

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-332**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Tadalafil

NDA 22-332

**PATENT INFORMATION**

The following patents cover the above referenced product, claiming the drug substance, the drug product, and/or a method of use. This drug substance is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA), under NDA number 21-368.

<b>Patent Number</b>	<b>Expiration Date</b>
5,859,006	Nov 21, 2017
6,821,975	Nov 19, 2020
7,182,958	Apr 26, 2020

The above patents are all owned or exclusively licensed by Lilly ICOS, which is a wholly-owned subsidiary of Eli Lilly and Company, Indianapolis, Indiana. Attached are FDA Forms 3542a for each of the above listed patents.

## EXCLUSIVITY SUMMARY

NDA # 22-332

SUPPL #

HFD # 110

Trade Name ADCIRCA

Generic Name tadalafil

Applicant Name Eli Lilly and Company

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years requested in submission although sponsor is eligible for 7

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-368

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

H6D-MC-LVGY

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

H6D-MC-LVGY

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # 71,871 YES  ! NO   
! Explain:

Investigation #2 !  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2 !  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Dan Brum, PharmD, RAC  
Title: Regulatory Project Manager  
Date: 4/1/09

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

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Norman Stockbridge  
4/1/2009 02:45:13 PM

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-332 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DCRP PDUFA Goal Date: 5/24/09 Stamp Date: 7/24/08

Proprietary Name: ADCIRCA

Established/Generic Name: tadalafil

Dosage Form: 20 mg tablets

Applicant/Sponsor: Eli Lilly and Company

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) Erectile dysfunction

(2) \_\_\_\_\_

(3) \_\_\_\_\_

(4) \_\_\_\_\_

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Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): one  
(Attach a completed Pediatric Page for each indication in current application.)

Indication: pulmonary arterial hypertension

Q1: Is this application in response to a PREA PMC/PMR? Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMC/PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMC/PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): .....
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. ____ mo.	____ wk. ____ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	____ yr. ____ mo.	____ yr. ____ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

<sup>#</sup> Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): .....

<sup>\*</sup> Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ____ mo.	___ yr. ____ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy):						

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/> Neonate	___ wk. ___ mo.	___ wk. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population	minimum	maximum
<input type="checkbox"/> Neonate	___ wk. ___ mo.	___ wk. ___ mo.
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpms@fda.hhs.gov](mailto:cderpms@fda.hhs.gov)) OR AT 301-796-0700.

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	___ wk. ___ mo.	___ wk. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	___ yr. ___ mo.	___ yr. ___ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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

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Dan Brum

4/13/2009 03:02:31 PM

**DEBARMENT  
CERTIFICATION**

**NDA 22-332**

**ADCIRCA™  
tadalafil**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

**ELI LILLY AND COMPANY**

By:  \_\_\_\_\_

Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs

Date: 23 July 2008

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-332 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: ADCIRCA Established/Proper Name: tadalafil Dosage Form: 20 mg Tablets		Applicant: Eli Lilly and Company Agent for Applicant (if applicable):
RPM: Daniel Brum, PharmD, RAC		Division: Division of Cardiovascular and Renal Products
<p><b>NDA:</b>                      NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated                      Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		5/24/09 5/22/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 6  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span> <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span> <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span> Subpart I <span style="margin-left: 200px;">Subpart H</span> <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span>  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments:	
❖ Application Integrity Policy (AIP) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• If yes, exception for review granted ( <i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i> )	<input type="checkbox"/> Yes
• If yes, OC clearance for approval ( <i>file communication in Administrative/Regulatory Documents section with Administrative Reviews</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: <input checked="" type="checkbox"/>	Orphan Designation; Note: Written Request Issued 11/16/06
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	Included
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**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 5/22/09
---	-------------------------------

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	5/22/09
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	5/22/09
❖ Original applicant-proposed labeling	7/24/09
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Cialis (tadalafil); Revatio (sildenafil); Levitra (vardenafil)
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> None

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/29/08

❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	5/20/09
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	5/21/09
❖ Original applicant-proposed labeling	7/24/08
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Cialis, Revatio, Levitra
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	5/21/09
❖ Labeling reviews (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative/Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	Filing Review 11/14/08
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> <li>• Incoming submissions/communications</li> </ul>	<input checked="" type="checkbox"/> None
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located)</li> <li>• Incoming submission documenting commitment</li> </ul>	<input checked="" type="checkbox"/> None
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	9/30/08: filing letter no issues
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (indicate date; approvals only)</li> <li>• Regulatory Briefing (indicate date)</li> <li>• Pre-NDA/BLA meeting (indicate date)</li> <li>• EOP2 meeting (indicate date)</li> </ul>	<input type="checkbox"/> Not applicable 3/24/09 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> No mtg 1/15/08 <input type="checkbox"/> No mtg 5/26/06

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
Version: 5/29/08

• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo (indicate date for each review)	<input checked="" type="checkbox"/> None
Division Director Summary Review (indicate date for each review)	<input type="checkbox"/> None 5/15/09
Cross-Discipline Team Leader Review (indicate date for each review)	<input type="checkbox"/> None 4/20/09
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	
• Clinical review(s) (indicate date for each review)	3/12/09
• Social scientist review(s) (if OTC drug) (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (indicate location/date if incorporated into another review)	see medical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	see medical review
❖ Clinical reviews from other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ REMS	<input checked="" type="checkbox"/> None
• REMS Document and Supporting Statement (indicate date(s) of submission(s))	
• Review(s) and recommendations (including those by OSE and CSS) (indicate location/date if incorporated into another review)	
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested
• Clinical Studies	12/24/08
• Bioequivalence Studies	n/a
• Clinical Pharmacology Studies	n/a
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/30/09
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/30/09
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 5/29/08

Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/27/09 CP; 3/26/09 pharmacometrics
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 3/19/09 CP; 3/20/09 pharmacometrics
❖ DSI Clinical Pharmacology Inspection Review Summary	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/6/09
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 3/6/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input type="checkbox"/> None 3/10/09
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 3/10/09
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input type="checkbox"/> None Pharmacometrics as described above.
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	3/10/09 (see CMC review)
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: 11/6/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ➤ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (date completed must be within	Date completed: <input type="checkbox"/> Requested

<i>60 days prior to AP)</i>	<input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

### Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

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Dan Brum  
5/22/2009 10:41:57 AM

**MEMORANDUM  
HUMAN SERVICES**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** December 12, 2008

**TO:** Dan Brum, Regulatory Project Manager  
Maryann Gordon, Medical Officer  
Division of Cardio-Renal Drug Products

**FROM:** Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspection

**NDA:** 22-332

**APPLICANT:** Eli Lilly and Company  
Indianapolis, Indiana

**DRUG:** Adcirca (tadalafil) 20 mg

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATION:** Pulmonary Arterial Hypertension (PAH)

**CONSULTATION REQUEST DATE:** February 15, 2009

**DIVISION ACTION GOAL DATE:** May 1, 2009

**PDUFA DATE:** May 24, 2009

## I. BACKGROUND:

Eli Lilly & Co. submits this NDA for the evaluation of Adcirca® in the treatment of patients with pulmonary arterial hypertension. The following protocol is considered pivotal for the proposed indication:

H6D-MC-LVGY: "A randomized, double-blind, placebo-controlled, Phase 3 Study of the Phosphodiesterase Type 5 (PDE5) Inhibitor Tadalafil in the Treatment of Patients with Pulmonary Arterial Hypertension"

Pulmonary arterial hypertension is a chronic and progressive disease of the small pulmonary arteries that is characterized by vascular proliferation and remodeling, resulting in elevation of the pulmonary arterial pressure and pulmonary vascular resistance (PVR). Idiopathic PAH occurs in the absence of known causes. PAH also occurs in association with collagen vascular diseases, human immunodeficiency virus (HIV) infection, as well as other conditions. The pathogenesis is not completely understood, but likely involves abnormalities in interaction between endothelial and smooth muscle cells. These abnormalities may facilitate narrowing of the pulmonary vascular lumen and increase vascular resistance as the result of vasoconstriction, vascular wall remodeling, and thrombosis. Phosphodiesterase type 5 (PDE5) is the main phosphodiesterase in the pulmonary vasculature; inhibiting PDE5 maintains high cGMP levels, which may promote antiproliferative and vasodilating effects of endogenous nitrous oxide.

**Tadalafil** (LY450190) is an orally administered, potent, and selective inhibitor of the phosphodiesterase type 5 (PDE5) enzyme, and is currently approved for the treatment of erectile dysfunction (ED), since November 2003. Tadalafil (Cialis™) is one of several PDE5 inhibitors (along with sildenafil and vardenafil) as a treatment for ED in North America, Europe and elsewhere. In vitro studies show that tadalafil is a more potent inhibitor of the PDE5 enzyme than other phosphodiesterases, and has a longer half-life (17.5 hours), compared to sildenafil and vardenafil (4.0-5.0 hours). The inhibition of PDE5 enhances erectile function by increasing the amount of cyclic guanosine monophosphate (cGMP) concentrations. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells. Pulmonary hypertension is associated with impaired release of nitric oxide, which results in a reduction of intracellular cGMP concentrations. The inhibition of PDE5 maintains high cGMP concentrations, and may potentiate the nitric-oxide mediated pulmonary vasodilator and antiproliferative effects in patients with PAH.

The primary objective in Study LVGY was to evaluate the efficacy and safety of tadalafil 2.5, 10, 20 and 40 mg administered once daily for 16 weeks in the treatment of subjects with PAH. Subjects completing Week 16 study visit were to have an additional study visit 2 weeks after treatment cessation (Week 18 visit). Eligible subjects were 12 years of age or older with PAH that were either idiopathic; related to collagen vascular disease, human immunodeficiency virus (HIV) infection; associated with an atrial septal defect; or associated with a surgical repair of at least 1-year duration of a congenital systemic-to-pulmonary shunt. Subjects younger than 18 years of age in North America and Europe were to provide written assent, in addition to parental or guardian consent, to participate in the study.

Efficacy was evaluated by the following endpoints:

Primary: 6-minute walk (6-MW) distance change from baseline to Week 16;

Secondary: World Health Organization functional class change from baseline to Week 16; time to first occurrence of clinical worsening (defined as any of the following: death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH therapy), Borg dyspnea score, and quality of life, as measured by various questionnaires.

Only one clinical investigator inspection occurred. Dr. Feldman's site was selected for inspection because he had high treatment responders and a larger effect size seen. Dr. Feldman has 10 IND studies in COMIS, with no inspectional history.

**II. RESULTS (by Site):**

Name of CI, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
Jeremy Feldman Arizona Pulmonary Specialists, Ltd 500 W Thomas Rd, Ste 950 Phoenix, AZ 85013	H6D-MC-LVGY 11 Subjects	October 28 – November 5, 2008	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Jeremy Feldman, Arizona Pulmonary Specialists, Ltd  
500 W Thomas Rd, Ste 950  
Phoenix, AZ 85013

**a. What was inspected:** The inspection covered 100% review of Informed Consent Documents, inclusion and exclusion criteria, case report forms (CRFs), source documents (SD), drug accountability records and SAE/AE reporting. The inspection compared source documents and CRFs with the data listings sent with the assignment for all 11 subjects. Records were reviewed for the primary efficacy endpoint (6-minute walk test) and secondary (WHO functional class change) efficacy endpoints.

**b. General observations/commentary:** At the conclusion of the inspection, a one-item FDA-483 was issued for failure to follow the investigational plan [21 CFR 312.60]. Specifically, the investigation found 1) Dr. Feldman enrolled Subject 1501 who was administered Flolan therapy for 6 days approximately 2.5 weeks before the subject

was randomized into the study. The protocol exclusionary criteria states “cannot have any new long-term treatment for pulmonary arterial hypertension added within 4 weeks before administration of study drug” - this was 2.5 weeks prior to study drug administration; 2) Subject 1506 was hospitalized on \_\_\_\_\_ for reported fluid overload. This SAE was not reported to the sponsor until \_\_\_\_\_ (4 days later); 3) Seven subjects (1501, 1502, 1504, 1505, 1507, 1510, 1511) had no physical examination and/or an eye exam as required by the protocol at the Screening Visit and/or Visit 9; 4) Subjects 1507 and 1508 had their screening (Visit 1) and baseline (Visit 2) 6-MWT on the same day, even though the protocol states that the subject must have a 6-MWT obtained within 3 months prior to baseline. Dr. Feldman has not yet responded in writing to the FDA-483, but promised to do so in 30 days.

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- c. **Assessment of data integrity:** In general, Dr. Feldman’s site adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. All but one of the subjects met the eligibility criteria, and even that one subject who was taking Flolan, a contraindicated medication, within 4 weeks of enrollment, had not been taking this medication more than 6 days. The inspection documented other minor protocol adherence deficiencies. However, the primary efficacy endpoints were corroborated with the source records, and found to be accurately reported. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, Dr. Feldman’s site adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. With a few minor exceptions, subjects met inclusionary criteria, received assigned study medication, the protocol was appropriately followed, and recordkeeping and documentation were done well. The efficacy endpoints were validated with source documents. DSI considers the data as acceptable in support of this NDA.

*{See appended electronic signature page}*

Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and  
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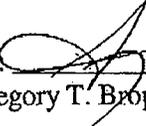
Tejashri Purohit-Sheth  
12/24/2008 10:14:43 AM  
MEDICAL OFFICER

## Field Copy Certification

**NDA 22-332**  
**ADCIRCA™**  
**(tadalafil)**

Pursuant to the provisions of 21 CFR 314.50(l)(3), Eli Lilly and Company, through Gregory T. Brophy, Ph.D., hereby certifies that the field copy of the Chemistry, Manufacturing and Control section for the above referenced new drug application is provided in its entirety in this application and by cross-reference to NDA 21-368 and its subsequent amendments. NDA 21-368 was submitted electronically to the Division of Reproductive and Urologic Products. Pursuant to 21CFR Part 11.2(b)(2), the FDA Office of Regulatory Affairs (ORA) should be able to access this application electronically through the Center of Drug Evaluation and Research's Electronic Document Room. A letter will be submitted to the ORA District Office to inform them of this submission.

ELI LILLY AND COMPANY

By  \_\_\_\_\_  
Gregory T. Brophy, Ph.D.

Title: Director, U. S. Regulatory Affairs

Date: 23 July 2008

Form Approved; OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See Instructions for OMB Statement, below.

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>FOOD AND DRUG ADMINISTRATION</b>		<b>PRESCRIPTION DRUG USER FEE COVERSHEET</b>	
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdufa/default.htm">http://www.fda.gov/cder/pdufa/default.htm</a>			
1. APPLICANT'S NAME AND ADDRESS ELI LILLY AND CO Peggy Basham LILLY CORPORATE CENTER DROP CODE 2546 INDIANAPOLIS IN 46285 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-332	
2. TELEPHONE NUMBER 317-2765185		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:	
3. PRODUCT NAME Adcirca ( Tadalafil )		6. USER FEE I.D. NUMBER PD3008533	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)		<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE	
<input checked="" type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act		<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY	
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			
<b>OMB Statement:</b> Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:			
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448		Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE Gregory T. Brophy, Ph.D.		TITLE Director, USRA	DATE July 22, 2008
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$ .00			
Form FDA 3397 (03/07)			

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## Meeting Minutes

**Date:** January 15, 2008 (amended February 2008)\*  
**Application:** IND 71,871  
**Drug:** tadalafil  
**Sponsor:** Lilly  
**Purpose:** Pre-NDA  
**Meeting Type:** B

### FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, DCRP
Ellis Unger, M.D.	Deputy Division Director
Thomas Marciniak, M.D.	Team Leader, Medical Officer
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Valeria Freidlin, Ph.D.	Statistician
Robert Kumi, Ph.D.	Clinical Pharmacologist
Mary Ross-Southworth, Pharm.D.	Safety Evaluator, OSE
Edward Fromm, R.Ph.	Chief, Project Management Staff
Dan Brum, Pharm.D., MBA	Regulatory Health Project Manager

### Lilly

David Riggs, PharmD	Associate Manager, US Regulatory Affairs
Gregory Brophy, Ph.D.	Director, US Regulatory Affairs
James McGill, MD	Medical Director, Global Brand Development Team
Chris Miskel, MBA	Team Leader, Global Brand Development Team
Anthony Beardsworth, MBBS	Medical Advisor, Global Brand Development Team
Melanie Chan, M.S.	Associate Senior Statistician
Rebecca Wrishko, Ph.D.	Principal Research Scientist, PK/PD
Malcolm Mitchell, MD	Director, Biopharmaceutics
Kristine Harper, MD	Medical Fellow, Global Patient Safety
Barbara Mallet, M.S.	Principal Research Scientist, Regulatory Affairs CMC
Kenneth Conrad	Sr. Clinical Development Associate
Dennis Brinker, PharmD	Team Leader, Global Patient Safety
Keith A Hibbetts	Statistical Analyst
Teresa M Sasher	Clinical Development Associate
Theresa A Bauer	Sr. Clinical Development Associate
Tera Deal	Clinical Development Associate
Elizabeth Bearby, PharmD	Scientific Director, US Regulatory Affairs

**Background:**

Eli Lilly and Company intends to submit a new drug application for the use of tadalafil (proposed tradename Adcirca) for the treatment of pulmonary arterial hypertension (PAH) in June 2008. Tadalafil was granted orphan designation on December 18, 2006. The purpose of this pre-NDA meeting was to discuss the proposed format and content of the anticipated eCTD including issues involving chemistry, nonclinical pharmacology, clinical pharmacology, clinical, as well as the Pediatric Written Request issued November 16, 2006.

\* The sponsor's submission dated February 5, 2008 recommended two updates to the meeting minutes with which the Division agrees are described in bold green font below.

**Meeting:**

The sponsor requested responses to the following questions listed in the meeting briefing package. The questions are repeated below, and the Division's preliminary responses are in bold. Italicized text reflects discussion during the meeting or any additional comments.

2.1.1. Does the FDA agree with the proposal to cross reference the drug substance to the current tadalafil NDA?

**FDA Response: Yes.**

*No further discussion.*

2.1.2. Does the FDA agree that the proposed lot size of — tablets is acceptable for the primary stability lots?

**FDA Response: Yes.**

*No further discussion.*

2.1.3. Given the similarity between Cialis and Adcirca tablets, does FDA agree that 3 months of Adcirca stability data at the time of submission, in addition to 24 months of data for Cialis, could be used to support 24 months dating for Adcirca?

**FDA Response: Your proposal to submit 3 months' accelerated and long-term stability data for Adcirca tablets at the time of submission is acceptable. However, it is expected that the stability studies will be on-going with additional data available during the review period. In addition to 24 months' long term data for Cialis, 6 months' accelerated data should also be provided for comparison. We cannot comment on expiration dating for Adcirca at this time – this will be decided only after review of all available primary and supportive stability data.**

*Further discussion: The sponsor agreed to submit the stability data as described above.*

2.2.1. Does the FDA agree with the proposal to include only the nonclinical overview and the report completed after the review and approval of the dossier for ED?

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**FDA Response: Yes.**

*No further discussion.*

- 2.3.1. Does the FDA agree with the proposal to include only relevant summaries (Module 2) from previously completed clinical pharmacology studies that supported the ED indication?

**FDA Response: Yes.**

*No further discussion.*

- 2.3.2. Does the FDA agree that the 5 additional clinical pharmacology studies (with full study reports and related data), the population PK analysis, and the in vitro P-gp interaction study conducted to directly support the PAH indication are sufficient to support filing and evaluation of this NDA?

**FDA Response: Yes.**

*No further discussion.*

- 2.4.1. Does FDA agree that the results from Study LVGY provide the necessary evidence to support filing and review of this application?

**FDA Response: Yes. We are, however, interested in the information defining the effect during the entire interdosing interval.**

*Further discussion: For clarification, the Agency expects the sponsor to submit data demonstrating durability of treatment effect. The Agency agreed that data collected at week 12 where doses had been withheld for 24 hours prior to study measurements would be representative. A final determination of adequacy would be a review issue.*

- 2.5.1. Does the FDA agree that the exposure numbers are appropriate to support filing of this application?

**FDA Response: Yes.**

*No further discussion.*

- 2.5.2. Does the FDA agree that the proposed list of special safety topics is acceptable?

**FDA Response: Yes.**

*No further discussion.*

- 2.5.3. Does the FDA agree with the above proposal for providing CRFs?

**FDA Response:** In addition, please include complete CRFs for all patients that discontinue study for any reason. Complete CRFs include all forms, including SAE worksheets, fax forms, Medwatch reports, etc. regardless of whether they are labeled a "case report form".

*Further discussion:* The sponsor explained that information from SAE worksheets is already contained within Medwatch forms and that fax forms would not be particularly helpful. In general, the Agency expects to receive all documentation that the sponsor received from clinical sites. Also, patient-related documents should be readily available such that the sponsor can fulfill an Agency request for information within a few days. The sponsor agreed to submit SAE worksheets for the clinical studies. The Agency agreed that fax forms for data queries did not have to be submitted provided that the data were included in the CRFs. The Agency also agreed that the sponsor did not have to submit CRFs for the single-dose pharmacokinetic studies.

- 2.5.4. Does the FDA agree with the proposed data cut-off dates and the proposal for providing patient narratives and CRFs for this submission?

**FDA Response:** The cut-off dates are acceptable. The narratives as presented in your briefing document are rather cumbersome (e.g., listing concomitant medications and tests vertically, duplicative data). Please accompany each narrative with a patient profile view.

*Further discussion:* The Agency urged the sponsor to use a commercial computer software tool to enhance the visual presentation of patient narratives (e.g., single page view including data such as lab values and concomitant medications as a function of time) which are currently described by the sponsor's data management printouts. The sponsor acknowledged that the SAS files contained the same data as the data management printouts. Lilly mentioned that they have submitted other new drug applications using similar formatting. The Agency believes cumbersome printouts are a review issue and would be unlikely to trigger a "Refuse-to-File" decision.

- 2.5.5. Does the Division agree with Lilly's approach for the 120-Day Safety Update?

**FDA Response:** Yes.

*No further discussion.*

- 2.5.6. Does the FDA agree with the proposal to incorporate the PAH Risk Management plan into the existing RMP for tadalafil?

**FDA Response:** The risk evaluation and mitigation strategies (REMS) for this drug should depend on the safety assessment for the drug and the estimated benefit for the proposed indication; concerns about safety may be different for a drug that is used on a daily basis rather than on an as needed basis and thus may require different REMS.

After the safety of tadalafil has been thoroughly evaluated, the risk management plan will be reviewed in light of the FDA assessment of risk. We will not have a position on whether your proposed risk management plan is sufficient until we have a better understanding of the risks of your product.

*No further discussion.*

- 2.6.1. Does the FDA agree that the proposed indication statement is appropriate for inclusion in labeling for Adcirca?

**FDA Response:** We recommend that the labeling include information about the functional class of the subjects studied in the pivotal trial.

*Further discussion:* Patients from all functional classes were included in the sponsor's pivotal study. The Agency noted that approved labeling would reflect those functional classes for which the data support safety and effectiveness.

- 2.6.2. Does the FDA agree that the proposed data package is appropriate to support approval of the 40-mg daily dose?

**FDA Response:** This will be a review issue. We require detailed discussion of the timing of the dose of tadalafil with regards to the primary efficacy endpoint (walk distance). We also require information about the timing of the bosentan dose in regard to the primary efficacy endpoint.

*Further discussion:* The sponsor did not track the timing of bosentan administration, particularly as it relates to administration of the six minute walk test. Given this fact, the Agency voiced concern that understanding the effect of bosentan on walk distance could be problematic, especially in light of the modestly-sized study population.

- 2.6.3. Does the FDA agree that it is appropriate to reflect data from patients taking tadalafil alone and from patients taking concomitant bosentan in the Clinical Studies section of the USPI?

**FDA Response:** This will in part depend on your ability to delineate when plasma levels were measured relative to dosing.

*Further discussion:*

Since data regarding the timing of bosentan administration were not collected, the Division suggested that, in the bosentan-user group, it would be helpful to consider other ways to differentiate improvements in the 6MWD that might be due to bosentan versus improvements that are attributable to tadalafil. The sponsor stated that the presence of bosentan at baseline in the placebo treatment group will fulfill this need.

Additional discussion considered that the placebo response seen in the bosentan-user subgroup could be a result of the 6MWD being conducted at "bosentan trough" at

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baseline and at “bosentan peak” post-baseline. The sponsor plans to address this issue by analyzing the distribution of the timing of the 6MWD evaluation at baseline compared to the distribution of timing of 6MWD evaluation at post-baseline visits. This may help confirm that the magnitude of change is reasonable.

2.6.4. Does the FDA agree with the proposed strategy regarding dose adjustments?

**FDA Response: This will be a review issue.**

*No further discussion.*

2.7.1. Does the FDA agree that the described Statistical Analysis Plans (Section 6.2) for the Clinical Summary of Safety are acceptable?

**FDA Response: Your statistical analysis plan for safety seems reasonable. If there is a safety signal, we will explore it and it may affect approval regardless of whether it is detected by a pre-defined statistical analysis plan.**

*No further discussion.*

2.7.2. Does the FDA agree with the approach described above to the presentation of safety and efficacy data for Study LVGX?

**FDA Response: Yes.**

*No further discussion.*

2.8.1. Does the FDA agree that it is acceptable to submit financial disclosure information for only this study?

**FDA Response: Yes.**

*No further discussion.*

2.8.2. Does the FDA agree that the draft, high-level Table of Contents for this NDA is appropriately structured and indicates appropriate content to support filing of this application?

**FDA Response: The draft Table of Contents is reasonable.**

*No further discussion.*

2.8.3. Does the FDA agree with the proposal to provide SAS transport files and the decision to not provide SDTM format?

**FDA Response: Yes.** The SAS transport files should include all data in the CRFs. If specific items from the CRFs are not included in SAS files, please provide an explanation of why they were not included.

*Further discussion: The sponsor confirmed that all data from the CRFs can also be found in the SAS files.*

- 2.8.4. Does the FDA agree with the proposal to not submit database creation programs and analysis programs in this NDA?

**FDA Response: No.** We recommend you submit efficacy data and CRF information in SAS transport files or provide justification for why it is not possible.

*Further discussion: The Agency expects the sponsor to explain their methods of converting raw data. The sponsor plans to provide a summary document and analysis program for the clinical studies as well as for the population PK/PD studies, and analysis dataset(s), data define documents, and key control streams for the population PK/PD evaluation of Study LVGY.*

- 2.8.5. Does the FDA agree with the proposal not to integrate these 2 databases (Study LVGY and Study LVGX)?

**FDA Response: Yes.**

*No further discussion.*

- 2.8.6. Does the FDA agree with proposed cross-referencing strategy?

**FDA Response: Yes.**

*No further discussion.*

- 2.8.7. Does the FDA have any preliminary comments on the proposed trademark?

**FDA Response: No.**

*No further discussion.*

- 2.8.8. Does the FDA agree that this application qualifies for the User Fee Orphan Drug Exception under Section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act?

**FDA Response: The Office of Orphan Products Development makes these determinations on a case by case basis.**

*Further discussion: Tadalafil was designated an orphan product for the indication of PAH; therefore, a user fee will not be required.*

- 2.9.1. Does the FDA agree that, at this time, there are no apparent issues or deficiencies that would result in a "Refusal to File?"

**FDA Response:** We are unaware of any issues or deficiencies at this time that would result in a "Refusal to File."

*No further discussion.*

- 2.9.2. Does the FDA agree that it is appropriate to amend the current WR once an alternative approach has been determined?

**FDA Response:** Yes.

*No further discussion.*

- 2.9.3. Is the FDA willing to amend the WR prior to the approval of the adult indication?

**FDA Response:** There may be an opportunity to amend the WR after review of the NDA.

*Further discussion: The Agency recommended that the sponsor plan to submit an amendment to the WR near the end of the review cycle assuming the adult program is approvable. The Agency is amenable to discussing a clock extension for the pediatric development program and reminded the sponsor of the more stringent requirements for PREA and BPCA under FDAAA.*

- 2.9.4. Due to the significant challenges associated with conducting meaningful clinical trials in this population, is the FDA willing to grant a separate meeting to discuss the pediatric development program?

**FDA Response:** Yes.

*No further discussion.*

Additional discussion during the meeting:

*The Agency explained that "priority" designation generally reflects an advance over existing treatment or a capacity to address an unmet medical need. Given tadalafil is not a first-in-class treatment for PAH and no head-to-head studies were conducted, the likelihood of being designated "priority" is low. However, the Agency encourages the sponsor to consider ways in which tadalafil might fulfill "priority" criteria (e.g., prolongs substantially time to clinical worsening). A modest effect, only defined post-hoc would not likely be convincing.*

Minutes preparation: *{See appended electronic signature page}*  
Dan Brum, Pharm.D., M.B.A.

Concurrence, Chair: *{See appended electronic signature page}*  
Norman Stockbridge, M.D., Ph.D.

Drafted – 1/15/08

Reviewed:  
Brum 1/15/08  
Srinivasachar 1/16/08  
Kumi 1/16/08  
Freidlin 1/16/08  
Marciniak 1/17/08  
Karkowsky 1/17/08  
Unger 1/18/08  
Fromm 1/18/08  
Stockbridge 1/18/08

Finalized – 1/22/08  
Amended – 2/26/08

Linked Applications

Sponsor Name

Drug Name

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IND 71871

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ELI LILLY CO

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CIALIS (TADALAFIL)

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NORMAN L STOCKBRIDGE

02/26/2008

LY450190  
IND 71,871

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



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**Attention:** Stephanie Turner  
**Company Name:** Lilly ICOS LLC  
**Phone:** 425-415-5360  
**Subject:** Meeting Minutes  
**Date:** 4/28/05  
**Pages including this sheet:** 7  
**From:** Melissa Robb  
**Phone:** 301-594-5313  
**Fax:** 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

MAY 02 2005  
G. Brophy

Minutes of a Meeting  
April 19, 2005

Pre-IND: 71,871  
Drug: Tadalafil  
Sponsor: Lilly ICOS LLC

Date Request Received: March 4, 2005  
Date Confirmation Faxed: March 10, 2005

Type: Pre-IND  
Classification: B

FDA Participants:

Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Clinical, HFD-110
Lydia Gilbert-McClain, M.D.	Team Leader, Clinical, HFD-570
Robert Kumi, Ph.D.	Pharmacokineticist, HFD-860
Charles Le, Ph.D.	Statistician, HFD-710
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Raj Mista, Ph.D.	Chemist, HFD-810
Ed Fromm	Chief, Project Management Staff, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

Lilly ICOS Participants:

Kenneth White, Pharm.D.	V.P., Regulatory Affairs and Clinical Quality Assurance ICOS Corp.
Gregory Brophy, Ph.D.	Director, US Regulatory Affairs Eli Lilly
Gaetano Crupi, B.S.	Product Team Leader Eli Lilly
Kenneth Ferguson, Ph.D.	Divisional V.P., Therapeutic Development ICOS Corp.
David Goodkin, M.D.	V.P., Development and Chief Medical Officer ICOS Corp.
Gregory Sides, M.D.	Medical Director Eli Lilly
Lyn Frumkin, M.D., Ph.D.	Senior Director, Clinical Research ICOS Corp.
Steve Whitaker, M.D.	Senior Director, Clinical Research ICOS Corp.
Paul Flyer, Ph.D.	Senior Director, Biometrics ICOS Corp.
Greg Dietsch, Ph.D.	V.P., Preclinical Studies ICOS Corp.
Stephanie Turner, B.S.	Manager, Regulatory Affairs ICOS Corp.
Catherine Melfi, Ph.D.	Scientific Director, US Regulatory Affairs Eli Lilly
Malcom Mitchell, M.D.	Medical Fellow, Clinical Pharmacology Eli Lilly

MAY 02 2005

G. Brophy

Background:

Tadalafil is a selective and potent inhibitor of the phosphodiesterase type (PDE5) enzyme. Tadalafil is currently marketed in approximately 100 countries under the trade name Cialis for the treatment of Erectile Dysfunction (ED). The Division of Reproductive and Urologic Drug Products (DRUDP) approved NDA 21-368 for this indication. The sponsor is now planning on developing tadalafil for the treatment of pulmonary arterial hypertension (PAH) in patients with World Health Organization Class ~~status to improve exercise ability~~

The sponsor requested this meeting to discuss the clinical development plan for this new indication. In addition, the sponsor would like to cross-reference information from NDA 21-368 and ~~both in DRUDP~~, both in DRUDP, to support their planned IND submission to the Division of Cardio Renal Drug Products (DCRDP) for PAH. The sponsor believes no further nonclinical and manufacturing data will be needed to support this new indication.

Meeting:

Dr. Karkowsky began stating that since the DCRDP did not review NDA 21-368, approved for ED by the DRUDP, the Division would need some clarification on various issues. It was noted that the sponsor is planning on using doses of 2.5 to 40 mg for treatment of PAH. However, tadalafil is currently approved for doses of only 5 to 20 mg for ED. The DCRDP would need further information about the 2.5 and 40 mg doses. The sponsor stated that patients given the 40 mg dose would take two 20 mg tablets and that data on a 2.5 mg tablet was included in the IND application submitted to the DRUDP for ED. The sponsor added that this dose is proportional to currently approved doses. In addition, the sponsor confirmed that of the four possible available diastereomeric isomers, tadalafil is a single enantiomer. Dr. Misra noted that in the Investigator's Brochure submitted for review, there is mention of oral ~~tablets~~. The sponsor stated that these were earlier investigative formulations and neither of these formulations is going to be used in this development program.

Dr. Karkowsky stated that after reviewing the sponsor's briefing document, it appears that the dose limiting effect seen in clinical trials was headache. In addition, it was noted that tadalafil affects the vascular beds. Dr. Karkowsky inquired if the sponsor had data which showed which vascular beds were affected by administration of tadalafil. The sponsor stated that tadalafil is a PDE5 inhibitor and, therefore, affects all vascular beds. However, the sponsor has seen the effect primarily arterially. The sponsor referred to an article in which patients were given 20, 40, and 60 mg doses of tadalafil and subsequently data was collected following a cardiac catheterization. The data revealed changes in mean PAP which leads the sponsor to believe the drug has a systemic effect.

Dr. Karkowsky stated that the sponsor is planning on performing only one study to support the indication of PAH, and has chosen a conservative p-value of ~~for robustness~~. However, Dr. Karkowsky was concerned with the sponsor's dose selection. He noted that the sponsor had provided some rationale for this dose selection. However, the DCRDP did not believe this rationale was very convincing. Dr. Karkowsky suggested the sponsor perform a preliminary study, evaluating higher doses, which could result in a wider dose range in the planned Phase 3 clinical trial. The sponsor stated that they believe it is difficult to assess efficacy in smaller studies and that based on the data from the ED population, 40 mg is a safe dose to proceed into a Phase 3 trial for PAH. In addition, the sponsor has hemodynamic data from the literature which indicates that there is not much of a dose response effect seen at higher doses. They believe the proposed dose range will provide a balance of safety and efficacy. Dr. Karkowsky stated that the DCRDP usually likes to see a wider dose range, somewhere between a factor of 3 to 10 fold increase. This would provide valuable information in labeling about increasing doses in patients who are deteriorating on tadalafil treatment. The sponsor stated that they had considered other doses, but believes that the 40 mg dose is the best choice for a high limit. Dr. Karkowsky stated that this is only a suggestion to help improve the quality of data collected in their trial. Typically, dose ranges are limited because of the size or volume of the drug to be administered, tolerance, or understood receptor interactions. This does not appear to be the case in this program. The sponsor agreed and stated that they are not concerned with safety issues, as they have given doses as high as 500 mg. Dr. Karkowsky reiterated that dose selection is a choice to be made by the sponsor and the Division is only

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providing a suggestion. However, he did not want the sponsor to have not shown efficacy due to the wrong dose selection.

Dr. Karkowsky noted that the sponsor is planning on doing subgroup analysis on only 40 patients in the trial. He inquired if the sponsor was confident that 40 patients would provide sufficient power to show an effect. The sponsor stated that they believe it is and that they used a system that will ensure equal representation of each dose group. The sponsor is predicting that there will be 8 patients from each group participating in this analysis. The sponsor added that those participating will be chosen at the time of enrollment. They noted that they will discuss this issue further internally to ensure that the number chosen will provide adequate and useful data for review. The sponsor inquired how this data was used for review by the Division. Dr. Karkowsky stated that it is helpful to provide context to other data submitted.

Dr. Karkowsky inquired about the timing of procedures in relation to dosing of the drug. The sponsor stated that they are planning on requesting that the centers have patients exercise sometime in the morning. In addition, the sponsor is planning on collecting data on the timing of drug administration and procedure for all patients. Dr. Karkowsky stated that the sponsor should attempt to standardize all testing in order to decrease variability related to diurnal effects of exercise. In addition, he suggested the sponsor perform exercise testing at trough in order to collect data to show that tadalafil has an effect during the entire inerdosing interval.

The next issue discussed was the proposed statistical analysis plan. Dr. Le stated that the imputation plan was acceptable, but the sponsor would need to ensure that a sensitive analysis was used. Dr. Le stated, however, that he did not have a specific method in mind. It is important to ensure that the results were consistent with various analyses. Dr. Karkowsky stated that the Division's concern was that with the population being studied, there is the possibility that patients will dropout due to disease progression. Imputed values may be misleading if patients worsen after withdrawing. The sponsor stated they plan to use a last value carried forward method. In addition, Dr. Karkowsky suggested the sponsor follow all patients that withdraw from the study until completion. This could help explain if there is a disproportionate number of withdraws in the active or placebo groups.

Dr. Karkowsky noted that the sponsor is planning on performing a step-down analysis looking at each treatment group vs. placebo. He inquired how the sponsor is planning on evaluating the secondary endpoints, if the primary endpoint is positive. The sponsor stated that they plan to look at each dose group separately and if the results are positive, look at the secondary endpoints for that dosing group. Dr. Karkowsky stated that with this type of analysis, it appears that the sponsor would be using the same alpha twice, once to look at the next dosing group for the primary endpoint and also to look at the secondary endpoint for the dosing group which revealed a positive result in the primary endpoint. The sponsor requested to discuss this issue at a later time with the statistician. The DCRDP agreed, but requested the sponsor also submit a formal statistical analysis plan for review prior to enrolling all patients.

Dr. Karkowsky requested the sponsor clarify their definition of clinical worsening. The sponsor referred to the submitted protocol which defined worsening as "death, lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of additional PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDES inhibitor), worsening WHO functional class, or other clinical worsening that requires study discontinuation in the judgment of the investigator". Dr. Karkowsky stated this was an acceptable definition.

Dr. Karkowsky noted that one of the secondary endpoints was quality of life measured by change in Short-Form-36v2 Health Survey scores from baseline to Week 16. Dr. Karkowsky stated that this proposal would need to be further evaluated by the Quality of Life working group. However, typically the Agency asks for specific domains not general improvements in health status. Dr. Karkowsky suggested the sponsor submit a request for a Special Protocol Assessment (SPA). The DCRDP would then consult this group to provide further input on this measurement.

Questions:

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1. A protocol for a phase 3 study (LVGY, see Appendix A) will be submitted with the initial IND. Dose DCRDP agree that Protocol LVGY as designed (e.g., study endpoints, patient population) will provide adequate clinical support for approval of tadalafil for the treatment of PAH, if successful?

Dr. Karkowsky stated that the concept of the study is acceptable with the prespecified endpoint of .01. The issues discussed previously (e.g., statistical, dose selection, quality of life measurements) should be considered. In addition, Dr. Karkowsky reiterated that the sponsor should consider submitting a SPA for review by the Division. He stated that this could be done with the IND submission.

2. The secondary endpoints (change in functional class status, Borg dyspnea score, time to clinical worsening, cardiopulmonary hemodynamics, and quality of life) in the proposed phase 3 study (LVGY) provide clinically meaningful information for patients and prescribers. Will the protocol as designed support the inclusion of information regarding secondary endpoints in labeling?

It was noted that further discussion will take place regarding statistical issues.

3. As summarized in this briefing document, tadalafil has been thoroughly tested in clinical pharmacology studies to support the ED indication for which it is marketed, with maximum dosing of 20 mg once per day. Lilly ICOS is interested in meeting with DCRDP Biopharmaceutics reviewers for an EOP2A meeting to discuss the clinical pharmacology package needed to support registration of tadalafil with dosing up to 40 mg daily for the treatment of PAH. Will DCRDP grant such a meeting?

Dr. Kumi stated that the Agency would grant such a meeting, but would be interested in the time-frame of the request. The sponsor stated they planned on requesting this meeting no earlier than fall 2005.

4. Lilly ICOS intends to conduct a study of tadalafil in pediatric patients with PAH once data from the adult and adolescent population in the phase 3 study are obtained. Can DCRDP provide guidance regarding our proposed pharmacodynamic and pharmacokinetic pediatric study as a basis to obtain a Written Request in order to qualify for pediatric exclusivity under Section 505A of the Act?

Dr. Karkowsky stated that in the absence of adult data, one trial would not be sufficient. However, if the sponsor were to show a benefit in the adult population, then one trial with a clinically meaningful endpoint would be acceptable. Age distribution would also need to be considered, as the current proposed trial is planning to enroll patients aged 12-15 years. A pediatric program would need to include the entire age range. In addition, a pediatric program would need to be powered appropriately so as to be able to detect an effect, if one was possible. Dr. Karkowsky stated that a pharmacokinetic trial would not be the basis of a Written Request (WR). The sponsor inquired if the Division would issue a WR prior to the submission of adult data for review. Dr. Karkowsky believed this would be difficult to do as there would be many gaps to such a request in the absence of clinical data from adults. Dr. Karkowsky stated he would discuss this issue further with the Division Director. He added that if the adult program was not positive, any pediatric program would require replicate studies.

5. As described in Section 6 of this briefing document, the nonclinical pharmacology and toxicology database are extensive for tadalafil. Therefore, no further nonclinical pharmacology and toxicology studies are planned before submitting the NDA for PAH. Does DCRDP agree that the current nonclinical database is adequate? If DCRDP feels that additional nonclinical studies are needed, please discuss.

The Division agrees.

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6. Does DCRDP agree with the proposed use of cross-referencing for the IND submission, as proposed in Section 8 of this briefing document? If the proposal is unacceptable, please discuss what will be acceptable to DCRDP.

The Division agrees. It was noted that it would be helpful if the sponsor submitted a copy of the cross-referenced sections with the submission to aid in review. The sponsor agreed to comply with this request.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 4/21/05      Finalized: 4/28/05

RD:

Karkowsky    4/27/05  
Marciniak    4/26/05  
Gilbert-McClain 4/25/05  
Kumi          4/25/05  
Le            4/25/05  
Resnick      4/21/05  
Misra        4/21/05  
Fromm        4/26/05

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/s/  
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Melissa Robb  
4/28/05 09:07:05 AM

Abraham Karkowsky  
4/29/05 03:40:17 PM

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