

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-086

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**

88

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE SENT:** December 24, 1999

**DUE DATE:** N/A

**OPDRA CONSULT #:** 99-080

**TO (Division):** Russell Katz, M.D.  
Director, Division of Neuropharmacological Drug Products  
(HFD-120)

**PRODUCT NAMES:**  
Zyprexa® Zydis® (olanzapine orally  
disintegrating tablets)

**MANUFACTURER:** Eli Lilly and Company

**NDA:** 21-086

**CASE REPORT NUMBER(S):** N/A

**SUMMARY:**

In response to a November 3, 1999 request by the Division of Neuropharmacological Drug Products, OPDRA conducted a review of the potential name confusion of the proposed proprietary name, Zyprexa Zydis, with other approved proprietary/generic names. This review includes a study conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of the proposed proprietary name.

**OPDRA RECOMMENDATION:**

OPDRA does not object to the use of the proprietary name, Zyprexa Zydis. See review.

*/s/* *12000*  
Jerry Phillips  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3246  
Fax: (301) 480-8173

*/s/* *11000*  
Peter Honig, M.D.  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm 15B-03  
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: December 24, 1999  
NDA: 21-086  
NAME OF DRUG: Zyprexa® Zydys® (olanzapine) orally disintegrating tablets  
NDA HOLDER: Eli Lilly and Company

I. INTRODUCTION

This consult is in response to a request sent on November 3, 1999, from the Division of Neuropharmacological Drug Products, to review a proposed proprietary drug name, Zyprexa Zydys, regarding potential name confusion with other proprietary/generic drug names. In addition, container labels and carton labeling were reviewed for possible interventions in minimizing medication errors.

The proposed proprietary name, Zyprexa Zydys, was previously reviewed by the Labeling and Nomenclature Committee (LNC) on November 2, 1999 and was found to be acceptable.

PRODUCT INFORMATION

Zyprexa is an antipsychotic agent that belongs to the thienobenzodiazepine class. It is a selective monoaminergic antagonist with high affinity binding to the following receptors: serotonin 5HT<sub>2A/2C</sub>, dopamine D<sub>1-4</sub>, muscarinic M<sub>1-5</sub>, histamine H<sub>1</sub>, and adrenergic  $\alpha_1$  receptors. Olanzapine binds weakly to GABA<sub>A</sub>, BZD, and  $\beta$  adrenergic receptors. The mechanism of action is unknown, but it has been proposed that the antipsychotic activity is mediated through antagonism of various receptors. Zyprexa is indicated for the management of the manifestations of psychotic disorders. Zyprexa is well absorbed and reaches peak concentrations in approximately six hours. It is eliminated extensively by first pass metabolism. Direct glucuronidation and cytochrome P450 mediated oxidation are the primary metabolic pathways. Half-life of the drug ranges from 21-54 hours. No modification is recommended for patients with impaired renal function. Pharmacokinetic studies showed that Zyprexa tablets and Zyprexa Zydys (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent. Zyprexa Zydys begins disintegrating in the mouth within seconds, allowing contents to be subsequently swallowed with or without liquid. Zyprexa Zydys is available in 5, 10, 15, & 20 mg strengths. The usual dose is 5 to 10 mg initially given once a day with a target dose of 10 mg per day within several days.

## **II. RISK ASSESSMENT**

In order to predict the potential medication errors and to determine the degree of confusion of the proposed proprietary name, Zyprexa Zydis, with other drug names, the medication error staff of OPDRA searched the MICROMEDEX Healthcare Intranet Series (1999), which includes the following: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, and Index Nominum. Other references include American Drug Index (43<sup>rd</sup> Edition), Drug Facts and Comparisons (Monthly Updates), PDR (53<sup>rd</sup> Edition, 1999), Electronic Orange Book, US Patent and Trademark Office online database, Drug Product Reference File (DPRF), Decision Support System (DSS), EES (Established Evaluation System), and the LNC database for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted a study of written and verbal analyses of the proposed proprietary name employing health practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

### **A. Study conducted within FDA**

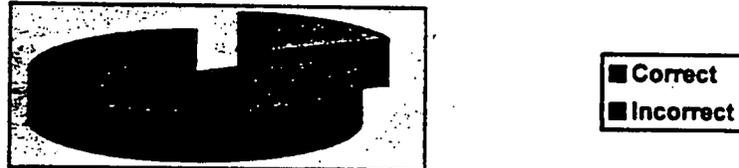
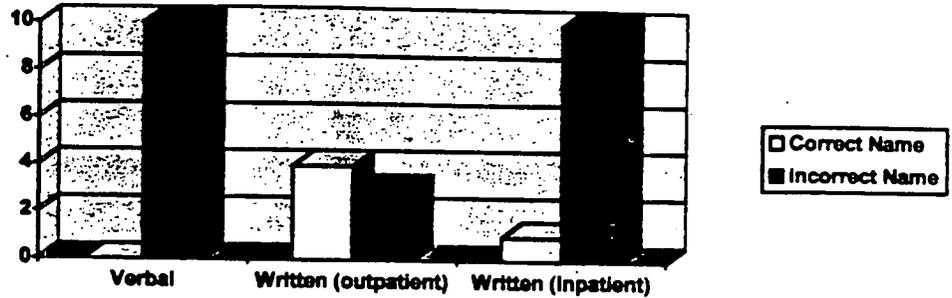
#### **1) Methodology**

This study involved forty-five health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Zyprexa Zydis with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of either inpatient or outpatient written orders were delivered to the participating health professionals via e-mail. In addition, verbal orders via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals.

#### **2) Results**

Inpatient written orders, verbal orders, and outpatient written orders were each sent to fifteen participants. We received responses from twenty-eight participants. Seven interpretations of outpatient written orders, ten interpretations of verbal orders, and eleven interpretations of inpatient written orders were received. Five (out of twenty-eight) participants interpreted Zyprexa Zydis correctly. The results are as follows:

Zyprexa Zydin



Verbal	Written (outpatient)	Written (inpatient)
Viprex vives	Zyprexa Zydir	Olanzapine
Zyprex (Zybase)	Zyprexa	Zyprexa Zadir
Zyprexa (Olanzapine)	Zyrexia Zydir	Zyprexa Zydir
Zebrex (Zivase)		Zyprexa Zydir
Zyprex		Zyprexa Zydir
Viprex		Zyprexa Zydir
Zyprexa		Zyprexa
Zyprex (Zyvase)		Zyprexa Zydir
Zyprex (Zyprexa)		Zyprexa Zydir
Zyprex		Imprexa

**B. Focus Group Findings**

Zydis is a registered trademark of R.P. Scherer Corporation. Therefore, permission to use this name should be acquired. There are many products already on the market with the rapidly disintegrating dosage forms such as Claritin Reditabs, Pepcid RPD, Maxalt-MLT, Zofran ODT, and Naprelan tablets.

**C. Discussion**

- 1) The results of the written and verbal analyses demonstrate that only five (out of twenty-eight) participants interpreted Zyprexa Zydin correctly. Three participants confused Zyprexa Zydin for Zyprexa. Nine participants correctly identified "Zyprexa" but misspelled Zydin. These findings are not surprising since Zyprexa is a familiar name and Zydin is a new dosage form for Zyprexa. However, once

this application is approved and health professionals are more familiar with the drug, the difference between Zyprexa and Zyprexa Zydis, may be clarified upon launch of the product. In addition, searches in available texts, databases, and the handwriting samples did not produce any significant new information.

### III. RECOMMENDATIONS

OPDRA does not object to the use of the proprietary name, Zyprexa Zydis.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301) 827-3243.

**/S/**

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Lauren Lee, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

**/S/**

\_\_\_\_\_  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

CC: NDA# 21-086  
HFD-120; DivFiles; Steven Hardeman, Project Manager,  
HFD-120; Russell Katz, Division Director  
Office Files  
HFD-400; Lauren Lee, Safety Evaluator, OPDRA  
HFD-400; Jerry Phillips, Associate Director, OPDRA  
HFD-400; Peter Honig, Deputy Director, OPDRA  
HFD-2 ; Mac Lumpkin, Acting Director, OPDRA

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1081b HFD# 120 PROPOSED PROPRIETARY NAME: Zypraxi Zydys PROPOSED ESTABLISHED NAME: Clanzapine  
ATTENTION: Steven D. Hardeman

A. Look-alike/Sound-alike

Potential for confusion:

Low  Medium  High   
Low  Medium  High   
Low  Medium  High   
Low  Medium  High   
Low  Medium  High

B. Misleading Aspects:

C. Other Concerns:

"Zydis" is a trademarked technology that is being licensed for use on this drug product. Zydis may be used, however, the holder of the patent should be cited and used by permission.

D. Established Name

Satisfactory  
 Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

ACCEPTABLE  UNACCEPTABLE  
 with concerns

F. Signature of Chair/Date

/S/

Application Establishment Status Milestones Comments Contacts Product

Application: 12-2867-01 Sponsor: [REDACTED]

Drug Name: [REDACTED]

Establishment CFN	Name	Profile Code	Milestone Name	Date	Last Compliance Status	Date	OAI Alert
1049418	APPLIED ANALYTICAL	CTL	DC RECOMMENDATION	26-MAR-1999	AC	26-MAR-1999	
1813682	ELI LILLY AND CO	CTL	DC RECOMMENDATION	26-MAR-1999	AC	26-MAR-1999	
1819478	ELI LILLY AND CO	CTL	DC RECOMMENDATION	26-MAR-1999	AC	26-MAR-1999	
1858438	APPLIED ANALYTICAL	CTL	DC RECOMMENDATION	26-MAR-1999	AC	26-MAR-1999	
9611006	ELI LILLY SA DELAWARE	CRU	DC RECOMMENDATION	30-MAR-1999	AC	30-MAR-1999	

Overall Compliance: [REDACTED]

Date: 17-AUG-1999 Recommendation: ACCEPTABLE

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*Lilly*

Page 4

**Lilly Research Laboratories**  
A Division of Eli Lilly and Company

Lilly Corporate Center  
Indianapolis, Indiana 46285  
(317) 276-2000



March 1, 1999

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room  
12229 Wilkins Avenue  
Rockville, MD 20852

CENTER FOR DRUG EVALUATION  
AND RESEARCH

MAR 02 1999

RECEIVED HFD-120

**Re: NDA 21-086, ZYPREXA® ZYDIS® (olanzapine) - Orally Disintegrating  
Tablets - INITIAL SUBMISSION**

This letter accompanies Eli Lilly and Company's original New Drug Application (NDA) for a new orally disintegrating tablet formulation for Zyprexa (olanzapine). Zyprexa was approved (NDA 20-592) September 30, 1996 for the management of the manifestations of psychotic disorders. This indication will also apply to the new tablet formulation, which has the trademark ZYPREXA ZYDIS.

This application is formatted and organized according to 21 CFR §314.50 and follows the "Guideline for the Format and Content of the Clinical and Statistical Section of New Drug Applications" and the "Guidelines on Formatting, Assembly, and Submitting New Drug and Antibiotic Applications." Cross-referencing to NDA 20-592 supports the enclosed NDA. Item 12 of the application, the Case Report Forms, is submitted as an electronic-only archival copy in accordance with the "Guidance to Industry: Archiving Submissions in Electronic Format - NDAs".

The electronic archival copy of Item 12 is contained on one CDROM. The CDROM is included in the front of the first blue binder (archived copy). All files on the CDROM are in Adobe PDF and can be viewed or printed by use of Adobe Acrobat Reader or Adobe Acrobat Exchange, version 3.0 or later.

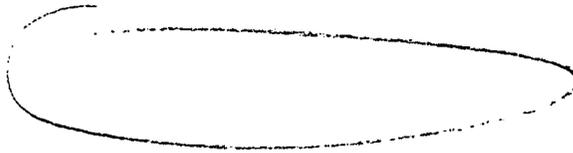
All electronic media have been checked and verified to be free of known viruses. The virus checking software was McAfee VirusScan 3.2.0 using virus definitions 3.0.3201 created on 01/15/99. As a review aid, a complete copy of the NDA is being provided in Adobe PDF format to Mr. Steve Hardeman under separate cover.

To coordinate our activities with yours, we suggest that any written communications concerning this file, regardless of subject be directed to:

Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285

Any calls dealing with general issues, clinical reports, labels, or literature should be made to:

J. Alan Webber, Ph.D.

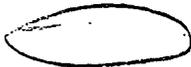


Gregory T. Brophy, Ph.D.



Any questions about the Electronic Submission should be directed to:

Steven T. Ward



Any telephone calls related to chemistry, manufacturing, or control issues should be made to:

Tobias Massa, Ph.D.



Or, in his absence, to:

Ms. Susan Lanham



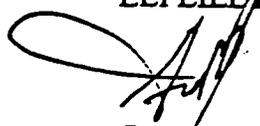
On holidays, Saturdays, or Sundays, call Dr. Webber or Dr. Brophy at home using the telephone numbers indicated.

Close liaison between the Lilly personnel listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Please call Dr. Al Webber at (317) 276-4255 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

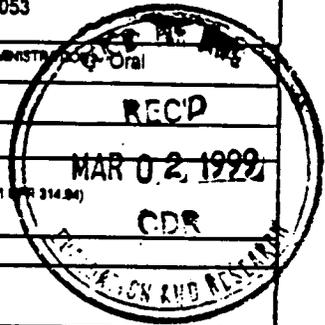
ELI LILLY AND COMPANY

A handwritten signature in black ink, appearing to read 'G. Brophy', is written over the company name.

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

Enc.

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> <b>FOOD AND DRUG ADMINISTRATION</b> <b>APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN</b> <b>ANTIBIOTIC DRUG FOR HUMAN USE</b> <small>(Title 21, Code of Federal Regulations, 314 &amp; 601)</small>		<small>Form Approved OMB No. 0910-0338</small> <small>Expiration Date: April 30, 2000</small> <small>See OMB Statement on last page</small>
		FOR FDA USE ONLY
		APPLICATION NUMBER <b>21-086</b>
<b>APPLICANT INFORMATION</b>		
NAME OF APPLICANT <b>Eli Lilly and Company</b>		DATE OF SUBMISSION <b>March 1, 1999</b>
TELEPHONE NO. (Include Area Code) <b>317-276-2000</b>		FACSIMILE (FAX) Number (Include Area Code) <b>317-276-1652</b>
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): <b>Lilly Corporate Center Indianapolis, IN 46285</b>		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, Country, ZIP Code, telephone and FAX number) IF APPLICABLE: <b>Gregory T. Brophy, Ph.D. Director, U.S. Regulatory Affairs Lilly Corporate Center Indianapolis, IN 46285 (317) 277-3799</b>
<b>PRODUCT DESCRIPTION</b>		
NEW DRUG OR ANTI-BIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) <b>NDA 21-086</b>		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) <b>Olanzapine</b>		PROPRIETARY NAME (trade name) IF ANY <b>Zyprexa®Zydis®</b>
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)		CODE NAME (if any) <b>LY170053</b>
DOSAGE FORM: <b>Orally disintegrating Tablet</b>	STRENGTHS: <b>5, 10, 15, 20 mg</b>	ROUTE OF ADMINISTRATION: <b>Oral</b>
(PROPOSED) INDICATION(S) FOR USE: <b>Psychotic Disorders</b>		
<b>APPLICATION INFORMATION</b>		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.60) <input type="checkbox"/> ABREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.84) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 605 (2) (1) <input type="checkbox"/> 605 (1) (2) <input type="checkbox"/> 607		
IF AN ANDA OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____    Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one) <input checked="" type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
REASON FOR SUBMISSION: <b>Registration of a new oral formulation of Zyprexa® (olanzapine)</b>		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED: <b>27</b>	THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	
<b>ESTABLISHMENT INFORMATION</b>		
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. <b>See Attached Information</b>		
Cross References (list related License Applications, NDAs, NDAs, PMAs, 518(b)s, IDEs, BMFs, and DMFs referenced in the current application) <b>See Attached Information</b>		



This application contains the following items. (Check all that apply)		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling	
<input checked="" type="checkbox"/>	3. Summary (21 CFR 314.50 (e))	
<input checked="" type="checkbox"/>	4. Chemistry section	
<input checked="" type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (e)) (Submit only upon FDA's request)	
<input checked="" type="checkbox"/>	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
<input checked="" type="checkbox"/>	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (M) (b), 21 CFR 601.2)	
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
<input checked="" type="checkbox"/>	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) (ELECTRONIC)	
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 335 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 335 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
<input checked="" type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k) (1))	
<input checked="" type="checkbox"/>	17. Field copy certification (21 CFR 314.5 (N) (3))	
<input checked="" type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input checked="" type="checkbox"/>	19. OTHER Financial Interests and Arrangements of Clinical Investigators (FDA Form 3484, Draft form)	
<b>CERTIFICATION</b>		
<p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:</p> <ol style="list-style-type: none"> <li>1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 620.</li> <li>2. Biological establishment standards in 21 CFR Part 600.</li> <li>3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 609.</li> <li>4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.</li> <li>5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.98, and 601.12.</li> <li>6. Regulations on reports in 21 CFR 314.80, 314.91, 600.80 and 600.81.</li> <li>7. Local, state and Federal environmental impact laws.</li> </ol> <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Gregory T. Brophy, Ph.D. Director, U.S. Regulatory Affairs	3/1/99
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
Lilly Corporate Center Indianapolis, IN 46285		(317) 277-3799
<p>Public reporting burden for this collection of information is estimated to average 40 hours 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:</p> <p>DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W.</p> <p>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</p>		
Please DO NOT RETURN this form to this address.		
FORM FDA 368b (4/87)		

# USER FEE COVER SHEET

See instructions on Reverse Before Completing This Form

<b>1. APPLICANT'S NAME AND ADDRESS</b>  Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285  c/o Gregory T. Brophy, Ph.D. Director U.S. Regulatory Affairs	<b>3. PRODUCT NAME</b> <p style="text-align: center;">Zyprexa®Zydis®</p> <b>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</b>  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
<b>2. TELEPHONE NUMBER (include Area Code)</b>  ( 317 ) 277-3799	

<b>4. USER FEE I.D. NUMBER</b>	<b>6. LICENSE NUMBER / NDA NUMBER</b>  21-086
--------------------------------	---

**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 (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

### FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 361 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

**8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**  YES  NO  
(See reverse side if answered YES)

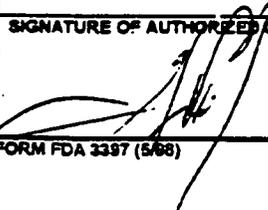
A completed form must be signed and accompany each new drug or biologic product application and each new Supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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:

DHHS, Reports Clearance Officer,  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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<b>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</b> 	<b>TITLE</b> Gregory T. Brophy, Ph.D. Director U.S. Regulatory Affairs	<b>DATE</b> December 7, 1999
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Printed by Steve Hardeman  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 20-Dec-1999 09:23am  
**From:** Peter Cooney  
COONEY  
**Dept:** HFD-160 PKLN 18B08  
**Tel No:** 301-827-7340 FAX 301-443-9281

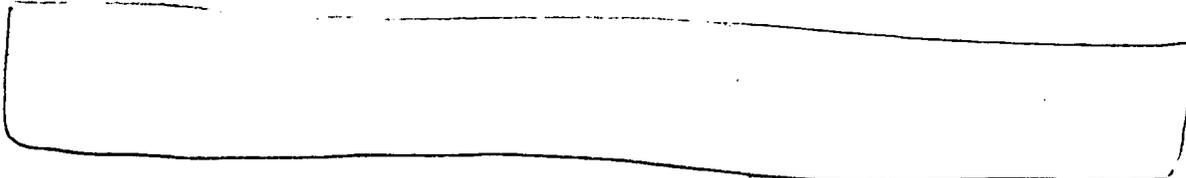
**TO:** Robert Seevers  
**TO:** Steve Hardeman

( SEEVERSR )  
( HARDEMANS )

**CC:** Melissa Maust  
**Subject:** NDA 21086 - Olanzapine Zydis

( MAUSTM )

Bob:



Experiments were carried out to determine the effectiveness of the parabens at total concentrations between 0.06% to 0.08%. Formulations containing 3.33% and 5% w/w olanzapine suspensions, with varying concentrations of parabens, were tested. Results indicate that all concentrations of parabens controlled growth of inoculated *Pseudomonas cepacia*.

The firm should be encouraged to monitor the bioburden of the olanzapine suspensions during the manufacturing process to control for the development of resistant microbial species with time. This could be accomplished on skip-lot basis, not necessarily on every production lot.

We will not provide a written, formal consult for this NDA - consider this it.

Peter