

Background: NDA 21-368, Cialis (tadalafil) was issued an Approvable (AE) letter on April 29, 2002, on the 10-month goal date. On two post-action meetings dated May 20, 2002 and June 3, 2002, it was recommended that Lilly ICOS request a meeting with the Division to discuss better communication procedures during the review of the Complete Response the sponsor plans to submit. The sponsor has stated that communication during that review of the original NDA was not timely and productive.

Discussion and Decision Points:

- Dr. Shames started the meeting by noting the two problems that occurred during the previous review process:
 - Late communication wherein issues were noted and communicated late in the review process. This was due mainly to insufficient resources (e.g., shortage of staff). The Division had the 3rd highest number of NDA/NMEs for review last year.
 - No or poor communication between the sponsor and FDA regarding specific issues. A major cause of this was incorrect assumptions by either the sponsor or FDA regarding thoughts on actions or issues. For example, DRUDP sent an Information Request (IR) letter to Lilly regarding disagreement with Lilly's statistical arguments supporting a claim of _____ for Cialis. DRUDP received the response from Lilly and again rejected Lilly's arguments. However, the Division did not communicate this position to Lilly and Lilly assumed that no response implied agreement with their statistical arguments.
- FDA proposed the following steps to enhance the communication between the Agency and the sponsor:
 - Increase the number of FTEs which should help with the overall resources within the DRUDP.
 - Improve dialogue by having the sponsor return for a pre-Complete Response meeting to provide the reviewers an overview of the data that will be provided in the submission addressing each AE deficiency. (The sponsor agreed and will contact the Project Manager for date and time.)
 - Sponsor to provide annotated label that will provide supportive information to the proposed labeling language. (The sponsor agreed to provide the label.)
 - The sponsor is encouraged to come in for an NDA orientation presentation to give an overview of the response and to navigate through the submission with the reviewers. This is an experimental procedure and has never been done with other sponsors. (The sponsor indicated that they will request this meeting at the time of submission.)
 - DRUDP will convey 74-day filing review issues via regulatory letter
 - The sponsor is encouraged to participate in an end-of-4-month review meeting which could be a face-to-face meeting or a teleconference. (The sponsor agreed.)
 -

Meeting Minutes

Page 3

- DRUDP will attempt to start labeling discussions as early as possible, in month 5 of the review. It was emphasized, however, that it will be difficult to negotiate labeling until the review is substantially complete. (The sponsor recommended utilization of technology means such as webcasts and on-line review to facilitate discussions.)
- The sponsor was requested to be more forthcoming with information on all ongoing and planned trials during the NDA review.
- There should be one main point of contact for FDA and the sponsor. All consults outside the Division will be arranged via the Project Manager. The sponsor was told not to assume that consult review results are final. The final decision rests with the DRUDP.
- The efficiency of communications between the sponsor and the Division should be improved. Communications should be collated and prioritized to reduce unnecessary interactions. Parallel interactions between various levels of the sponsor and FDA are usually redundant and unnecessarily expend resources.

Action Items:

- Meeting minutes will be sent to the sponsor within 30 days.

(See appended electronic signature page)

Daniel Shames, M.D.
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Meeting Minutes
Page 4

cc:
NDA Arch:
HFD-580/DeGuia/Shames/Houn/Hirsch/Batra/Parekh/Kober
drafted: DeGuia021903
concurrences: Shames,Kober031003,Batra030703
final: DeGuia031203

MEETING MINUTES

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/s/

Daniel A. Shames
3/12/03 06:20:57 PM



NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
1209 Orange Street
Wilmington, DE 19801

Dear Dr. Melfi:

We received your November 27, 2002, correspondence on November 29, 2002, requesting a meeting to discuss expected interactions and communications between Lilly ICOS and the Division during the review of the NDA. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You were informed via telephone on December 12, 2002 that your request for a Type C meeting has been granted and it is scheduled for:

Date: February 10, 2003

Time: 10:30 AM - 12:00 PM

Location: TBD

The following representatives from CDER are invited: Drs. Florence Houn, Daniel Shames, Mark Hirsch, Moo Jhong Rhee, Alex Jordan, Ameeta Parekh and Ms. Margaret Kober and Eufrecina DeGuia.

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If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
12/31/02 02:14:08 PM
Chief, Project Management Staff

Teleconference Minutes

Date: December 16, 2002 **Time:** 3:00 – 3:15 PM **Location:** Room 17B-45

NDA 21-368 **Drug Name:** Cialis (tadalafil tablets)

Indication: treatment of erectile dysfunction

Sponsor: Lilly ICOS LLC

Type of Meeting: Guidance

Meeting Chair: Dr. Moo Jong Rhee **External Participant Lead:** Dr. Cathie Melfi

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Moo Jong Rhee, M.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)

Eufrecina DeGuia – Regulatory Health Project Manager, DRUDP (HFD-580)

Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Participants:

Sally Anliker, Ph.D. – Manager, Regulatory Affairs (CMC)

Cathy Melfi, Ph.D. – Senior Regulatory Research Scientist

Tobias Massa, Ph.D. – Executive Director, Global Regulatory Affairs

Carol Van Auwelaer – Senior Regulatory Associate

Diane Zezza, Ph.D. – Director, Regulatory Affairs (CMC)

Susan Sullivan – Manager, Regulatory Affairs

Jeff Hesselberg, MBA – Supervisor, Regulatory Affairs

Ken Ferguson, Ph.D. – Chief Scientific Officer

Steve Hadley, Ph.D. – Quality Assurance/QC

Objective: To discuss site specific stability information which is to be included in the resubmission of previously “Approvable” NDA.

Meeting Minutes

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Discussion and Decision Points:

The sponsor was asked to submit the following in the re-submission:

1. List of equipment used in Puerto Rico (including model numbers) for a site by site comparison with US site to confirm operating procedures.
2. Certificate of Analysis with numerical test data for three validation batches of 10 mg and 20 mg of Cialis tablets manufactured at Puerto Rico site.
3. Three months of stability data (accelerated and long term) on a site specific developmental batch (this can be submitted within 3 months of the NDA).
4. Stability protocol for the Puerto Rico site should be submitted in order for the sponsor to get 24 months expiration date for the 20 mg and 36 months expiration date for the 10 mg.

The sponsor agreed to all the above requests.

Action Items: none

(See appended electronic signature page)

Moo Jhong Rhee, Ph.D.

Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Meeting Minutes
Page 3

cc:
NDA Arch:
concurrences: Chatterjee, Agarwal, Rhee030603
final: DeGuia030703

MEETING MINUTES

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/s/

Moo-Jhong Rhee
3/7/03 11:04:27 AM
I concur

Teleconference Minutes

Date: November 26, 2002 **Time:** 11:00 AM – 12:00 PM **Location:** Room 17B-45

NDA 21-368 **Drug Name:** Cialis (tadalafil tablets)

Indication: treatment of erectile dysfunction

Sponsor: Lilly ICOS LLC

Type of Meeting: Guidance

Meeting Chair: Dr. Moo Jhong Rhee **External Participant Lead:** Dr. Cathie Melfi

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:

Moo Jhong Rhee, M.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products; DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Health Project Manager, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

External Participants:

Catherine Melfi, Ph.D. – US Regulatory Affairs
Sally Anliker – Regulatory Affairs, CMC
Eldemar Cabotage – Analytical Development

Martha Kral – Process Development
Susan Sullivan – Regulatory Affairs
Carol Van Auwelaer – Regulatory Affairs, CMC

Objective: To reach agreement regarding CMC information to be included in the Complete Response to Approvable (AE) letter issued on April 29, 2002.

Discussion and Decision Points:

As part of the Complete Response, the sponsor propose to include the following changes to the CMC section of the NDA:

1. An alternative manufacturing, control and packaging site in Puerto Rico
2. A shelf life of 24 months for both 10 and 20 mg tablets based on 24 months of real time data from the primary stability batches.

After review of the information provided in the meeting package, the following recommendations to better address the above changes were conveyed to the sponsor:

Meeting Minutes

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- **Changes in the manufacturing and Packaging sites:** This level 3 change consists of a transfer of the manufacturing and packaging site to a different campus. To qualify as a level 3 change the same equipment, SOPs and controls should be used in the manufacturing process at the new site and no change may be made to the manufacturing batch records. Applicant states that no changes to the manufacturing process are being made, therefore, the proposed site change is acceptable upon satisfactory inspection of the manufacturing and packaging sites. Updated batch records of the drug product manufacturing should be included in the submission for review. Release data from three batches (comparative) of each commercial strength (10 and 20 mg) manufactured at PR and Indiana sites should be included. And a stability protocol of the validation batches should be provided.
- **Shelf life:** Addition of the PR site as a commercial site would require a 3 months of site specific accelerated stability data on one validation batch of each strength in order to grant — months expiration date for both strength. Expiration date beyond — months would require additional site specific stability data that could be submitted as a CBE-30 to grant a 24 months of expiration date.
- Dissolution profiles comparing US site to Puerto Rico site should be provided.

Action Items:

- The sponsor indicated that they will discuss internally the impact of our recommendations and will get back to the Division regarding the projected timeline of the submission of the Complete Response.

(See appended electronic signature page)

Moo Jhong Rhee, Ph.D.
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

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Page 3

Concurrences: Agarwal, Rhee030703
Final: DeGuia030703

MEETING MINUTES

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/s/

Moo-Jhong Rhee
3/7/03 11:07:13 AM
I concur

From: Venkateswar Jarugula, Ph.D., HFD-870

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified
IND/NDA submission

DATE: 11/08/02

IND No.:

NDA No. 21-368,
IC351

DATE OF DOCUMENT
9/5/02

NAME OF DRUG
Tadalafil

PRIORITY CONSIDERATION

Date of informal/Formal
Consult:

NAME OF THE SPONSOR: Lilly ICOS LLC

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE

- | | | |
|--|--|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input checked="" type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | | |

REVIEW ACTION

- | | | |
|---|---|--|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input checked="" type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | | <input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

In the current submission, the sponsor submitted the following five final protocols with amendments to address the FDA comments (conveyed in meeting minutes dated 7/3/02 and in a letter dated 08/29/02).

Protocol H6D-EW-LVET(a) – Randomised, placebo-controlled, three-period, crossover study to further investigate a potential pharmacodynamic interaction between alcohol and 20 mg IC351 in healthy volunteers.

Protocol H6D-EW-LVEV(a) - A study to assess the effect of ritanovir and ketoconazole on the pharmacokinetics of 20 mg IC351 in healthy subjects.

Protocol H6D-EW-LVFG(a) - A pharmacodynamic study to evaluate the interaction between 20 mg IC351 and 8 mg q.d. Doxazosin, an alpha 1 adrenergic antagonist, in healthy male subjects

Protocol H6D-EW-LVEX (b) - The effects of 20 mg of IC351 on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects

Protocol H6D-EW-LVEY(a) -A study to assess the effects of 20 mg IC351 on aspirin induced prolongation of bleeding time

Recommendation.

Sponsor has adequately addressed the FDA comments on these protocols. Therefore, the final protocols submitted herein are acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: HFD # [870]; TL: [Parekh]; DD: [Malinowski]; PM: []

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/s/

Venkateswar Jarugula
11/8/02 01:28:32 PM
BIOPHARMACEUTICS

Ameeta Parekh
11/22/02 12:57:30 PM
BIOPHARMACEUTICS
Concur

TELECONFERENCE MEETING MINUTES

MEETING DATE: October 7, 2002
TIME: 4:00 p.m. – 5:00 p.m.
LOCATION: PKLN 17B-45
APPLICATION: NDA 21-368
SPONSOR: LILLY ICOS
TYPE OF MEETING: Guidance
MEETING CHAIR: Daniel Shames
MEETING RECORDER: Dornette Spell-LeSane

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Daniel Shames	Director	Reproductive and Urologic Drug Products (HFD-580)
2. David Hoberman	Statistician	DRUDP HFD-580
3. Dornette Spell-LeSane	Regulatory Project Manager	DRUDP HFD-580

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Ken Ferguson,	Chief Scientific Officer	Lilly, ICOS
2. Mark Barbato,	Team Leader	Lilly, ICOS
3. Greg Brophy,	Regulatory	Lilly, ICOS
4. Cathy Melfi,	Regulatory	Lilly, ICOS
5. Susan Sullivan,	Regulatory	Lilly, ICOS
6. Charles Beasley,	Medical	Lilly, ICOS
Sanjeev Ahuja	Medical	Lilly, ICOS

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
7. Wei Shen	Statistics	Lilly, ICOS
8. Aileen Murphy	Statistics	Lilly, ICOS

BACKGROUND:

This NDA 21-368 received an approvable action on April 29, 2002. Lilly ICOS, in a correspondence dated August 8, 2002, request a teleconference to further clarify and discuss statistical comments made during the June 3, 2002, Type A meeting where approvable issues were discussed.

DISCUSSION POINTS:

- DRUDP stated that the Division would not discuss in detail any labeling; however would discuss the _____ statement proposed for the label
- DRUDP expects that some information regarding the trial may be included in labeling, however, DRUDP is uncomfortable with the wording _____
- DRUDP stated that the clinical trial was not designed to provide data to support _____ the language in the proposed label do not reflect results of the trial
- the draft proposal for study LVFD entitled "A Randomized, Double-Blind, Parallel, Placebo-Controlled Study to Evaluate the Efficacy of Tadalafil When Administered as Specific Time Points Prior to Sexual Activity in Men with Erectile Dysfunction" submitted August 8, 2002; participants were not having sex at the same dose at the 24 and 36 hour timepoints
- the sponsor should review results of the data and fashion language for labeling that accurately reflects the results of the study
- DRUDP does not object to the study design only the language proposed for labeling that describes the study results
- DRUDP is uncomfortable discussing labeling when data has not yet been analyzed

DECISIONS (AGREEMENTS) REACHED:

Language for labeling needs to be explicit of what was observed during the clinical trials; sponsor may propose language for labeling on resubmission

ACTION ITEMS:

None

Minutes Preparer: _____
SIGNERS NAME & TITLE

Chair Concurrence: _____
SIGNERS NAME & TITLE

|S|

|S|

NDA 21-368

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cc: Original

HFD-580/Div. Files

HFD-580/Meeting Minutes files

HFD-580/Spell-LeSane, Kober, Shames, Batra, Hoberman, Hirsch

Drafted by: SPELL-LESANE, 11.6.02

Initialed by: Shames, 11.7.02

final: Spell-LeSane, 11.7.02

MEETING MINUTES

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/s/

Daniel A. Shames
11/8/02 10:30:21 AM



NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
1209 Orange Street
Wilmington, DE 19801

Dear Dr. Melfi:

We received your September 30, 2002, correspondence on October 1, 2002, requesting a meeting to discuss chemistry, manufacturing and control issues associated with Cialis. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a type B meeting. However, based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C. The meeting is scheduled for:

Date: November 26, 2002
Time: 11:00 a.m. - 12:00 p.m.
Location: Teleconference
CDER participants: Drs. Rhee, Agarwal, Parekh, Jarugula and Ms. Spell-LeSane

Provide the background information for this meeting at least one month prior to the meeting. If we do not receive it by October 26, 2002, we may need to reschedule the meeting.

NDA 21-368

Page 2

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Dornette Spell-LeSane, R.N., NP-C, MHA
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Dornette Spell-LeSane
10/6/02 02:00:40 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-368

Lilly ICOS LLC
Attention: Catherine Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Melfi:

We received your August 8, 2002, correspondence on August 9, 2002, requesting a meeting to discuss 1) statistical and clinical comments made during our June 3, 2002, meeting and 2) proposed content and format of study reports to be included in the complete response to the Approvable letter. We have considered your request and conclude that a meeting is premature. However, in order to assist you in your drug development program, we are providing the following comments regarding clinical deficiencies in the April 29, 2002, Approvable letter.

1. Regarding study LVDN (nitrate study) it is uncertain if the "alternate design" proposed at the June 3, 2002, meeting will be required for approval. Please submit a final protocol based upon comments conveyed to you during the June 3, 2002, meeting. After review of this protocol, you will be notified if the alternate design proposed by our Cardio-Renal Division will be necessary.
2. Regarding the protocol for study LVET (alcohol interaction study), the Division's comments were conveyed to you during the June 3, 2002, meeting. Please submit a revised protocol for final concurrence.
3. Regarding the protocols for studies LVEV, LVEW, LVEX and LVEY (drug interaction studies) we have the following comments that were communicated to you previously:
 - a) The study design for protocol H6D-EW-LVEV should ensure that ketaconazole and ritonavir are dosed to steady state before the administration of IC351 and maintained at steady state until the IC351 and its metabolites are cleared from the body.
 - b) We recommend that you change the dose of ritonavir to 600 mg twice daily, as this is the recommended dose for adults in the physician package insert.
 - c) The inclusion criterion for BMI in the proposed drug interaction studies should be consistent with the studies submitted in the original NDA.
4. Regarding LVES (visual study), please submit a revised protocol based upon comments conveyed to you by Dr. Chambers.

5. Regarding a "renal blood flow" and "MRF" studies, we recommend that you submit all protocols intended to resolve Approvable deficiencies prior to study initiation.
6. Regarding the results of studies LVBG, LVBS and LVBU and their potential to address clinical deficiency number three, of the April 29, 2002, Approvable letter, (the QT issue), these results do not appear sufficient to respond to this deficiency. First, there are few subjects in these 3 studies, particularly for evaluation of effects near the time of peak plasma levels of tadalafil. Second, the studies have no positive control for purposes of establishing assay sensitivity. Your proposal to use baseline data to establish assay sensitivity is not sufficiently detailed to allow for comment.
7. It is premature to discuss the content and format of study reports that are intended for the complete response.

If you disagree with our decision to not grant this meeting, you may discuss the matter with Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260. If the issue cannot be resolved at the Division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fml.htm>.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
8/29/02 03:12:00 PM

Meeting Minutes

Date: June 3, 2002 **Time:** 9:00 a.m.-10:30 a.m. **Location:** Parklawn; Chesapeake CR

NDA: 21-368

Drug: Cialis

Sponsor: Lilly ICOS

Indication:

erectile dysfunction

Type of Meeting:

Guidance Meeting (post approvable action)

Meeting Chair:

Daniel Shames, M.D.

External Lead:

Greg Brophy, Ph.D.

Meeting Recorder:

Dornette Spell-LeSane, NP-C

FDA Attendees:

Daniel Shames, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Florence Houn, M.D., Director, Office of Drug Evaluation III (ODE III; HFD-103)

Mark Hirsch M.D., Medical Team Leader, DRUDP (HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Zili Li, M.D., Medical Officer, DRUDP (HFD-580)

Norman Stockbridge, M.D., Division of Cardio-Renal Drug Products, DCRDP (HFD-110)

Wiley Chambers, M.D., Deputy Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550)

David Hoberman, Ph.D., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Venkat Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer (OCPB) @ DRUDP (HFD-580)

Margaret Kober, R.Ph., Chief, Project Management Staff, DRUDP (HFD-580)

Kassandra Sherrod, R.Ph., Regulatory Project Manager, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

External Attendees:

Greg Brophy, Ph.D., Director, US Regulatory Affairs, Lilly

Jennifer Stotka, MD, US Regulatory, Lilly

Mark Barbato, Product Team Leader, Lilly

Timothy Costigan, Ph.D., Research Scientist, Statistics, Lilly

Jeff Hesselberg, MBA, Regulatory, Lilly

Malcolm Mitchel, M.D., Medical Advisor, Clinical Pharmacology, Lilly

Vish Watkins, M.D., Sr. Clinical Research, Lilly

Steve Whitaker, M.D., Director of Clinical Research, ICOS

Ken Ferguson, Ph.D., Team COO and CSO, ICOS

Charles Beasley, M.D., Medical Director, Lilly

Susan Sullivan, B.S., Sr. Regulatory Affairs, Lilly ICOS

Meeting Objectives: To discuss the approvability deficiencies related to the Cialis application.

Background:

Cialis, Tadalafil, is a selective and potent inhibitor of the GMP-specific phosphodiesterase PDE5. An approvable action was taken April 29, 2002, on the 10-month goal date. The sponsor included protocols in their meeting packages dated May 16, 22, and 31, 2002, in response to deficiencies in the approvable letter. This meeting is to discuss the acceptability of the protocols and the response to those deficiencies in preparation for the complete response to the action.

Discussion:

Question A1

Is Protocol H6D-EW-LVDN adequate to address clinical deficiency #1 in the April 29, 2002 approvable letter? If not, what needs to be changed so that the study adequately addresses this issue?

Response:

- DRUDP considers this protocol generally acceptable with the following revisions:
 - diabetics are excluded, this is inappropriate for the ED population; diabetics should not be excluded
 - the lower age limit should be no less than 40 years of age
 - this is a safety study with only one primary endpoint, DRUDP will review all the safety data in totality in determining safety
- DCRDP recommends an alternate study design; first the sponsor should characterize the blood pressure response to a test dose of nitrate as a function of the time interval between the dose of tadalafil and the dose of nitrate, then the sponsor should generate data to produce a dose-response curve for nitrate alone; finally, the two separate curves could be used together to "work out" a dose of nitrate appropriate to produce a given effect on blood pressure for any given time from a dose of tadalafil; Dr Stockbridge would be agreeable to cooperating with the sponsor on the design of such a study
- the Office expressed a concern regarding patients experiencing chest pain within six hours after a dose of Cialis; patients will be self administering nitrates during this time-frame yet the sponsor does not propose to evaluate the nitrate/Cialis interaction within six hours of the last Cialis dose
- DRUDP stated that a risk management plan additional to a contraindication for nitrates should be provided; the sponsor may submit a protocol or protocols for DRUDP and DCRDP to review

Question A2

Is Protocol H6D-EW-LVET adequate to address clinical deficiency #2 in the April 29, 2002 Approvable letter? If not, what needs to be changed so that the study can adequately address this issue?

Response:

- the design of the protocol should be modified to make the study blinded for both the subject and investigator
- the study should be placebo controlled for alcohol by including a placebo beverage (immediately prior to consumption, the rim of the orange juice container can be rubbed with small amount of alcohol to make a placebo beverage)
- vital signs measurements should be extended by including 4.5, 5, 6, 7, 8, 10, 12 and 24 hours post-IC351 or placebo dose (similar to study LVDO)
- the IC351/Placebo and alcohol/placebo should be administered under fasting conditions (similar to studies LVDO and LVAE)

- the inclusion criteria for Body Mass Index should be the same as that in the previous two alcohol interaction studies
- the baseline for the measurement of vital signs should be pre-IC351 or placebo administration value (similar to study LVAE)
- the washout period between treatments should be adequate considering the long half-lives of parent and metabolites
- the following should be included in the final study report:
 - mean and individual maximum reduction in supine and standing systolic and diastolic blood pressure and mean and individual maximum compensatory increase in supine and standing heart rate and the time of maximum change (Tmax) in these parameters
 - mean and individual changes in supine and standing vital signs over time from baseline for the three treatment groups
 - incidence of adverse events for the three treatment groups
- it should be noted that the conclusion of the study results will be based on the overall analysis of the study results, not just based on the 95% confidence intervals on maximum drop in blood pressure

Question A3

If analysis of the QTc data from Study LVBG indicates that Cialis does not affect QTc. Does DCRDP agree that an additional study to assess the effect of Cialis on QTc is not needed?

Response:

- it is unknown at this time if an additional protocol is necessary; whether information from LVBG, LVBS and LVBU will be sufficient is dependent on a review of the actual data from those trials
- the sponsor should be aware that the timing of ECGs should capture effects at Cmax

Question A4

If a study is still required, even if data from LVBG (LVBS and LVBU addendum) do not show an effect on QTc, then can Lilly ICOS conduct the additional QTc study post-approval?

Response:

- if it is determined that a QTc study is necessary, the QTc study cannot be done post-approval

Question A5

If an additional study to confirm that Cialis does not affect QTc is needed, please provide additional details regarding required study design

- protocols have not been submitted for review; therefore specific comments cannot be provided; nevertheless, DRUDP understood that the sponsor had previously discussed these issues with DCRDP via teleconference prior to this meeting

Question B1

Analysis of myalgia and back pain from the proposed work up and additional studies will be provided when they are completed as a post-approval commitment. Does FDA concur that the analysis and timing proposed by Lilly ICOS to address this issue is adequate?

Response:

- the analysis algorithm is acceptable
- the results from the algorithm in approximately 50 patients must be included in the complete response, not as a post-approval commitment
- renal blood flow and MRI studies are acceptable and should be completed and results submitted prior to approval

Question B2

Information relevant to the cardiovascular safety of Cialis (as listed as #1 under additional recommendations in approvable letter). Lilly ICOS proposes that all parts of this request be completed by the time of their response to the Approvable letter. Is this proposal by Lilly ICOS to address this issue acceptable?

Response:

- the proposal is acceptable

Question B3

Information to support labeling regarding interactions of 20 mg Cialis with various medications (listed as #2 under additional recommendations in the approvable letter). (a) Are the proposed study designs, including the doses and number of days of dosing, to address the specified interactions acceptable? (b) Please confirm that NDA approval is not contingent upon completion of these interactions studies and it is acceptable to develop mutually agreed-upon label language regarding some of the interactions specified, if the study design results are not available at the time of approval. (c) Does FDA concur that no additional interaction studies with antihypertensives are needed based on the prior 20 mg studies, the post hoc analysis of antihypertensive use in Phase 3 studies, as well as, the final results of Study LVDV, and that appropriate label language can be developed based on these analyses?

Response:

- it is acceptable to conduct ketoconazole and ritonavir studies _____; however, if the 20 mg dose is requested for approval, the warfin and ASA interaction studies (with 20 mg) must be conducted prior to approval
- the study results of LVDV (patients on multiple antihypertensives) may provide valuable information and should preferably be submitted prior to approval
- a post-hoc analysis of adverse events in Phase 3 trials will not be useful

Question B4

Data labeling on quantitative effects of Cialis on color vision and retinal physiology (listed as #3 under additional recommendations in Action letter). Is the proposed study design to address this issue acceptable?

Response:

- the data provided do not support the requested labeling statement ' _____'; appropriate language reflective of drug class effects will be included in labeling if no additional studies are conducted prior to approval
- a positive control study design would be helpful in obtaining additional information regarding effect on vision
- the multiple dose study proposed is deficient; the number of patients is too small, some testing parameters are not sufficiently specified and some testing parameters are missing

Question B5

Safety in diabetics not screened for orthostatic hypotension (listed as #4 under additional recommendations in Action Letter) please provide additional input on this issue

Response:

- the fact that no patients were excluded from study LVBK based on the results of the orthostasis test resolves this issue in large part; however; a retrospective analysis of adverse events in the diabetic subpopulation might be helpful and should still be submitted with the complete response

Question B6

Information to show that results from clinical trials can be applied to the US population (listed as #5 under additional recommendations in the approvable letter)

Response:

- insufficient information was available during the review of the NDA to determine applicability to the US population; the attempt to "match" the trial population to the Massachusetts male aging study population does not adequately address this issue; it may be acceptable to use information from the US trials to meet this deficiency; data from LVCR and LVEF were not submitted to the NDA for review and should be submitted as part of the complete response

Question B7

Is the proposal by Lilly ICOS regarding the requested safety update acceptable?

Response:

- the proposed cut-off date of June may not be acceptable depending on the timing of the response to the approvability issues; the safety update should include information regarding deaths and adverse events using a cut-off of 30 days prior to the response; for discontinuations due to adverse events, a cut-off of 60 days is acceptable (based upon practicality of collecting the information)

Question B8

Does FDA agree that 10 mg and 20 mg are appropriate starting doses; will FDA work with Lilly ICOS to develop mutually agreed upon dosing instructions?

Response:

- this question falls under the category of labeling; labeling discussions are premature
(Addendum to meeting minutes:
 - if all previous long-term safety data is derived from trials using a starting dose of 10 mg, a starting dose of 20 mg may not be supported
 - DRUDP contends that treatment-limiting adverse events may be avoided by starting therapy with lower doses)

Question B9

What is the timeline for responses by DRUDP on protocols provided by Lilly in response to requests from the approvable letter? Will comments be provided prior to receipt of the final piece of the complete response?

Response:

- comments to draft protocols submitted in response to deficiencies, prior to the complete response, will be reviewed within 45 days
- the complete response submission should contain all information intended as a response and should be submitted at the same time

Question B10

Will comments be provided on parts of the label not affected by issues raised in the approvable letter?

Response

- labeling is impacted upon results of proposed protocols; therefore, labeling discussions will be initiated after the resubmission

Question B11

Lilly ICOS request that video and teleconferences be held occasionally to ensure adequate responses to the issues in the approvable letter; will DRUDP provide feedback to Lilly ICOS on submitted information prior to conclusion of DRUDP's review of the finalized complete response

Response:

- scientific opinions are not generally shared until after all data are reviewed and input received from all disciplines and management; opinions are provided once a conclusion has been formulated to avoid contradictory information being communicated; meetings with sponsors during an ongoing review are scheduled as necessary and feasible by the Division

Question C1

Does Study LVAY fulfill your request for a 20 mg interaction study with an alpha-blocker?

Response:

- it is necessary to study the interaction between Cialis and an alpha-blocker used for BPH other than tamsulosin; a study design similar to that of the tamsulosin study is acceptable

Question C2

Response:

- DRUDP prefers to limit discussion of these issues at this time since it is tangential to the main objectives of the meeting and since the May 31, 2002 document was received only recently
- the current claim that a given patient can anticipate being able to have sex 36 hours after taking Cialis is not supported by the data
- the statement ' _____' is ambiguous
- data from the period of responsiveness trials supports some labeling but current labeling misleads patients into believing that they can derive benefit early after dosing and again later after dosing; this concept is not supported by the actual data

Decisions Reached:

- the sponsor may submit proposed protocols for review and comment
- the sponsor may submit a request for a meeting with the Chief of the Project Management staff to further discuss past and future communications during the review of the NDA

Action Items:

- Meeting minutes will be conveyed within 30 days

Minutes Preparer:

Meeting Chair

Meeting Minutes
Cialis
June 3, 2002
Page 8

cc:
Original NDA 21368
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 6.12.02
Concurrence: Houn, Sherrod, Stockbridge, 6.12.02/Batra, 6.24.02/Jarugula, 6.27.02/Hirsch, Shames, 7.3.02
final: Spell-LeSane, 7.3.02

MEETING MINUTES

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/s/

Daniel A. Shames
7/3/02 02:36:07 PM



NDA 21-368

Lilly Research Laboratories
Attention: Catherine A. Melfi, Ph.D.
U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Melfi:

We received your May 10, 2002, correspondence on May 13, 2002, requesting a meeting to discuss action plans to address the issues identified in the approvable letter dated April 29, 2002. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

- Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
- Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
- Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at <http://www.fda.gov/cder/guidance/2125fnl.htm>.

You requested a type A meeting. The meeting is scheduled for:

Date: June 3, 2002
Time: 9:00 a.m. - 10:30 a.m.
Location: Parklawn Building
CDER participants: Drs. Shames, Houn, Stockbridge, Hirsch, Parekh, Jarugula, and Ms. Kober, Spell-LeSane, and Sherrod

Provide the background information for this meeting at least two weeks prior to the meeting. If we do not receive it by May 20, 2002, we may need to reschedule the meeting.

If you have any questions, call me at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Kassandra Sherrod
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Kassandra C. Sherrod
5/22/02 07:53:17 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Clinical Pharmacology & Biopharmaceutics (HFD 870) Tracking/Action Sheet for Formal/Informal Consults
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From: Venkateswar Jarugula, Ph.D., HFD-870	To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission
--	---

DATE: 5/20/02	IND No.:	NDA No. 21-368, IC351	DATE OF DOCUMENT 5/10/02	
NAME OF DRUG Tadalafil		PRIORITY CONSIDERATION	Date of informal/Formal Consult:	

NAME OF THE SPONSOR: Lilly ICOS LLC

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
|---|--|--|
| <input type="checkbox"/> PRE-IND
<input type="checkbox"/> ANIMAL to HUMAN SCALING
<input type="checkbox"/> IN-VITRO METABOLISM
<input checked="" type="checkbox"/> PROTOCOL
<input type="checkbox"/> PHASE II PROTOCOL
<input type="checkbox"/> PHASE III PROTOCOL
<input type="checkbox"/> DOSING REGIMEN CONSULT
<input type="checkbox"/> PK/PD- POPPK ISSUES
<input type="checkbox"/> PHASE IV RELATED | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> IN-VIVO WAIVER REQUEST
<input type="checkbox"/> SUPAC RELATED
<input type="checkbox"/> CMC RELATED
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> SCIENTIFIC INVESTIGATIONS
<input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> ANNUAL REPORTS
<input type="checkbox"/> FAX SUBMISSION
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):
BE proposal |
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REVIEW ACTION

- | | | |
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| <input type="checkbox"/> NAI (No action indicated)
<input type="checkbox"/> E-mail comments to:
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox
<input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | <input type="checkbox"/> Oral communication with
Name: []
<input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input type="checkbox"/> Formal Review/Memo (attached)
<input checked="" type="checkbox"/> See comments below
<input type="checkbox"/> See submission cover letter
<input type="checkbox"/> OTHER (SPECIFY BELOW):
[] |
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REVIEW COMMENT(S)

NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

In response to an approvable letter (dated ...), the sponsor submitted two protocols to address the interaction of Cialis (Tadalafil) with alcohol and nitrates.

Draft Protocol H6-EW-LVET (Interaction with alcohol)

Title: "Randomized, placebo-controlled, three-period, cross-over study to further investigate a potential pharmacodynamic interaction between alcohol and 20 mg IC351 in healthy volunteers".

Primary Objective: To further evaluate changes in blood pressure following administration of 0.7 g/kg alcohol and 20 mg IC351 to healthy volunteers.

Secondary Objective: To further assess the safety and tolerability of 20 mg IC351.

Design: This is a randomized, placebo-controlled (for IC351 only), subject blind (with respect to IC351, open label with respect to alcohol), three-period, cross-over study with the following treatments:

1. IC351 (20 mg) + alcohol (0.7 g/kg)
2. IC351 Placebo+alcohol (0.7 g/kg)
3. IC351 (20 mg)

fty four (54) healthy subjects will complete the study. Doses will be administered morning of Day 1. Alcohol will be administered proximately two hours after the IC 351 or placebo dose. Sponsor stated that the timings were chosen such that the presumed maximum plasma concentrations of IC351 and alcohol will coincide. Subjects will be encouraged to consume alcohol (mixed with orange juice to final volume of 250 ml) within two minutes. Subjects will be resident in the clinical unit for approximately 2 days for each of the three treatment periods separated by at least a 7 day washout period.

Study Measurements:

Vital signs: Blood pressure and heart rate (supine and standing) at screening, admission to each study period (Day-1), at the post study assessment, pre-IC351 or placebo dosing, 1, 1.5 hour post dose, pre-alcohol dose, and then at 2.25, 2.5, 2.75, 3, 3.25, 3.5 and 4 hours post IC351/placebo dose in each study period.

Pharmacokinetic sampling:

IC351: Pre-IC351 or placebo dose, and at 1, 2, 3, and 4 hours post IC351/placebo (5 samples) in each treatment period. No pharmacokinetic analysis will be pursued for IC710 and total IC710 (methylcatechol and its glucuronide) as these will not be assayed. IC351 concentrations will be assayed by LC/MS/MS method.

Alcohol: Blood concentrations of alcohol will be determined at 2 hours post IC351 or placebo dose (just prior to the alcohol dosing) and then at 2.25, 2.5, 2.75, 3, 3.25, 3.5 and 4 hours post IC351/placebo dose in each study period where alcohol is administered. Blood alcohol concentrations will be determined by a validated — method.

Pharmacodynamic Analysis:

The primary endpoint will be the maximal post-baseline drop in systolic blood pressure. The following will be secondary endpoints:

- Maximal post-baseline drop in supine systolic blood pressure
- Maximal post-baseline drop in standing and supine diastolic blood pressure
- Maximal post-baseline compensatory increases in standing and supine heart rate.

The baseline values will be taken as the mean of 1, 1.5 and 2 hour measurements prior to alcohol administration.

The maximal drop in standing and supine systolic and diastolic blood pressure and compensatory increase in hear rate will be analyzed using the following mixed effects model:

$$\begin{aligned} \text{RESPONSE} &= \text{SUBJECT} \\ &+ \text{PERIOD} \\ &+ \text{TREATMENT} \\ &+ \text{RANDOM ORDER} \end{aligned}$$

The terms period and treatment will be fitted as fixed effects and the term subject will be fitted as a random effect. Least squares means will be calculated for each treatment. The following treatment comparisons will be carried out:

- 1). IC351 (20 mg) + alcohol (0.7 g/kg) Vs. IC351 Placebo + alcohol (0.7 g/kg)
- 2). IC351 (20 mg) + alcohol (0.7 g/kg) Vs. IC351 (20 mg)
- 3). IC351 (20 mg) Vs. IC351 Placebo + alcohol (0.7 g/kg)

reatment 1) will be the primary comparison. Non-inferiority will be declared between the two treatments if the upper 95% confidence limit for the difference is above -8 mm Hg.

Comments to Sponsor:

1. The design of the protocol should be modified to make the study blinded for both the subject and investigator. The study should be placebo controlled for alcohol by including a placebo beverage (immediately prior to consumption, the rim of the orange juice container can be rubbed with small amount of alcohol to make a placebo beverage)
2. Vital signs measurements should be extended by including 4.5, 5, 6, 7, 8, 10, 12 and 24 hours post-IC351 or placebo dose (similar to study LVDO).
3. The IC351/Placebo and alcohol/placebo should be administered under fasting conditions (similar to studies LVDO and LVAE).
4. The inclusion criteria for Body Mass Index should be same as that in the previous two alcohol interaction studies.
5. The baseline for the measurement of vital signs should be pre-IC351 or placebo administration value (similar to study LVAE).
6. The washout period between treatments should be adequate considering the long half-lives of parent and metabolites.
7. The following should be included in the final study report:
 - Mean and individual maximum reduction in supine and standing systolic and diastolic blood pressure and mean and individual maximum compensatory increase in supine and standing hear rate and the time of maximum change (Tmax) in these parameters.
 - Mean and individual changes in supine and standing vital signs over time from baseline for the three treatment groups.
 - Incidence of adverse events for the three treatment groups
8. It should be noted that the conclusion of the study results will be based on the overall analysis of the above mentioned results in Comment 7, not just based on the 95% confidence intervals on maximum drop in blood pressure.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: HFD # [870]; TL: [Parekh]; DD: [Malinowski]; PM: [Colangelo]

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/s/

Venkateswar Jarugula
6/10/02 03:21:17 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/15/02 10:23:21 AM
BIOPHARMACEUTICS
I concur

MEETING MINUTES

MEETING DATE: May 20, 2002
TIME: 12:30 – 1:00 pm
LOCATION: Parklawn Building, Rm. 17B-43
APPLICATION: NDA 21-368; Cialis (tadalafil) Tablets
INDICATION: treatment of erectile dysfunction
SPONSOR: Lilly ICOS LLC
TYPE OF MEETING: Discussion of process of application responses
MEETING CHAIR: Daniel Shames, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
MEETING RECORDER: Cassandra Sherrod, R.Ph., Regulatory Project Manager, (DRUDP, HFD-580)

FDA ATTENDEES

Daniel Shames, M.D., Acting Director, DRUDP (HFD-580)
Margaret Kober, R.Ph., Chief Project Management Staff, DRUDP (HFD-580)
Cassandra Sherrod, R.Ph., Regulatory Project Manager, DRUDP (HFD-580)

EXTERNAL CONSTITUENT ATTENDEES

Jen Stotka, M.D.; Executive Director, US Regulatory Affairs; Lilly
Greg Brophy, PH.D.; Director, US Regulatory Affairs; Lilly
Cathy Melfi, Ph.D.; Regulatory Scientist, US Regulatory Affairs; Lilly

BACKGROUND: NDA 21-368 for Cialis is under review in the Division of Reproductive and Urologic Drug Products (DRUDP). The proposed indication is treatment of erectile dysfunction at a dose of 20 mg. Lilly ICOS requested this meeting to discuss the process of review after receiving an approvable letter dated April 29, 2002.

DISCUSSION

Utilization of meeting scheduled for June 3, 2002

- Scientific issues will be discussed
- Review of protocols may not be completed by the meeting date. Therefore results may not be known at that time.
- Questions in meeting briefing package will be discussed.

Labeling Opportunities

Labeling cannot be discussed until the reviews are completed and the safety issues are resolved.

Ways to Enhance Communication

- All communications should be directed to the project manager.
- Try to be straightforward and more forthcoming regarding drug development.
- A “lessons learned” debriefing meeting should be scheduled with Dr. Houn and Dr. Franson present.

Minutes Preparer: Kassandra Sherrod, R.Ph.
Regulatory Project Manager
DRUDP

Chair Concurrence: Daniel Shames, M.D.
Acting Director
DRUDP

NDA 21-368
Meeting Minutes
May 20, 2002
Page 3

cc:

Original NDA 21-368
HFD-580/Div. Files
HFD-580
HFD-580/Spell-LeSane

Drafted by: Sherrod, 5.29.02
Concurrence: Shames, 5.29.02/Kober, 6.7.02
Final by: Sherrod, 6.11.02

MEETING MINUTES

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/s/

Daniel A. Shames
6/11/02 02:39:22 PM

MEMORANDUM

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

DATE: April 29, 2002
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: NDA 21-368 Cialis (tadalafil) tablets, Lilly ICOS LLC

This memo documents my decision to issue an approvable action letter to Lilly ICOS, LLC, for its marketing application of Cialis for treatment of erectile dysfunction (ED). The Division of Reproductive and Urologic Drug Products has recommended a not approvable action. While deficiencies do exist and will require clinical investigations, the drug has demonstrated efficacy for the treatment of erectile dysfunction. The nature of the deficiencies and their severity at this point do not hands down preclude eventual approval of this drug. Most investigations will clarify existing information for adequate labeling of the product. However, as happens at the time with all resubmissions addressing deficiencies, especially safety deficiencies, the new information is re-evaluated with the overall context of risks and benefits and FDA has another opportunity at that time to determine approval status.

Efficacy for 5mg, 10mg titration dosing regimen, and 20mg of Cialis exists in the NDA. I note the discussion that the 20mg dose is not concluded to be more efficacious than the 10mg from statistics and medical team. However, in the subpopulation with worse erectile dysfunction, 20mg is more efficacious. The action letter tells the sponsor that 5mg 10mg, and 20mg are approvable. Additional information beyond what is needed for 5mg and 10mg is conveyed for the 20mg dose. In a discussion with Lilly ICOS on April 26, 2001, the company stated that if approved for all 3 doses, it most likely would manufacture the 5mg and 20mg.

— I believe during the next review cycle, we will be directly discussing with them the need to label a recommendation of starting with 10mg. I plan to convey this concern in the action letter by including a statement that a range of Cialis is needed to allow patients to take the lowest effective dose and thereby minimizing dose-related side-effects.

Safety data is missing from the NDA about nitrate interaction, alcohol interaction, and QT effects. More work up on "myalgias" and "back pain" is needed. The manufacturing site is not acceptable.

Nitrate Interaction

Cialis relaxes smooth muscle and potentiates vasodilation. Mean systolic BP decrease related to 10mg of Cialis is about 2-3 mmHg. Nitrates also cause venous pooling and lower of blood pressure. More information is needed to adequately label nitrate interaction with Cialis the 20mg dose. Because, 1) nitrates are expected to be used in the same population with ED, elderly men with concomitant conditions, 2) the Agency has received many adverse event reports relating to chest pain, MI, and ASCVD after marketing of Viagra, and finally, 3) FDA has received a plea from cardiologists and emergency room physicians' groups about needing guidance on the administration of nitrates t

1. The current Viagra label states that it is unknown when it is safe to administer nitrates. This is unacceptable. We expect anginal adverse events with increased sexual activity in this population at risk for ASCVD. These patients will be given nitrates, in emergency situations, despite labeling.

Labeling should guide safe use. .

— Thus, this issue is being treated equitably as possible. The argument that we should approve Cialis

first and relabel after is not acceptable. Because outlier data is worrisome, having this labeled for Cialis before approval is needed for patient safety and to provide guidance to the medical community on handling anticipated cardiac emergencies.

20mg Cialis dose was not studied in any of the submitted nitrate interaction studies. A synopsis of a study with CAD patients exercised, SL nitro, and 10 mg of Cialis was sent to me by email 4-22-02 and reviewed on 4-24-02. This study was "recently completed and available on request." Outlier analysis showed 30% (n=7) patients experienced a sitting systolic blood pressure of less than 85mmHg after single dose 10mg Cialis and SL nitro compared to 4% placebo patients. Also, in a fax dated 4-22-02 to me and reviewed on 4-25-02, Lilly ICOS presents an outlier analysis of study LVBV parts A and LVCM. LVBV Part A shows Cialis 10mg and 5 mg single dose have statistically significant differences from placebo of numbers of subjects with systolic and diastolic drops in standing BP and systolic BP drop while sitting at Day 1 following nitro 0.4 SL. For clinically significant sBP drop, 26% and 22% of Cialis patients (10mg and 5mg) had this compared to 2% of PL plus nitro. Part B used a single dose of Cialis, Viagra 50mg, gave SL nitro 0.4 and measured pressure on Day 1 and 2. Outline analysis showed decreases in Day 1 standing sBP in 47% of Cialis patients vs. 24% PL plus nitro. Day 2 had decrease from standing sBP of over 30 mmHg in 20% of Cialis patients vs. 12% in PL plus nitro.

These data suggest a nitrate interaction that needs to be studied with the 20mg dose of Cialis and multiple time points measuring BP with nitrate administration should be collected. On April 26, 2002, the company stated that a 20mg/nitrate interaction study out to 72 hours is commencing and getting IRB approval. FDA has not been given the protocol, but the company states it will be submitted to the IND.

Alcohol Interaction

Data about alcohol/Cialis drug interaction is contradictory. More information is needed to clarify if an alcohol interaction exists and the magnitude of the interaction. Because alcohol is frequently linked to sexual activity, this information is needed prior to approval to be described on the label. A contraindication is not practical. Rather, the interaction should be labeled to help guide treating physicians about the effects and the information should be conveyed to patients. If the interaction at 20mg is very concerning, this may be the basis for non-approval, even with a 10mg dose, because of low safety margin. The interaction studies cannot be done post-marketing because absence of this information, if a safety concern were demonstrated, would reflect FDA delinquency in this matter.

Study LVAE with 0.7g/kg alcohol and 10mg of Cialis showed a mean change of standing diastolic BP of -12mmHg, the greatest and most rapid decrease of all the arms studied. This is 2mmHg more than alcohol alone. In the 20mg study, less alcohol was used (0.6g/kg of alcohol) and no alcohol blood measurements were taken. This study did not show interaction. This seems paradoxical. The sponsor believes there is no alcohol interaction. FDA would like confirmatory data with 20mg and 0.7g/kg alcohol taken with blood measurements. If no alcohol interaction exists, we can label this; if it does exist and is acceptable, it should be warned about and described. If surprising data reveal a severe interaction, we will evaluate for non-approval.

QT Effects

More information is needed to be assured there is no QT effect by the drug. Higher dose multiples to provide this assurance will be required prior to approval. Should QT effects be present, and given the other risks of the drug for drug interaction (200mg of ketoconazole increases Cialis exposure 100%), and hypotension risks with alcohol and nitrates, the threshold for the presence and magnitude of QT effects being is low. In other words, if a QT effect is present, this will be an additional safety risk making approval unlikely. That is why this information is needed prior to approval.

On April 26, 2002, Lilly's own consultant for QT, Dr. —, stated that he would like additional data in order to conclude there is no QT affect. We agree with this. Lilly plans to submit a phase 1 study already completed (the protocol was not reviewed by FDA) that has 43 individuals on daily dosing of 100mg. FDA stated that this data may be acceptable to address the question, but since the protocol was never reviewed and it was not designed to specifically be a QT study, there may be shortcomings.

Other Information Needed

The etiology of myalgias and neck pain is unknown. FDA would like some further attempts to clarify what is the pathophysiology of these events. The medical team is concerned if this relates to animal findings of arteritis. Since studies are being done for resubmission, information will be collected to investigate possible etiologies.

Finally, the drug product manufacturer has substantial violations of current good manufacturing practices. Compliance is recommending withholding approval.

Other Information Desired

I've reviewed the other deficiencies as recommended to me by the division.

More cardiac event analyses are desired. These analyses are requested for a few patients. Overall impact on safety is expected to be small.

Some drug interaction studies have been done. We expect a greater exposure level with 400mg of ketoconazole, based on the 100mg study with 10mg of Cialis. It is likely that the lowest effective dose should be recommended. The other interaction information with ritonavir, BPH drugs, hypertensives, warfarin, and ASA are desirable, but the effects for 10mg on warfarin and ASA were negative and it is unlikely to be positive with 20mg. The safety database did allow antihypertensives. Most likely the ketoconazole interaction is greater, not ritonavir.

The ophthalmology consult recommends further studies, but feels labeling can address deficiencies.

The diabetic population needs more descriptive information. We do not know the impact on prescreening for orthostasis.

Finally, the non-representativeness of the US study is noted, but it is unclear if race is a correlate with safety and efficacy of ED drugs. Non-US reporting of safety data does differ by principle investigators. In addition, it is always desirable to have studies where individuals' use of the drug is varies and perception of success varies, done in the U.S.

At this time, the total amount of information missing is sufficiently large and important to not approve the drug even with consideration to phase 4 studies because I do not feel there is enough information for labeling to provide adequate information for safe use. I also note the ongoing, unsatisfactory compliance with quality control manufacturing at Lilly.

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/s/

Florence Houn
4/29/02 03:50:05 PM
MEDICAL OFFICER

Acting Deputy Division Director Memorandum

FROM Dena R. Hixon, MD
Acting Deputy Director, DRUDP

TO Florence Houn, MD
Director, ODE III

THROUGH Daniel Shames, MD
Director, DRUDP

REGARDING Opinion and Rationale for Regulatory Action on
NDA 21-368

Date of submission June 28, 2001
Date of memorandum April 29, 2002

Sponsor Lilly ICOS LLC

Drug name **Cialis™**
Generic Drug Name **tadalafil**

Drug Class phosphodiesterase (PDE)-5 inhibitor

Indication male erectile dysfunction

Dose 20 mg taken before anticipated sexual intercourse, no more than once daily

Formulation oral tablet

Related INDs 54,553

1.0 BACKGROUND

Lilly ICOS is seeking approval of Cialis™ (tadalafil), a phosphodiesterase (PDE)-5 inhibitor for the (oral) treatment of erectile dysfunction (ED) in men. The only other product of this class, and the only other oral treatment, currently approved for ED is Viagra® (sildenafil), which was approved on March 27, 1998. Cialis™ has a longer duration of action than Viagra® with a mean half-life of 17.5 hours (compared to 4 hours for Viagra®). One tablet is to be taken before anticipated sexual intercourse. The maximum dosing frequency is once daily.

2.0 NDA DATA AND ANALYSIS

2.0.1 Clinical Pharmacology

The following findings from the clinical pharmacology review are relevant to the risk:benefit analysis of this product for the treatment of erectile dysfunction.

- Cialis™ is rapidly absorbed after oral administration with a T_{max} of approximately 2 hours.
- Cialis™ is extensively metabolized, mainly by the CYP3A4 hepatic enzyme. Although the parent drug has been shown in *in vitro* studies to be highly selective for the phosphodiesterase (PDE) receptor, the major active metabolite, the methylcatechol glucuronide (MCG), is not selective for PDE5.
- Elimination of MCG depends on renal clearance. Clinical pharmacology studies found the systemic exposures of the parent drug Cialis™ to be 2-fold higher in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment, and concentrations of MCG were 3.5 times higher in patients with moderate renal impairment, compared to those with normal renal function.
- In the elderly, systemic exposure of Cialis™ was also increased by 25% and the half-life was 5 hours longer compared to younger subjects.
- In diabetics, exposure was decreased by 20% and half-life was 3 hours less.
- Daily dosing resulted in steady-state plasma concentrations approximately 1.6 times higher for Cialis™ and almost 3 times higher for MCG compared to single doses.

Treatment with Cialis™ is not highly selective for the type-5 PDE receptor, and may therefore cause adverse events related to effects on other PDE receptors. Also, the maximum serum concentrations and duration of action may be affected by age, renal function, frequency of dosing, and diabetes, which are all factors of importance in the ED population.

2.0.2 EFFICACY

2.0.2.1 Conduct of trials

The sponsor has presented a total of 16 clinical trials, including six multi-center placebo-controlled phase 3 studies to support the efficacy of Cialis™. All of the phase 3 trials were conducted outside of the U.S. They included a total of 1328 men with ED with a range of severity (from mild to severe) and etiological classification (psychogenic, organic, and mixed). Fifty to 100 patients per treatment arm received doses ranging from 2.5 mg to 20 mg of Cialis™ or placebo.

All of the phase 3 trials consisted of a 4-week run-in period followed by active treatment “on demand” over 12 weeks and evaluated three co-primary endpoints, each presented as the mean change from baseline:

- International Index of Erectile Function (IIEF), Erectile Function (EF) Domain score
- Per-patient proportion of “yes” responses on the Sexual Encounter Profile (SEP) question 2, assessing the ability to penetrate the partner’s vagina
- Per-patient proportion of “yes” responses on the SEP question 3, assessing the ability to maintain the erection.

2.0.2.2 Efficacy results

As summarized in the following table, both the 10 and 20 mg doses of Cialis™ provided statistically and clinically significant improvement in ED in all of the primary endpoints tested in these trials. Statistically significant improvement in the IIEF EF Domain was observed at all doses except 2.5 mg. The 20 mg dose provided only a small benefit compared to the 10 mg dose, and this benefit was seen mostly in patients with more severe ED.

EFFICACY OF CIALIS™ IN CLINICAL TRIALS

IIEF/EF Domain					
End (change)					
	Placebo	2.5 mg	5 mg	10 mg	20 mg
LVCE	14.4 (+1.1)	16.6 (+3.2)	17.5(+5.1)	20.6(+6.0)	
LVBN	14.9 (+0.7)		18.2 (+4.0)	19.8 (+5.6)	
LVBK	12.2(+0.1)			19.3 (+6.4)	18.7 (+7.3)
LVCO	18.1 (+2.6)			22.6(+8.1)	25.0 (+8.0)
LVDJ	14.5 (-0.9)			21.2 (+6.6)	23.8 (+8.0)
LVCQ	13.0 (-1.3)				23.7 (+7.7)
SEP 2					
End (change)					
	Placebo	2.5 mg	5 mg	10 mg	20 mg
LVCE	45.9 (+2.4)	55.9(+15.3)	55.9(+17.6)	68.4(+15.1)	
LVBN	48.9 (+5.6)		57.8 (+14.5)	72.3 (+29)	
LVBK	29.9 (-4.1)			56.7(+22.2)	54.4(+22.6)
LVCO	54.5 (+9.5)			76.9 (+34.5)	84.9 (+35.3)
LVDJ	45.3 (-6.4)			72.5 (+21.3)	76.0 (+21.3)
LVCQ	42.4 (-7.2)				81.3 (+26.5)
SEP 3					
End (change)					
	Placebo	2.5 mg	5 mg	10 mg	20 mg
LVCE	27.8 (+3.5)	37.2(+19.7)	41.5(+24.0)	51.1(+25.8)	
LVBN	26.3 (+3.7)		41.6 (+19.0)	54.3(+31.7)	
LVBK	20.0 (+1.9)			48.0 (+28.4)	41.8 (+29.1)
LVCO	42.8 (+14.7)			70.0(+47.9)	78.0 (+49.7)
LVDJ	31.9 (+4.9)			56.7 (+32.8)	61.5 (+29.0)
LVCQ	26.2 (+0.4)				74.1(+40.7)

2.0.3 SAFETY

2.0.3.1 Preclinical concerns

Preclinical studies revealed irreversible seminiferous testicular atrophy and arteritis in multiple species. Subsequent 6 month safety studies designed to assess semen characteristics in humans showed no evidence of gonadal toxicity.

Arteritis was observed in multiple species treated with Cialis™ in preclinical studies at various doses. The exposure in one of those studies was approximately the same as in men taking the 20 mg dose of Cialis™. The clinical significance of these findings remains uncertain.

2.0.3.2 Adverse events

A small number of serious adverse events were reported, including cases of syncope, angina pectoris, myocardial infarction, sudden death, and gastrointestinal bleeding. Although there were confounding factors in most of these cases, some of these events occurred soon after taking Cialis™, and it is plausible that Cialis™ contributed to these events.

Unexplained complaints of myalgia and back pain have been reported by up to 10% of subjects in some studies with “on demand” use of Cialis™, particularly with higher doses, with longer duration of exposure and in patients with renal insufficiency. In clinical pharmacology studies, these complaints coincided with the peak concentrations of the active MCG metabolite. There is not adequate information to explain this finding or to assure that it is not related to any significant pathology. The reports of myalgia and back pain are of particular concern in view of the finding of arteritis in animal studies. Arteritis has not been identified in humans exposed to this drug; however, this possibility has not been comprehensively addressed in the clinical trials.

The most common adverse events reported with any dose of Cialis™ were similar to those known to occur with the use of Viagra® (headache, dyspepsia, flushing, rhinitis, each occurring in up to 11% of patients in the phase 3 studies of Cialis™). All adverse events were reported by a higher proportion of subjects in the 6-month semen concentration studies conducted in the U.S. with daily dosing of the 20 mg dose (up to 20% for dyspepsia and headache and up to 12% for back pain) compared to studies with “on demand” dosing.

In a clinical pharmacology study the incidence of AEs was 83% in patients with moderate renal impairment (creatinine clearance 31 to 50 mL/min) compared to 20% with mild renal impairment (creatinine clearance 51 to 80 mL/min) and 12.5% with normal renal function (creatinine clearance >80 mL/min).

2.0.3.3 Drug Interactions

Nitrates

Interaction with nitrates was studied only with the 10 mg dose of Cialis™ and with subjects who could tolerate a nitrate at baseline. An additional reduction in blood

pressure was seen when Cialis™ was co-administered with nitrates compared to treatment with nitrates alone, similar to the effects seen with Viagra®.

Alcohol

A study of Cialis™ 10 mg co-administered with alcohol 0.7 g/kg showed a decrease of 12 mm Hg at 4 hr in mean standing diastolic blood pressure for the Cialis™ and alcohol combination, which was larger than that seen with Cialis™ alone, alcohol alone, or placebo. One subject had a decrease in supine diastolic blood pressure of 29 mm Hg at 2 hours after dosing, and another had a decrease in standing systolic blood pressure of 33 mm Hg at 6 hours after dosing. A separate study using the 20 mg dose with alcohol 0.6 g/kg did not duplicate these findings.

CYP3A4 inhibitors or inducers

Ketoconazole (200 mg), a selective inhibitor of CYP3A4, increased Cialis™ exposure by 107%, and Rifampin, a CYP3A4 inducer, reduced exposure by 88%. The 400 mg dose of ketoconazole was not studied with Cialis™.

Antihypertensives

An increased incidence of clinically significant decreases in blood pressure was seen when Cialis™ was co-administered with amlodipine, angiotensin AT1 receptor antagonist, metoprolol, and enalapril, compared to placebo administered with the same drugs.

Aspirin/Warfarin

No increase in bleeding time was seen when 10 mg of Cialis™ was co-administered with aspirin, and no increase in prothrombin time was seen when it was co-administered with warfarin.

2.0.3.4 Concern based on experience with Viagra®

Color vision abnormalities are known to occur with the use of Viagra®, caused by the inhibition of PDE type 6 receptors in the retina. Review of the studies of Cialis™ on vision found them to be inadequate to show any difference between Cialis™ and Viagra® in their effect on vision.

2.0.3.5 Deficiencies in safety data:

Cardiovascular safety

- The sponsor has not provided information to determine how soon after Cialis™ dosing it may be safe to administer nitrates when urgently needed. Interaction between Cialis™ and nitrates has not been comprehensively studied, especially with the 20 mg dose of Cialis™. Although use of Cialis™ should be contraindicated for patients on chronic or intermittent nitrate therapy (as with Viagra®) the longer duration of exposure following Cialis™ dosing warrants evaluation to identify an interval beyond dosing after which use of nitrates would be safe. This is especially important for elderly men or men with renal insufficiency for whom Cialis™ exposure may be higher and of longer duration.

- Studies of the effect of Cialis™ on the QT interval were not conducted at high enough doses or with enough patients to completely assess the safety of Cialis™, and the potential for the metabolite methylcatechol glucuronide to prolong QT was not assessed. This is particularly important in view of several cases of syncope and one sudden death in the clinical trials that was attributed to a cardiac arrhythmia.
- Certain clinically significant adverse events were not adequately characterized or analyzed, including syncope, angina pectoris, chest pain, unstable angina, myocardial infarction, heart failure, cerebrovascular accident, and cardiac arrest.
- Patients with more than a mild degree of cardiac failure were excluded from the trials, although it is reasonable to assume that patients with cardiac failure would seek therapy for ED with this regimen.

Back pain and myalgia

- The dose-related incidence of myalgia and back pain has not been adequately characterized or explained. Especially in light of the preclinical finding of arteritis in animal studies, the potential for Cialis™ to induce arteritis has not been adequately assessed in humans.

Dosing considerations

- The safety of chronic administration of Cialis™ as proposed, (especially for the 20 mg dose) has not been adequately studied. The majority of patients in the long-term safety studies started treatment with a 10 mg dose with titration to 20 mg. There is inadequate information to support the safety of a 20 mg starting dose.

Special populations

- Safety of Cialis™ for patients with renal insufficiency has not been adequately addressed. Patients with clinically significant renal insufficiency were excluded from the phase 3 clinical trials, and clinical pharmacology studies showed increased exposure to both Cialis™ and MCG and a significant incidence of AEs in patients with mild or moderate renal insufficiency.
- Safety of Cialis™ has not been adequately studied in diabetics. All but 47 of the 119 diabetic patients who received the 20 mg dose in phase 3 trials were pre-screened to exclude those with orthostatic hypotension at baseline. Exposure was shown to be lower in diabetics, and Study LVBK conducted exclusively in diabetic patients reported an unusually low number of adverse events.
- Less than 1% of the clinical trials population was black, and 2 to 3 % was hispanic, providing inadequate evidence of safety or efficacy for these populations.
- The reporting of adverse events varied significantly between studies in different countries, raising some question about whether these results would be different in a US population.

Drug interactions

- The sponsor has not acknowledged the interaction between Cialis™ and alcohol that was seen in the study results with the 10 mg dose of Cialis™
- The sponsor has not acknowledged that some clinically significant interactions were seen between the 10 mg dose of Cialis™ and anti-hypertensive medications and has not explored the effect of the 20 mg dose or the potential for more severe interactions with multi-drug regimens.

- The assessment of interaction between Cialis™ and alpha adrenergic antagonists was not adequate given that many men who may receive Cialis™ may also receive concomitant treatment for symptoms of benign prostatic hypertrophy (BPH)

Platelet inhibition

- The effect of the 20 mg dose on bleeding time or the potential for interaction with warfarin or aspirin has not been evaluated. In addition, several bleeding-related AEs were reported and considered by investigators to be not drug-related (hematemesis and heme-positive diarrhea).

4.0 CMC DEFICIENCY

This inspection of the drug product manufacturing site has disclosed continued non-compliance with current good manufacturing practices. Based on the district's findings, the firm is unacceptable at this time. The Office of Compliance recommendation is Withhold Approval.

3.0 CONCLUSIONS

Although erectile dysfunction is not life-threatening, it can seriously diminish quality of life for a large number of men. As evident by the overwhelming success of Viagra® sales, the availability of a safe and effective treatment for ED has made an important contribution to the well-being of a significant number of men.

Because there is a higher incidence of ED with aging and with certain chronic diseases (including diabetes and vascular disease), it is not surprising that a significant number of deaths and serious cardiovascular adverse events have been reported postmarketing in Viagra® users, and it is impossible to determine the contribution of Viagra® to many of these events. It is clear that Viagra® is associated with a life-threatening interaction with nitrates and a modest interaction with anti-hypertensive drugs. Therefore, product labeling for Viagra® includes a contraindication for use by patients who use either continuous or intermittent nitrate therapy and warns that the drug should be used with caution in men with advanced heart disease.

Clinical trial results clearly show that Cialis™ is effective for treatment of ED at doses lower than the sponsor's initially proposed dose. The longer duration of action may offer an advantage over Viagra® by allowing earlier dosing prior to anticipated sexual intercourse and therefore more spontaneity. However, this longer duration of action also presents safety concerns that cannot be adequately addressed with product labeling given the above-noted deficiencies in the available information, particularly for middle-aged and elderly men with ED who may have known or unknown confounding factors such as chronic diseases, concomitant medications, and sexual activity after long periods of abstinence.

The risk:benefit ratio for a product intended to treat erectile dysfunction clearly must emphasize safety of the product, and any potential for serious or life-threatening consequences must be carefully considered before approval of the product. This is of particular concern because the individuals who will likely use the drug tend to be older and have more diagnosed or undiagnosed health problems. Furthermore, it is likely that

some individuals may use the drug in higher doses than recommended or with medical conditions that warrant caution or contraindication.

4.0 RECOMMENDATIONS

I agree with the conclusions of the primary and secondary reviewers that this application is not approvable because there is inadequate information available to support the safe use of Cialis™ for the treatment of erectile dysfunction.

The following are needed to resolve this deficiency:

1. Cialis™ should be contraindicated for patients on continuous or intermittent nitrate therapy. Nonetheless, it is expected that men with cardiovascular disease will use Cialis and experience cardiovascular events and be given nitrates in emergency situations. The sponsor must provide information to label the effects of blood pressure with nitroglycerin and Cialis 20mg for a period of time after Cialis™ dosing until no blood pressure interaction is seen.
 - A study is needed on patients treated with daily doses of Cialis (20 mg or higher) at steady state with administration of nitrates at various times following the last dose of Cialis to determine at what point after Cialis dosing there is no apparent interaction
 - This study should include elderly subjects (who may have higher exposure and a longer half-life than younger subjects)
 - The sponsor must provide risk management plans for patient and physician education about nitrate contraindication and nitrate interaction.
 - The final protocol should be submitted so that consultation by the Division of Cardio-Renal Drug Products (DCRDP) can be requested to assess the acceptability of the protocol to fulfill this requirement.
2. Alcohol is expected to be used in social situations where Cialis may be taken. The NDA provided data on alcohol interaction; however, results from the 10mg study appeared to differ from the 20mg Cialis study with respect to clinically significant changes in blood pressure.
 - The sponsor must conduct another study of alcohol interaction with the 20 mg dose of Cialis and alcohol at a dose of 0.7 g/kg. Monitor blood alcohol and Cialis levels during the study.
3. QT prolongation may be a signal for life-threatening cardiac adverse events. Cialis has known drug interactions that can significantly elevate drug exposure. Therefore, it is important to rule out QT effects from Cialis. Although the NDA contains QT studies, this information is insufficient to make such a conclusion. More clinical information is needed to ensure there is no QT effect.
 - These studies must include a sufficient number of patients to provide reliable results on doses of 80 mg or higher of Cialis.
 - A placebo control arm is needed, and an additional positive control arm is optimal.

- The potential for the methylcatechol glucuronide metabolite to prolong the QT interval should be assessed
 - The final protocol should be submitted so that consultation by DCRDP can be requested to assess the acceptability of the protocol to fulfill this requirement.
4. The adverse events coded as “myalgia” and “back pain” are unexplained. Clinical pharmacology review found that these events tend to occur at the time of the peak concentration of the methylcatechol glucuronide metabolite, which is not specific for PDE5 receptors. They also occur more commonly with higher exposures of Cialis, as seen in the elderly.
- The sponsor should analyze reports of back pain for severity, concomitant drug therapy required, hospitalization, discontinuation from study, etc. Patients who develop “myalgia” and “back pain” in on-going and new studies initiated as part of your resubmission (as stated above), especially studies utilizing higher doses of Cialis, must be analyzed in this respect and must undergo further work up to rule out medically significant disease process. An assessment for vasculitis and for any direct effect of Cialis or the methylcatechol glucuronide metabolite on the kidney should be included. Plans for medical work up of these adverse events should be submitted to the Division of Reproductive and Urologic Drug Products for concurrence.
5. A satisfactory resolution to the deficiencies in current good manufacturing practices noted in the Indiana manufacturing site inspection is needed.
6. The cardiovascular safety of Cialis™ should be supported with the following:
- A full characterization and analysis of the medically significant cardiovascular adverse events reported in the NDA (including syncope, angina pectoris, chest pain, unstable angina, myocardial infarction, heart failure, cerebrovascular accident, and cardiac arrest) that addresses any potential relationship to Cialis. This should include an evaluation from time of last dose to time of event and any plausible mechanism for a drug-related effect.
 - Insufficient diary, medicine card or other primary data should be addressed for some patients who experienced serious adverse events including death (including 602-6077, 007-3072, 105-2107, 043-4065, 102-2036,220-3256, 817-8600,408-1084,004-4087, and others).
 - Results from Study LVBZ that investigates the effect of Cialis on coronary blood flow should be submitted.
 - Results from Study LVCP that investigates the effect of Cialis on exercise tolerance in men with stable coronary artery disease should be submitted.
7. Information should be provided to support labeling regarding interactions of 20mg Cialis with: ketoconazole 400mg, ritonavir, and doxazosin or terazoxin (in doses used for symptoms of benign prostatic hypertrophy). Additional information is also needed to support labeling regarding interactions with the 20 mg dose of Cialis with other relevant anti-hypertensive medications, warfarin, and aspirin if the sponsor wishes to market the 20 mg dose.

8. Data are needed for labeling regarding quantitative effects of Cialis on color vision and retinal physiology (as measured by ERG testing). Testing after repeat dosing must be performed.
9. All but 47 of the 119 diabetic patients who received the 20 mg dose in pivotal phase 3 trials were pre-screened to exclude those with orthostatic hypotension at baseline. Information is needed on those diabetics excluded from the trial, and safety should be adequately addressed for diabetic patients .

10. Less than 1% of the clinical trial population (all performed outside US) was of African origin and only 2 to 3 % of Spanish origin. Information is needed to show that results from these trials can be applied to the U.S. population.

5.0 LABELING

Labeling cannot be finalized because there is inadequate information to support marketing approval of the proposed product.

6.0 PHASE IV COMMITMENTS

Agreements on postmarketing commitments are deferred until submission of a complete response to the action letter.

Dena R. Hixon, M.D., FACOG
Acting Deputy Director/DRUDP

Daniel Shames, M.D., FACS
Acting Director/DRUDP

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

/s/

Dena Hixon
4/29/02 04:08:11 PM
MEDICAL OFFICER

Daniel A. Shames
4/29/02 04:12:17 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Drug Products

Date: April 26, 2002
From: Mark S. Hirsch, M.D., Medical Team Leader, HFD-580
To: Dena R. Hixon, M.D., Acting Deputy Division Director, HFD-580
Subject: NDA 21-368, Lilly ICOS LLC
Cialis™ (tadalafil) for treatment of erectile dysfunction

1. Executive summary

The purpose of this memo is to provide the Acting Deputy Division Director with my recommendation regarding regulatory action on this NDA. At this time, I recommend that the Division should **not approve** this NDA. In brief, while I believe that the drug is effective, and while the prolonged systemic exposure compared to sildenafil could offer something of a benefit, I cannot now recommend approval yet because I believe that clinical information is not yet adequate to support the safe use of Cialis tablets.

There are several medically significant issues that have not been adequately explored (e.g. etiology of back pains and myalgias, relationship of drug to infrequent but significant cardiovascular adverse events, potential drug effect on the QT interval, safety in those with renal insufficiency). There are several drug risks that have not been acknowledged by the sponsor (e.g. alcohol interaction at the 10 mg dose, increased exposure in those with renal insufficiency and in the elderly). Finally, the sponsor has not paid sufficient attention to the post-marketing management of risk. (e.g. post-dosing nitrate use in those with chest pain).

In summary, safe use of Cialis in the marketplace cannot be reasonably assured at this time. In my opinion, based upon my own assessment of risks and benefits, we should not approve Cialis for marketing in the U.S. until safe use can be reasonably assured.

Major reasons for recommending not approval at this time:

1. **The application requests approval for a dosage strength that is not the lowest effective dose or dose regimen.** The sponsor requests approval of only one dosage strength (20 mg), despite findings that confirm efficacy of 5 mg and 10 mg dosage strengths individually. In fact, a 5 mg to 10 mg dose-titration regimen, wherein 5 mg was the initial dose for all patients, was effective.
2. **Assessments of chronic safety were not adequate to assess the risks of a starting and fixed dose of 20 mg.** The application requests approval for a single dosage strength of 20 mg despite the designs of the chronic safety studies calling for a lower starting dose (10 mg), and allowing for down-titration to an even lower dosage strength (5 mg). In fact, the majority of