-2003
Amendment	12-NOV-2003
Amendment	17-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC

Address: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

Representative: Ms. Catherine A. Melfi, Ph.D

Telephone: 317-277-2905

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cialis
b) Non-Proprietary Name (USAN): Tadalafil
c) Code Name/# (ONDC only): IC351, LY450190
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

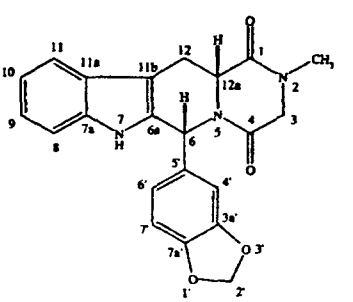
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

Chemical Name: Pyrazino [1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R, 12aR)-



Molecular Formula: $C_{22}H_{19}N_3O_4$

Molecular weight: 389.41

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:** Refer to CMC reviews # 1 and 2 dated 27-FEB-2002 and 29-APR-2002, respectively.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
—	IV	[redacted]		1	Adequate	24-SEP-2003	Reviewed by Dr. Rajiv Agarwal
—	IV	[redacted]		1	Adequate	31-OCT-2003	Reviewed by Dr. Rajiv Agarwal

[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:

- Chemistry Review # 1 dated 27-FEB-2002.
- Chemistry Review # 2 dated 29-APR-2002
- IR letter dated 11-FEB-2002.
- Teleconference minutes dated 26-NOV-2002 and 15-DEC-2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	**Acceptable**	13-NOV-2003	Office of Compliance
DMETS	**Acceptable**	25-SEP-2003	Ms. Marci Ann Lee
Methods Validation	The method validation package will be sent to and validated by FDA laboratories.		

Chemistry Review Data Sheet

The Chemistry Review for NDA 21-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA may be **APPROVED** from the CMC point of view.

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

None

II. Summary of Chemistry Assessments

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

Drug product:

Cialis (tadalafil), 5,10 and 20 mg tablets are ——— almond shaped, and film-coated tablets and depending on strength, tablets have varying shades of yellow. Tablets are also debossed on one side with "C 5", "C 10" or "C 20" to reflect strengths. The primary stability and clinical batches of the Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana). However, the tablets are also manufactured, tested and packaged in Carolina, Puerto Rico. The tablets manufactured at Carolina, PR are comparable to tablets manufactured at Indianapolis, IN as evident by the comparative Certificate of Analysis and dissolution profiles.

Due to continued non-compliance with cGMP, applicant withdrew the manufacturing site in Indianapolis from the application on 20-OCT-2003. The alternative site in **Carolina, Puerto Rico** is in compliance with cGMP.

The ——— tadalafil is incorporated into a ——— to consistently produce tablets with good homogenecity and the desired dissolution characteristics.
The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, total related substances, individual related substances, water and dissolution. The proposed — time-points of dissolution acceptance criterion are deemed adequate after acceptance criterion at 30 min. was tightened to Q=—%.

All the test methods and respective acceptance criteria are satisfactory except for the "Individual related substance (LIRS)" and "Total related substances (TRS)". Applicant proposed to re-evaluate the acceptance criteria for the "Largest individual related substance" and "Total related substances" after sufficient experience is gained. Since the toxicologist in the division confirmed that the proposed limit is within the qualified level, the proposal is accepted. Post approval stability commitment has been satisfactorily revised as requested by the division.

The tablets will be marketed in ——— bottle configurations containing — 30 tablets, respectively. Tablets in — bottles are samples for physician and tablets in 30 count bottles are for pharmacy. All packaging components are adequate for protecting the drug product during the shelf life.

Based on the updated stability data on primary stability batches, ——— of expiration dates is granted for the ——— While, ——— of expiration dates is granted for the ———

The trade name "Cialis" has been accepted by DMETS (25-SEP-2003). Applicant has accepted the division's proposal to use ——— bottle (physician sample for 10 mg and 20 mg tablets) and indicated that an appropriate container will be provided by the pharmacist to fill the prescription from ——— bottle. Per our recommendation, storage statement is revised and dosage form is indicated in both the physician insert and labels after established name. Primary container/closure labels for bottles are provided for all three strengths and revised according to the recommendations.

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). Tadalafil structure includes two asymmetric chiral centers but X-ray studies indicate that only ——— is present in the drug substance. Tadalafil has an unusually high melting point ——— and is practically insoluble in water ——— but is very soluble in ethanol and classified as a low soluble and highly permeable drug ——— This suggests that tadalafil is a ——— compound in the Biopharmaceutics Drug Classification system.
——— of tadalafil is obtained by ——— from ——— This form is most thermodynamically stable form in aqueous solutions and is the least soluble form in water. The drug substance is non- hygroscopic. The tadalafil is ——— and is in **compliance with cGMP**. The rate of release of tadalafil from the core tablets increases with decreasing particle size. The particle size is controlled by ——— to provide a particle size for ——— of the drug substance ——— and the particle size specification has been established at NMT ——— as measured by ———

The quality of the tadalafil is controlled by specification set by the manufacturer, which includes, identity by — identity by ——HPLC, assay, related substances (excluding ——— All the test methods and respective acceptance criteria are satisfactory.

Eli Lilly manufacturing site in **Lafayette, IN**, is in compliance with cGMP.

Based on the updated stability information, ——— of the re-test period is granted.

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

This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5.
The recommended starting dose of CIALIS in most patients is 10 mg, taken prior to anticipated sexual activity. The dose may be increased to 20 mg or decreased to 5 mg, based on individual efficacy and tolerability. The maximum recommended dosing frequency is once per day in most patients.

C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1(dated 27-FEB-2002) and # 2 (dated 29-APR-2002) of NDA 21-368 have been satisfactorily resolved.
- The final recommendation from the Office of Compliance on the manufacturing, packaging and control testing sites is "Acceptable" (**See Appendix-1**).

III. Administrative

A. Reviewer's Signature *Electronically captured in DFS*

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ FDeguia/JMercier/ Date: 20-NOV-2003

C. CC Block

HFD-820/EDuffy/Duu Gong Wu

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page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

generally <10% of glucuronide concentrations. The catechol, methylcatechol, and methylcatechol glucuronide (LY559171) metabolites were evaluated *in vitro* for potency and selectivity against PDEs. The catechol and methylcatechol were highly selective for PDE5, when compared with the other PDEs, but were 45-fold and 230-fold less potent for PDE5, respectively, compared with tadalafil. The methylcatechol glucuronide was not selective for PDE5 and was at least 13,000-fold less potent for PDE5 than tadalafil. Since this metabolite is primarily cleared by the renal route, in moderate renal impairment the exposure to methylcatechol glucuronide was 3.6-fold higher. This patient population also had higher incidence of musculoskeletal adverse events such as myalgia and back pain. The onset of these adverse events generally occurs approximately 20 hours after peak plasma concentrations of tadalafil, and when the methylcatechol glucuronide concentrations are high. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil. In another study comparing elderly and young subjects, clearance was reduced by approximately 20% in the elderly subjects. Two (17%) elderly subjects (but no young subjects) reported a total of three severe adverse events (one episode of pain and two episodes of myalgia) that were related to the study drug. Creatinine clearance was approximately 17% lower in the elderly subjects.

Tadalafil pharmacokinetics in patients with erectile dysfunction are essentially similar to pharmacokinetics in healthy subjects. Systemic exposure of tadalafil was reduced by almost 20% in subjects with diabetes. AUC increased in a dose proportional manner across the 2.5 to 20 mg dose range, whereas increase in C_{max} was less than dose proportional at doses higher than 10 mg. Steady-state plasma concentrations are attained by Day 5 and are approximately 1.6-fold higher than the single dose values. Concentrations of methylcatechol glucuronide were approximately 3-fold higher than single dose values. *In vitro* studies suggested that, tadalafil is predominantly metabolized by CYP3A4. Ketoconazole, a selective inhibitor of CYP3A4, increased tadalafil exposure by 107%. Rifampin, a CYP3A4 inducer, reduced tadalafil AUC by 88%. Results with cultured human hepatocytes indicated that tadalafil produces both mechanism-based inhibition of CYP3A activity and induction of CYP3A protein expression. Tadalafil inhibited the catalytic activities for CYP1A2, CYP2C9, and CYP3A, with apparent K_i values of [redacted] respectively. Once-daily administration of 20 mg tadalafil for 10 days resulted in a mean C_{max} value of [redacted] the highest individual plasma concentration was 785 µg/L (2.02 µM). With tadalafil concentration of 2.02 µM at the active site of the enzymes, the projected *in vivo* inhibition of metabolism mediated by CYP3A4, CYP2C9, and CYP1A2 was 4.7%, 3.0%, and 12.8%, respectively. The I/K_i ratio for CYP3A4 was 0.05, which indicated that the likelihood of an interaction is remote. Daily dosing of 10 mg tadalafil for 14 days resulted in small reduction in AUC (13%) and increase in CL/F (14%) for midazolam. This effect may be even more pronounced with a higher dose tadalafil.

Tadalafil undergoes extensive metabolism in the liver. Thus, hepatic impairment is expected to reduce the metabolic clearance of tadalafil. However, mild and moderate hepatic impairment did not compromise metabolic clearance of tadalafil and systemic exposure (AUC) to tadalafil was similar across subject groups. On the other hand,

systemic exposure was ~2-fold higher in subjects with mild and moderate renal impairment. Renal impairment had a greater effect on the disposition of methylcatechol glucuronide than on tadalafil, as expected for a renally-cleared metabolite. Mean AUC of total IC710 (methylcatechol glucuronide) was approximately 3.6- fold and 2.2- fold higher in moderate and mild renally impaired subjects, respectively. Due to the increased incidence of adverse events in moderately impaired subjects, no subjects with severe renal impairment received tadalafil.

Pharmacodynamic drug-drug interaction studies were conducted with drugs that are likely to be co-administered with tadalafil. Interaction studies with nizatidine, Maalox, theophylline, warfarin, metoprolol, bendrofluazide, enalapril, Aspirin, isosorbide mononitrate, and sublingual nitroglycerin used only 10 mg tadalafil. Studies with lovastatin, angiotensin II receptor antagonists, and tamsulosin (PD) were conducted in presence of 20 mg tadalafil. Both 10 mg and 20 mg doses of tadalafil were used to investigate interaction with alcohol and the calcium channel blocker, amlodipine. More drug-related adverse effects were observed when each of these drugs were administered with tadalafil than with placebo. However, only clear evidence of significant pharmacodynamic interaction was noted with 20 mg tadalafil in chronically administered angiotensin AT_1 receptor antagonists in hypertensive subjects, based on ambulatory systolic blood pressure.

Following co-administration of 10 mg tadalafil with 0.7 mg/kg alcohol, there were trends for greater impairment of some parameters (postural stability and word recognition), larger decrease in mean standing diastolic blood pressure (–12 mmHg at 4 hr), and greater increase in heart rate compared to the administration of alcohol with tadalafil placebo. In addition, the overall incidence of adverse events was highest following administration of tadalafil with alcohol compared to other combinations. In another study conducted in 48 male subjects to investigate the pharmacodynamic interaction between alcohol and 20 mg tadalafil clinically significant interaction was not observed. However, the dose level of alcohol used in this study was lower (0.6 g/kg). In the previous study, an oral dose of 0.7 g/kg resulted in blood levels (80 mg/dL) that correspond to legal intoxication as defined in the UK and in several states in the USA. The sponsor did not measure alcohol blood levels in the study conducted with 20 mg tadalafil.

Tadalafil potentiates the hypotensive effect of organic nitrates. A similar number of subjects had clinically significant changes in standing systolic and diastolic blood pressure following administration of 0.4 mg sublingual nitroglycerin with 10 mg tadalafil and with 50 mg sildenafil, the frequency of which was generally up to two-fold higher than for nitrate administered with placebo.

Population analyses were conducted in three Phase 2 studies (LVAC, LVBF and LVBG), and in one Phase 3 trial (CSR.LVCE). Response scores to IIEF Question 3 and Question 4 were used as endpoints in all three phase 2 studies. The pharmacodynamic model was based on the pharmacologically relevant E_{max} model describing a saturable drug response with increasing dose. Based on the results of these studies, it appears that the probability

APPENDIX-1

18-NOV-2003 FDA CDER EES Page 1 of 4
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21368/000	Action Goal:	
Stamp:	29-JUN-2001	District Goal:	29-SEP-2003
Regulatory Due:	28-NOV-2003	Brand Name:	CIALIS (TADALAFIL) 20MG
Applicant:	LILLY ICOS	Estab. Name:	TABLETS
	LILLY CORPORATE CENTER	Generic Name:	TADALAFIL
	INDIANAPOLIS, IN 45285		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	580	Strength:	5 MG, 10 MG, 20 MG

Application Comment: THIS IS AN NME COMPOUND WHICH WILL BE FORMULATED INTO A 20 MG STRENGTH I [redacted] TABLET. (on 23-AUG-2001 by D. LIN (HFD-830) 301-827-2003)

FDA Contacts: R. AGARWAL , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 13-NOV-2003by S. ADAMS (HFD-322)301-827-9051
WITHHOLD on 25-AUG-2003by J. D AMBROGIO(HFD-322)301-827-9049
WITHHOLD on 17-JUN-2002by J. D AMBROGIO(HFD-322)301-827-9049
WITHHOLD on 29-APR-2002by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN 1813682 FEI 1813682
ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: CSN OAI Status: NONE

Estab. Comment: DRUG SUBSTANCE MANUFACTURER. (on 23-AUG-2001 by D. LIN (HFD-830) 301-827-2003)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	30-NOV-2001	PS			MROBINSO
INSPECTION SCHEDULED	11-DEC-2001		15-FEB-2002		MROBINSO
INSPECTION SCHEDULED	07-FEB-2002		29-MAR-2002		MROBINSO
INSPECTION SCHEDULED	11-MAR-2002		28-APR-2002		MROBINSO
INSPECTION PERFORMED	18-APR-2002		18-APR-2002		MROBINSO
EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.					
INSPECTION PERFORMED	18-APR-2002		18-APR-2002		MROBINSO

This was a drug pre-approval, follow-up and cGMP inspection of a large API manufacturer

APPEARS THIS WAY
ON ORIGINAL

DO RECOMMENDATION	29-APR-2002	ACCEPTABLE INSPECTION	MROBINSO
EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.			
OC RECOMMENDATION	29-APR-2002	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
DO RECOMMENDATION	28-MAY-2002	ACCEPTABLE INSPECTION	MROBINSO
EI 4-1-18/02 WAS CLASSIFIED VAI.			
OC RECOMMENDATION	28-MAY-2002	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	11-JUN-2003		AGARWALR
OC RECOMMENDATION	11-JUN-2003	ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN 2619243 FEI
ELI LILLY INDUSTRIES INC
12.6 KM 65TH INFANTRY RD
CAROLINA, PR 00985

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE

Estab. Comment: TADALAFIL TABLETS WILL BE MANUFACTURED AT THIS ALTERNATE FACILITY. THIS FACILITY ALSO PERFORMS THE PACKAGING,LABELING AND CONTROL TESTING OF THE FINISHED PRODUCT. (on 11-JUN-2003 by R. AGARWAL ())

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUN-2003				AGARWALR
OC RECOMMENDATION	11-JUN-2003			ACCEPTABLE BASED ON FILE REVIEW BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO DO	17-SEP-2003	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	02-OCT-2003	PS			MSOSA
INSPECTION SCHEDULED	15-OCT-2003		15-NOV-2003		MTORRES
INSPECTION PERFORMED	10-NOV-2003		10-NOV-2003		MSOSA
DO RECOMMENDATION	13-NOV-2003			ACCEPTABLE INSPECTION	MSOSA
OC RECOMMENDATION	13-NOV-2003			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CRU OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
DO RECOMMENDATION	07-JAN-2002			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
OC RECOMMENDATION	07-JAN-2002			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
SUBMITTED TO OC	11-JUN-2003				AGARWALR
OC RECOMMENDATION	11-JUN-2003			ACCEPTABLE BASED ON FILE REVIEW BASED ON PROFILE	DAMBROGIOJ

18-NOV-2003 FDA CDER EES Page 4 of 4
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment:

DMF No: AADA:
Responsibilities:

Profile: TCM OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUN-2003				AGARWALR
SUBMITTED TO DO	11-JUN-2003	10D			DAMBROGIOJ
DO RECOMMENDATION	02-JUL-2003			ACCEPTABLE BASED ON FILE REVIEW	MSOSA
RECOMMENDATION	02-JUL-2003			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

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/s/

Rajiv Agarwal
11/20/03 12:58:06 PM
CHEMIST

Moo-Jhong Rhee
11/20/03 01:16:56 PM
CHEMIST
I concur

NDA 21-368

CIALIS (tadalifil) 5, 10, 20 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Lily ICOS LLC
[Joint venture between Lilly and ICOS]

Indication: For treatment of erectile disfunction.

Presentations: — bottles . —

EER Status: Acceptable 13-NOV_2003

Consults: OCPB - — dissolution test is acceptable
DMETS - CIALIS is acceptable
Statistics – recommendations re statistical treatment of matrixing approach provided

CIALIS was submitted 28-JUN-2001

The **drug substance** is manufactured by Lilly at the Lafayette IN site – CGMP compliant. Drug substance characterization and manufacturing are adequate. —

— CGMP compliant.

Specifications are considered adequate with the exception of impurities, which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. The specifications will be established —. A re-test period o — months is supported by submitted stability data.

Conclusion

Drug substance is acceptable.

The **drug product** is a 10 and 20 mg — film coated tablet. The product will be manufactured at the Lilly Carolina, Puerto Rico site. The Indianapolis site has been withdrawn. The manufacturing process — and controls are considered acceptable. Specifications are considered adequate with the exception of impurities which the sponsor has agreed to re-evaluate after additional manufacturing experience is gained. The specifications will be finalized within 1 year. Expiry of 24 months supported by submitted stability data. Labels and labeling are acceptable. All associated DMFs are acceptable.

Conclusion

Drug product is acceptable

Overall Conclusion
From a CMC perspective the application is recommended for an approval action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
11/20/03 04:40:02 PM
CHEMIST

NDA 21-368

CIALIS (tadalifil) 10, 20 mg Tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Lily ICOS LLC
[Joint venture between Lilly and ICOS]

Indication: For treatment of erectile disfunction.

Presentations: — bottles

EER Status: Withold 4/29/2002

Consults: OCPB - no review provided
OPDRA – no review provided – CIALIS is acceptable
Statistics – recommendations re statistical treatment of matrixing approach provided

CIALIS was submitted 28-JUN-2001. A IR letter was issued 11-FEB-2002, and was responded to in the amendment dated 6-MAR-2002.

The **drug substance** is manufactured by Lilly at the Lafayette IN site – 483 was issued. Drug substance characterization and manufacturing are adequate. performed by - compiance OK. Specification are considered adequate with the exception of impurities, which the sponsor has areed to re-evaluate after additional manufacturing experience is gained. A re-test period of is supported by submitted stability data.

Conclusion
Drug substance is acceptable.

The **drug product** is a 10 and 20 mg tablet. The product is manufactured at the Lilly Indianapolis site – 483 issued. The manufacturing process and controls are considered acceptable. Specifications are considered adequate with the exception of impurities which the sponsor has agreed to re-evaluater after additional manufacturing experience is gained. Expiry of 24 months supported by submitted stability data.

All associated DMFs are acceptable.

Overall Conclusion
From a CMC perspective the application is reccomended for an approvable action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
5/13/02 10:28:18 AM
CHEMIST
CMC Div Director review - thought this had already been signed off.

NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal, Ph.D

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

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Amendment	25-MAR-2002
Amendment	04-APR-2002
Amendment	05-APR-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC

Address: 1209 Orange Street, Wilmington, DE 19801

Representative: Dr. Gregory T. Brophy

Telephone: 317-277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cialis
b) Non-Proprietary Name (USAN): Tadalafil
c) Code Name/# (ONDC only): IC351, LY450190
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

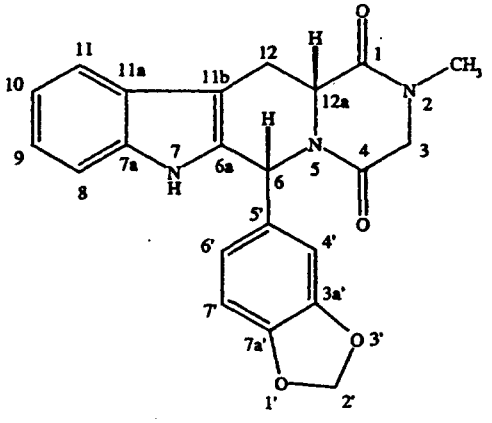
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

Chemical Name: Pyrazino{1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R, 12aR)-



Molecular Formula: $C_{22}H_{19}N_3O_4$

Molecular weight: 389.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	—	—	1	Adequate	26-MAR-2002	Reviewed by Dr. Rajiv Agarwal

[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:
- Chemistry Review # 1 dated 27-FEB-2002.
- IR letter dated 11-FEB-2002.

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	**Withhold**	29-APR-2002	Office of Compliance
OPDRA	(see page 20 of this review for recommendation)	19-APR-2002	Dr. Alina R. Mahmud
Methods Validation	The method validation package will be sent to and validated by FDA laboratories.		

The Chemistry Review for NDA 21-368

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **approvable** from the CMC point of view.

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

Based on the ICH-Q6A (decision tree # 1 and # 2), applicant is asked to tighten the proposed acceptance criteria for impurities identified in the drug substance and drug product. In an amendment, 06-MAR-2002, submitted in response to the IR letter dated 11-FEB-2002, applicant requests that at this time, it would be inappropriate to set acceptance criteria that may be too tight and a "***re-evaluation of the acceptance limits of impurities will be performed when sufficient production experience has been gained in the case of both drug substance and drug product***".

The division accepts the request. Based on their experience in the production of drug substance and drug product, the applicant should notify the division of their final acceptance criteria within ——— from the action date (approval date).

II. Summary of Chemistry Assessments

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

Drug product:

CIALIS (tadalafil), 20 mg, is an ——————— tablet, which is yellow, almond shaped, film coated and debossed on one side with "C20". This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. The Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana).

Inspection of the drug product manufacturing site has disclosed continued non-compliance with cGMP, therefore, the final recommendation from the Office of Compliance for the Eli Lilly manufacturing site is "Withhold".

The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, total related substances, largest individual related substances, water and dissolution. ——time-point of dissolution acceptance criterion are deemed adequate. All the test methods and respective acceptance criteria are deemed satisfactory except for the ' ——————————— " and ' ——————————
Applicant proposed to re-evaluate the acceptance criteria for the "Largest individual related substance" and "Total related substances" after sufficient experience is gained. Since the toxicologist in the division confirmed that the proposed limit is within the qualified level, the proposal is accepted. Post approval stability commitment has been satisfactorily revised as requested by the division.

The tablets will be marketed in ——————— bottle configurations containing —— ' 30 tablets, respectively. Tablets (20 mg) in ——— bottles are for physician samples only

and tablets in 30 count bottles are for Pharmacy. All packaging components are deemed adequate for protecting the drug product during the shelf life.

Based on the stability studies (12 months at long term and 6 months at accelerated testing conditions) on primary batches, 18-month of expiration date can be granted for the 20 mg tablets packaged in bottles and blister.

The trade name "Cialis" has been accepted by OPDRA. Applicant has accepted the division's proposal to . bottle (physician's sample) and indicated that an appropriate container will be provided by the pharmacist to fill the prescription from bottle. Per our recommendation, storage statement is revised and dosage form is indicated in both the physician insert and labels after established name. Primary and secondary container/closure labels for both bottles *However, there were some minor comments from OPDRA, of which clarification with the applicant will be deferred to next review cycle.*

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). Tadalafil structure includes two asymmetric chiral centers but X-ray studies indicate that only is present in the drug substance. Tadalafil has an unusually high melting point and is practically insoluble in water but is shown to be soluble in DMSO. A form of tadalafil is obtained by and is in **compliance with cGMP**.

The quality of the tadalafil is contolled by specification set by the manufacturer, which includes, identity by IR, identity by HPLC, assay, related substances (excluding chiral impurities), They are deemed satisfactory. All the test methods and respective acceptance criteria are deemed satisfactory except for the **acceptance criteria of impurities as discussed earlier.**

The final recommendation from the **Office of Compliance** for Eli Lilly manufacturing site is "acceptable".

Based on the updated stability information, can be granted.

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

The proposed dose of CIALIS is 20 mg and is taken orally prior to anticipated sexual activity without regard to food. The maximum recommended dosing frequency is once a day.

C. Basis for Approvability or Not-Approval Recommendation

- Outstanding issues from Chemistry Review # 1 of NDA 21-368 has been satisfactorily resolved (see attached Chemistry Review notes).
- There were some comments from OPDRA which need to be clarified with the applicant (see OPDRA review dated 19-APR-2002 and page 20 of this review).
- Inspection of the drug product manufacturing site has disclosed continued non-compliance with cGMP, therefore, the final recommendation from the Office of Compliance for the **Eli Lilly site is "Withhold"** (see Appendix-1).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ D Spell Le-Sane/ Date: 29-APR-2002

C. CC Block

HFD-820/EDuffy/Duu Gong Wu

13 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

APPENDIX-1

29-APR-2002 FDA CDER EES Page 1 of 2
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21368/000
Stamp: 29-JUN-2001
Regulatory Due: 29-APR-2002
Applicant: LILLY ICOS
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 45285
Priority: 1S
Org Code: 580

Action Goal:
District Goal: 28-FEB-2002
Brand Name: CIALIS (TADALAFIL) 20MG TABLETS
Estab. Name:
Generic Name: TADALAFIL

Dosage Form: (TABLET)
Strength: 20 MG

Application Comment: THIS IS AN NME COMPOUND WHICH WILL BE FORMULATED INTO A 20 MG STRENGTH [redacted] TABLET. (on 23-AUG-2001 by D. LIN (HFD-580) [redacted])

FDA Contacts: R. AGARWAL , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: WITHHOLD on 29-APR-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1819470
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PKY/EAST DR
INDIANAPOLIS, IN 46200
DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
Profile: TCM OAI Status: OAI ALERT
Estab. Comment: DRUG PRODUCT MANUFACTURER AND SITE OF STABILITY TESTING. (on 23-AUG-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
DO RECOMMENDATION	23-APR-2002			WITHHOLD INADEQUATE QA FUNCTIONS	MROBINSO
PREVIOUS PROFILE IS CLASSIFIED NOT ACCEPTABLE. A GMP INSPECTION IS IN PROGRESS BUT WILL NOT BE COMPLETED BY 4/29/2002. DETROIT DISTRICT CANNOT MAKE A FINAL RECOMMENDATION UNTIL EI IS COMPLETED.					
OC RECOMMENDATION	23-APR-2002			WITHHOLD DISTRICT RECOMMENDATION	ALCOCKP

Establishment: 1813682
ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: CSN OAI Status: NONE

APPEARS THIS WAY
ON ORIGINAL

Estab. Comment: DRUG SUBSTANCE MANUFACTURER. (on 23-AUG-2001 by D. LIN (HFD-580) 301-827-4230)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
ASSIGNED INSPECTION	30-NOV-2001	PS			MROBINSO
INSPECTION SCHEDULED	11-DEC-2001		15-FEB-2002		MROBINSO
INSPECTION SCHEDULED	07-FEB-2002		29-MAR-2002		MROBINSO
INSPECTION SCHEDULED	11-MAR-2002		28-APR-2002		MROBINSO
INSPECTION PERFORMED	29-APR-2002		18-APR-2002		MROBINSO
EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.					
DO RECOMMENDATION	29-APR-2002			ACCEPTABLE INSPECTION	MROBINSO
EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.					
OC RECOMMENDATION	29-APR-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]
Profile: CRU OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
DO RECOMMENDATION	07-JAN-2002			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
OC RECOMMENDATION	07-JAN-2002			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Rajiv Agarwal
4/29/02 11:44:38 AM
CHEMIST

Moo-Jhong Rhee
4/29/02 11:55:47 AM
CHEMIST
I concur

NDA 21-368

Cialis
Tadalafil tablets

Lilly ICOS LLC

Rajiv Agarwal

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA # 21-368
2. REVIEW #: 1
3. REVIEW DATE: 26-FEB-2002
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-JUN-2001
Amendment	18-SEP-2001
Amendment	25-SEP-2001
Amendment	22-OCT-2001
Amendment	23-JAN-2002
Amendment	01-FEB-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Lilly ICOS LLC

Address: 1209 Orange Street, Wilmington, DE 19801

Representative: Dr. Gregory T. Brophy

Telephone: 317-277-3799

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cialis
b) Non-Proprietary Name (USAN): Tadalafil
c) Code Name/# (ONDC only): IC351, LY450190
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Phosphodiesterase Type 5 inhibitor/ Erectile Dysfunction

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION: Oral

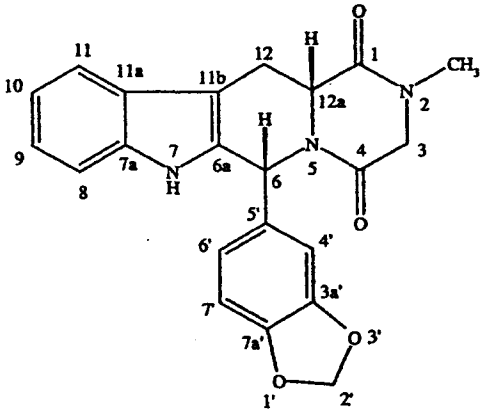
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

Chemical Name: Pyrazino{1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R, 12aR)-



Molecular Formula: $C_{22}H_{19}N_3O_4$

Molecular weight: 389.41

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	1	Adequate	14-FEB-02	Reviewed by Dr. Rajiv Agarwal
[redacted]	III	[redacted]	[redacted]	3	Adequate	27-SEP-00	Reviewed by Dr. Rick Lostritto for DMF strike force, dated 27-9-00
[redacted]	III	[redacted]	[redacted]	1	Adequate	14-FEB-02	Reviewed by Dr. Rajiv Agarwal

Chemistry Review Data Sheet

	III		3	Adequate	14-AUG-00	Reviewed by Dr. Raj Uppoor for 21-290 dated 14-8-00
	III		3	Adequate	06-MAR-00	Reviewed by Dr. S. D. McLamore for 21-086 dated 6-3-00
	III		3	Adequate	25-FEB-99	Reviewed by Dr. Ray Frankewich for 21-103/S-016 dated 23-02-99
	III		3	Adequate	01-SEP-99	Reviewed by Dr. James Vidra for 1-9-99
	III		3	Adequate	01-SEP-99	Reviewed by Dr. James Vidra for 1-9-99
	III		3	Adequate	27-SEP-00	Reviewed by Dr. James Vidra for DMF dated 27-9-00
	III		1	Adequate	14-FEB-02	Reviewed by Dr. Rajiv Agarwal
	III		3	Adequate	02-MAY-99	Reviewed by Dr. Mike Adams for 20-675/SCP-002 dated 2-5-99
	III		1	Adequate	14-FEB-02	Reviewed by Dr. Rajiv Agarwal
	III		1	Adequate	14-FEB-02	Reviewed by Dr. Rajiv Agarwal
	III					***Under Review***
			3	Adequate	07-SEP-01	Reviewed by Dr. [illegible] for DMF dated 7-9-01

[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:

- IND 54,553
- IND [redacted]
- Patent # 5,859,006 for compound (expiry date 12-JAN-2016)
- Patent # 6,140,329 for method of use (expiry date 11-JUL-2016)
- Filing meeting minutes 20-AUG-2001

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Completed	04-FEB-02	Dr. Wen-Jen Chen
EES	**Pending**		Office of Compliance
Biopharm	**Pending**		Dr. Sandip Roy
Methods Validation	The method validation package will be sent to and validated by FDA laboratories.		
OPDRA	Approved	10-JAN-02	Ms. Jennifer Fan
EA	Categorical exclusion Granted	22-FEB-02	Dr. Rajiv Agarwal
Microbiology	Applicant is asked to justify for not providing microbial limit specification in the [redacted] letter by this reviewer.		

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is **approvable.**

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

None

II. Summary of Chemistry Assessments

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

Drug product:

CIALIS (tadalafil), 20 mg, is an [redacted] tablet, which is yellow, almond shaped, film coated and debossed on one side with "C20". This product is indicated for erectile dysfunction based on potent, selective, reversible inhibition of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. The Cialis tablets are manufactured, packaged, and tested by Eli Lilly in Indianapolis (Indiana). The final recommendation from the Office of Compliance for the **Eli Lilly site is still pending.**

The quality of the tablets is controlled by tests: appearance, identification, assay, uniformity of dosage unit, totals related substances, largest individual related substances, water and dissolution. All the respective acceptance criteria are deemed satisfactory except for the **acceptance criteria of impurities. It should be further tightened, unless justified.**

The tablets are packaged in [redacted]

The tablets (10 tablets) . [redacted]

Sponsor is requesting a 24 months of shelf life. Based on the stability studies on primary batches, 18 months of expiry date can be granted for the product packaged in bottles [redacted] Moreover, the **post approval stability commitment is not satisfactory** and needs to be further revised.

To validate the analytical procedures, applicant is asked to submit three copies of **method validation package.**

The trade name "Cialis" has been accepted by OPDRA, and adequate chemistry information is presented in the labeling. However, the statement in **How supplied section,** as well the **storage statement** should be revised as delineated in draft deficiency letter and a warning statement "
Additionally, the dosage form **"tablets"** should be added to both **physician insert** and **labels** after established name. The **labels for bottles** :

Drug Substance:

Tadalafil is a new molecular entity and is manufactured by Eli Lilly and Company in Lafayette (Indiana). The final recommendation from the Office of Compliance for **Eli Lilly site is still pending.**

The quality of the tadalafil is contolled by specification set by the manufacturer, which includes, identity by IR, identity by HPLC. assay, related substances (excluding chiral impurities),

They are deemed satisfactory. All the respective acceptance criteria are deemed satisfactory except for the **acceptance criteria of impurities. It should be further tightened, unless justified.**

To further ensure the quality of the drug substance, a **reference standard** of highest purity is warranted. Therefore, **a summary of manufacturing, characterization, analytical testing, COA and storage information** is requested.

The bulk drug substance will be stored in the and it is deemed necessary to have it tested for its suitability as a container. Therefore, results of test are requested.

Microbial testing and limits are not included, therefore, applicant is asked to justify for not providing **microbial limit specification.**

Applicant is requesting a Only 18-month is granted.

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

The recommended dose of CIALIS is 20 mg and is taken orally prior to anticipated sexual activity without regard to food. The maximum recommended dosing frequency is once per day.

C. Basis for Approvability or Not-Approval Recommendation

This application is **approvable** from Chemistry, Manufacturing and Control standpoint. This recommendation is based upon several issues identified during the review. The level of impurities, both in the drug substance and in the drug product were rather generous, therefore needs to be revised to reflect the actual manufacturing capability and stability characteristics of the product. Similarly, adequate information on the drug

substance reference standards is not provided and must be addressed to guarantee the highest purity of the drug substance. The system suitability of the analytical methods, which establishes the performance of the chromatographic method (HPLC) for meaningful interpretation of the drug substance specifications, needs to be provided.
Sponsor must provide the required ~~~~ results (for maintaining the quality) on the ———— , which stored the drug substance.
The post approval stability commitment needs to be revised to control the quality of the future drug product batches.
Lastly, the final recommendation from the Office of Compliance for Eli Lilly sites (Drug product and Drug substance manufacturing sites) is still pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/RAgarwal/ MRhee/ D Spell Le-Sane/ Date: 26-FEB-2002

C. CC Block

HFD-820/EDuffy/Duu Gong Wu

REVIEW NOTES

52 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

/s/

Rajiv Agarwal
2/27/02 09:06:47 AM
CHEMIST

Moo-Jhong Rhee
2/27/02 09:44:53 AM
CHEMIST
I concur

APPENDIX-1

18-NOV-2003 FDA CDER EES Page 1 of 4
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 21368/000	Action Goal:	
Stamp:	29-JUN-2001	District Goal:	29-SEP-2003
Regulatory Due:	28-NOV-2003	Brand Name:	CIALIS (TADALAFIL) 20MG
Applicant:	LILLY ICOS	Estab. Name:	TABLETS
	LILLY CORPORATE CENTER	Generic Name:	TADALAFIL
	INDIANAPOLIS, IN 45285		
Priority:	1S	Dosage Form:	(TABLET)
Org Code:	580	Strength:	5 MG, 10 MG, 20 MG

Application Comment: THIS IS AN NME COMPOUND WHICH WILL BE FORMULATED INTO A 20 MG STRENGTH [redacted] TABLET. (on 23-AUG-2001 by D. LIN (HFD-830) 301-827-2003)

FDA Contacts: R. AGARWAL , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation:
ACCEPTABLE on 13-NOV-2003by S. ADAMS (HFD-322)301-827-9051
WITHHOLD on 25-AUG-2003by J. D AMBROGIO(HFD-322)301-827-9049
WITHHOLD on 17-JUN-2002by J. D AMBROGIO(HFD-322)301-827-9049
WITHHOLD on 29-APR-2002by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN 1813682 FEI 1813682
ELI LILLY CO/TIPPECANOE
BOX 685 LILLY RD
LAFAYETTE, IN 47902

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: CSN QAI Status: NONE

Estab. Comment: DRUG SUBSTANCE MANUFACTURER. (on 23-AUG-2001 by D. LIN (HFD-830) 301-827-2003)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	30-NOV-2001	PS			MROBINSO
INSPECTION SCHEDULED	11-DEC-2001		15-FEB-2002		MROBINSO
INSPECTION SCHEDULED	07-FEB-2002		29-MAR-2002		MROBINSO
INSPECTION SCHEDULED	11-MAR-2002		28-APR-2002		MROBINSO
INSPECTION PERFORMED	18-APR-2002		18-APR-2002		MROBINSO

EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.

INSPECTION PERFORMED	18-APR-2002		18-APR-2002		MROBINSO

This was a drug pre-approval, follow-up and cGMP inspection of a large API manufacturer

**APPEARS THIS WAY
ON ORIGINAL**

DO RECOMMENDATION	29-APR-2002	ACCEPTABLE INSPECTION	MROBINSO
EIR 4/1-18/2002 WILL BE CLASSIFIED VAI.			
OC RECOMMENDATION	29-APR-2002	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
DO RECOMMENDATION	28-MAY-2002	ACCEPTABLE INSPECTION	MROBINSO
EI 4-1-18/02 WAS CLASSIFIED VAI.			
OC RECOMMENDATION	28-MAY-2002	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	11-JUN-2003		AGARWALR
OC RECOMMENDATION	11-JUN-2003	ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN 2619243 FEI
ELI LILLY INDUSTRIES INC
12.6 KM 65TH INFANTRY RD
CAROLINA, PR 00985

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE

Estab. Comment: TADALAFIL TABLETS WILL BE MANUFACTURED AT THIS ALTERNATE FACILITY. THIS FACILITY ALSO PERFORMS THE PACKAGING, LABELING AND CONTROL TESTING OF THE FINISHED PRODUCT. (on 11-JUN-2003 by R. AGARWAL ())

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUN-2003				AGARWALR
OC RECOMMENDATION	11-JUN-2003			ACCEPTABLE BASED ON FILE REVIEW BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO DO	17-SEP-2003	10D			DAMBROGIOJ
ASSIGNED INSPECTION T	02-OCT-2003	PS			MSOSA
INSPECTION SCHEDULED	15-OCT-2003		15-NOV-2003		MTORRES
INSPECTION PERFORMED	10-NOV-2003		10-NOV-2003		MSOSA
DO RECOMMENDATION	13-NOV-2003			ACCEPTABLE INSPECTION	MSOSA
OC RECOMMENDATION	13-NOV-2003			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: CRU OAI Status: NONE

Estab. Comment: [redacted]

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-AUG-2001				LINDAV
SUBMITTED TO DO	23-AUG-2001	PS			DAMBROGIOJ
DO RECOMMENDATION	07-JAN-2002			ACCEPTABLE BASED ON FILE REVIEW	DPAGANO
OC RECOMMENDATION	07-JAN-2002			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS
SUBMITTED TO OC	11-JUN-2003				AGARWALR
OC RECOMMENDATION	11-JUN-2003			ACCEPTABLE BASED ON FILE REVIEW BASED ON PROFILE	DAMBROGIOJ

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment:

DMF No: AADA:
Responsibilities:

Profile: TCM OAI Status: NONE

Estab. Comment:

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-JUN-2003				AGARWALR
SUBMITTED TO DO	11-JUN-2003	10D			DAMBROGIOJ
DO RECOMMENDATION	02-JUL-2003			ACCEPTABLE BASED ON FILE REVIEW	MSOSA
OC RECOMMENDATION	02-JUL-2003			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ