CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-253

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ITEM 13: PATENT INFORMATION

NDA 21-253
ZYPREXA® —
(Olanzapine for Injection)

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of olanzapine, as indicated. This product is the subject of this application for which approval is being sought:

Patent Number	Expiration Date	Claim Type
5,229,382	April 23, 2011	Compound, method of use, formulation
5,736,541	March 24, 2015	Compound, method of use, formulation

U. S. Patent No. 5,229,382 claims olanzapine which is the subject matter of this NDA.

U.S. Patent No. 5,736,541 claims an olanzapine polymorph which is the polymorph contained in the short-acting intramuscular formulation which is the subject matter of this NDA.

The above patents are all owned by Eli Lilly and Company, Indianapolis, Indiana and/or its wholly owned subsidiary Lilly Industries, Limited.

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

6/15/00
Date

ITEM 14: PATENT CERTIFICATION

NDA 21-253
ZYPREXA®
(Olanzapine for Injection)

Eli Lilly and Company (Lilly) claims a three year period of exclusivity for the use of short-acting intramuscular olanzapine in the treatment of agitation, as provided by 21 C.F.R. 314.108(b)(4).

Clinical trials conducted which are essential to approval of this NDA are identified as follows:

F1D-MC-HGHB

F1D-MC-HGHV

F1D-MC-HGHW

As required by 21 C.F.R. 314.50(j)(4), Lilly certifies that to the best of Lilly's knowledge:

1. each of the above clinical investigations included in this application meets the definition of "new clinical investigation" as set forth in 21 C.F.R. 314.108(a);

2. the above clinical investigations are "essential to approval" of this application. Lilly, through its employees and others, electronically searched the Scientific literature as of March 3, 2000 via Medline, Derwent Drug File, SciSearch, Embase, PsycINFO, Biosis and Inside Conferences and has not discovered any published studies or publicly available reports for which Lilly is seeking approval. In Lilly's opinion and to the best of Lilly's knowledge, there are no published studies or publicly available reports to provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the new clinical investigations in this application.

3. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND number 55.342 under which the new clinical investigation(s) that is essential to the approval of this application was conducted.

Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs

6/15/00
Date

0.D

ITEM 13 AND ITEM 14- PATENT INFORMATION AND PATENT CERTIFICATION

EXCLUSIVITY SUMMARY for NDA # 21-253 SUPPL #

Trade Name Zyprexa IntraMuscular Generic Name Olanzapine

Applicant Name Lilly HFD-120
Approval Date 3-29-04

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ * / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / * /

      If yes, what type(SE1, SE2, etc.)?

   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?

Three

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

YES /___/ NO /_*_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_*_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_*_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 20-592

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study # F1D-MC-HGHB
Investigation #2, Study # F1D-MC-HGHV
Investigation #3, Study # F1D-MC-HGHW
Investigation #4, Study # _____

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 thru #4 No

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

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 thru #4: No

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1 thru #4: all essential

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 thru #4: Yes

(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 /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Steve Hardeman
3/29/04 01:40:23 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-253 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: _____ Action Date: 3/29/04

HFD 120 Trade and generic names/dosage form: Zyprexa IntraMuscular (olanzapine) for injection

Applicant: Lilly Therapeutic Class: schizophrenia, mania

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for the treatment of agitation associated with schizophrenia and bipolar I mania.

Is there a full waiver for this indication (check one)? No

- No: Please check all that apply: ____Partial Waiver _____*Deferred ____Completed

  NOTE: More than one may apply

  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____

Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	kg____	mo.____	yr. 13	Tanner Stage____
Max____	kg____	mo.____	yr. 17	Tanner Stage____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: studies ongoing

Date studies are due (mm/dd/yy): 11-30-06

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-253
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-253
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Steve Hardeman
3/29/04 01:59:36 PM

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ITEM 16- DEBARMENT CERTIFICATION

CERTIFICATION

NDA Application No.: **21-253**

Drug Name: **Zyprexa®—**

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.

Title: Director, U.S. Regulatory Affairs

Date: June 15, 2000

9/25/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-253	Efficacy Supplement Type SE-	Supplement Number	
Drug: ZYPREXA IntraMuscular (Olanzapine) for Injection		Applicant: Lilly	
RPM: Steven D. Hardeman, R.Ph.		HFD-120	Phone # 301-594-5525
Application Type: (*) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(*) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	May 3, 2004
❖ Special programs (indicate all that apply)	(*) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(*) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (*) No
• This application is on the AIP	( ) Yes (*) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(*) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(*) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	COMPLETED
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (*) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(*) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE - 3/29/01
• Status of advertising (approvals only)	(*) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (*) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(*) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	FPL already submitted
• Most recent applicant-proposed labeling	n/a
• Original applicant-proposed labeling	In package
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	In package
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	n/a
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	In package
• Reviews	See Original cmc review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	none
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In package
❖ Memoranda and Telecons	In package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	n/a
• Pre-NDA meeting (indicate date)	In package
• Pre-Approval Safety Conference (indicate date; approvals only)	n/a
• Other	n/a

Advisory Committee Meeting	
• Date of Meeting	2-14-01
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	In package
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	In package
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	In package
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	n/a
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	In package
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	In package
❖ Biopharmaceutical review(s) *(indicate date for each review)*	In package
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	In package
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	In package
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	In package
❖ Facilities inspection (provide EER report)	Date completed: 1-14-04 (*) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (*) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	In package
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

MEMORANDUM

DATE: March 29, 2001

FROM: Division Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-253

SUBJECT: Action Memo for NDA 21-253, for the use Zyprexa IntraMuscular (olanzapine) Injection for the control of acute agitation

NDA 21-253, for the use Zyprexa IntraMuscular (olanzapine) Injection for the control of acute agitation, was submitted by Eli Lilly and Company on 6/15/00. The application proposes the use of intramuscular olanzapine in the control of acute agitation. The sponsor conducted 4 randomized, placebo-controlled trials (2 studies evaluated several doses of olanzapine, and all studies included an active control) in patients with schizophrenia (2 studies), bipolar disorder (1 study) [redacted] who were also acutely agitated. The studies examined the effects of a single acute dose of olanzapine; although the studies did permit up to 3 doses (separated by 2-4 hours from the previous dose), most patients received only a single dose of study drug, and the protocol specified primary outcomes in all 4 studies was the effect of the first dose.

The application has been reviewed by Dr. Gregory Dubitsky, medical officer in the division (review dated 3/10/01), Dr. Ohidul Siddiqui, statistician (review dated 3/23/01), Dr. Lois Freed, pharmacologist (review dated 3/22/01), Dr. Sherita McLamore, chemist (reviews dated 11/20/00, 1/18/01, 2/20/01, and 3/28/01), Dr. Hong Zhao, clinical pharmacologist (review dated 3/8/01), Dr. Brian S. Riley, microbiologist (review dated 1/31/01), Dr. Maryann Gordon, cardiology consultant (review dated 12/27/00), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 3/13/01). All reviewers, except the chemistry team and Dr. Gordon, recommend that the application be considered Approvable. The Chemistry team recommends that the application be considered Not Approvable because the Office of Compliance has found that the sponsor's procedures for [redacted] drug manufacturing deviated from Current Good Manufacturing Practices regulations, and has recommended that approval be withheld. The deficiencies uncovered by the inspection of the sponsor's Indianapolis plant were the subject of a Warning letter from the Director of the Detroit District office to the sponsor on 3/2/01. Dr. Gordon has recommended that the application not be approved because of several cases of sinus pause and hypotension; this has been discussed by Drs. Laughren and Dubitsky, and I will comment on this as well.

In this memo, I will describe the support for the division's action on the NDA.

As noted above, the sponsor has submitted the results of 4 studies designed to examine the effects of olanzapine IM in the control of patients with acute agitation in the context of either schizophrenia, bipolar disorder, [redacted] All studies yielded statistically significant differences between olanzapine and placebo on the primary outcome, which in all studies was the Change from Baseline in the Mean PANSS Excited Component at 2 hours after the initial injection.

One of the studies in schizophrenic patients (HGHB) and the study in bipolar patients (HGHW) studied only one dose level of olanzapine, 10 mg. One study in schizophrenic patients (HGHV) studied single doses of 2.5, 5, 7.5, and 10 mg of olanzapine: [redacted] In Study HGHV, all doses were statistically significantly superior to placebo, but the effect sizes for the 2.5 and 5 mg doses were in general smaller than those seen with the 2 highest doses, both for the primary outcome as well as on multiple secondary outcome measures. [redacted]

As with the ziprasidone studies, patients with the most severe degrees of agitation were excluded from these studies.

Regarding the safety profile of IM olanzapine, the only issues of potential concern relate to cardiovascular issues; specifically, sinus pause and orthostatic hypotension.

As both Drs. Dubitsky and Laughren describe, the cases of sinus pause seen in healthy volunteers have been attributed to Neurally Mediated Reflex Bradycardia; as Dr. Laughren notes, these cases were discussed in detail at the 2/14/01 Psychiatric Drugs Advisory Committee meeting, and there was general agreement that this is an event that is well described and self limited.

Regarding orthostatic hypotension, oral olanzapine is known to be associated with this event, presumably related to its alpha$_1$-antagonist effects, and orthostatic hypotension was seen in these studies of the IM formulation.

Of particular concern to me, however, were the results of Study HGJA, which examined the effects of 3, 10 mg doses given 4 hours apart. The sponsor proposes to recommend a maximum dose of 30 mg/day; 10 mg followed by 10 mg 2 hours later, followed by 10 mg given 4 hours after the second dose. The experience in HGJA represents the only well-monitored experience at a regimen approximating the proposed maximum daily dosing regimen (importantly, there were only a few patients in the clinical trials who received 3 doses of 10 mgs, so there is not a robust clinical experience attesting to how well this regimen is tolerated; in addition, those few patients did not have systematic measurement of their blood pressure).

In Study HGJA, almost one-third (32.6%) of the 37 patients who received 3 doses (out of a total enrollment of 43) experienced at least 1 episode of significant orthostatic hypotension (defined by the sponsor as a drop in systolic BP upon standing of at least 30 mm Hg; see Dr. Dubitsky's review, pages 66-7). While Dr. Dubitsky concludes that this study provides evidence of "relatively safe passage" at this regimen, I am not yet convinced that this is so. It seems to me that if significant orthostatic hypotension **actually** occurs in one-third of patients at a given dose regimen, this is a regimen that either should not be recommended, or, if it is, at the very least prescribers should be clearly warned of the relatively high incidence of this event. While the sponsor has made a minimal attempt to address this concern (for example, these patients were stable and not agitated, more of the cases of orthostatic hypotension occurred in patients naïve to anti-psychotic medications), I do not believe that this establishes the safety of this maximum proposed regimen in the indicated population. For this reason, we will ask the sponsor to further support the safety of 10 mg given q2-4 hours.

As I noted earlier, the Chemistry review team has recommended that the application be judged Not Approvable because of the deficiencies in the production of sterile products at the sponsor's Indianapolis plant, and the Office of Compliance's recommendation that approval be withheld. I agree completely that this application may not be approved until this issue has been satisfactorily resolved. Nonetheless, I believe that the clinical data are sufficiently robust to justify an Approvable letter in this case.

For the reasons stated above, then, I will issue the attached Approvable letter, with the appended draft label.

Russell Katz, M.D.

/s/

Russell Katz
3/29/01 08:10:22 AM
MEDICAL OFFICER

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

March 7, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 21-253 - ZYPREXA® IntraMuscular (olanzapine for injection)
Submission of revised draft labeling (packaging)

Please reference the initial June 15, 2000 submission of the subject NDA. Please also reference our October 24, 2000 submission of alternative tradename proposals (ie, to the original tradename proposal of " ——— "), and the December 1, 2000 e-mail response from Mr. Steve Hardeman (FDA) indicating that the alternative proposal of "ZYPREXA® IntraMuscular" was acceptable based upon consultation with the Office of Post-Marketing Drug Risk Assessment (OPDRA).

As outlined in the enclosed Note to Reviewers, we are providing with this submission revised draft packaging labeling incorporating the ZYPREXA IntraMuscular tradename and several additional changes. Please note that revised draft package insert labeling incorporating the updated tradename and several additional text revisions to the package insert was previously submitted to the subject NDA on December 20, 2000.

We thank you for your continued cooperation and assistance, and ask that you please call Dr John Roth at (317) 433-3523 or me at (317) 277-3799 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

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

Enclosures

THIS DOCUMENT CONTAINS TRADE SECRETS,
OR COMMERCIAL OR FINANCIAL INFORMATION,
PRIVILEGED OR CONFIDENTIAL DELIVERED
IN CONFIDENCE AND RELIANCE THAT SUCH
INFORMATION WILL NOT BE MADE AVAILABLE
TO THE PUBLIC WITHOUT EXPRESS WRITTEN'
CONCENT OF ELI LILLY AND COMPANY

Note to Reviewer

Re: NDA 21-253 - ZYPREXA® IntraMuscular (olanzapine for injection)
Submission of revised draft labeling (packaging)

Enclosed is revised draft packaging labeling being submitted to replace the draft packaging labeling previously provided in the initial NDA submission (Item 2.A.1, Volume 1, pages 123-128). The changes made to the enclosed revised draft packaging labels and the rationale for the changes are as follows:

- The "ZYPREXA® IntraMuscular" tradename has been substituted for the previously proposed ——— tradename based on the December 1, 2000 e-mail communication from Mr. Steve Hardeman (FDA) indicating the acceptability of the "ZYPREXA IntraMuscular" tradename.
- The web address "www.lilly.com" has been added according to current Lilly corporate labeling standards.
- The phrase ——— has been deleted from the single vial and multi-vial cartons (ie, "vials alone" product presentation) [———]

[———] The stability of olanzapine has been shown to improve as the temperature decreases. Further, the container-closure integrity of this vial and stopper combination has been demonstrated at -20°C (-4°F). Thus, the sterility of the "vials alone" product presentation would be maintained at -20°C.

- On [ ] the phrase "Sterile Single Use Vials" has been revised to "Sterile Single Use Vial" to be more grammatically correct.

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA#21253
Consultation

MEMORANDUM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of CardioRenal Drug Products
Consultation

Date: 12/27/00

To: Russell Katz, MD
Division Director, HFD-120

From: Maryann Gordon, MD
Medical Reviewer, HFD-110

Through: Norman Stockbridge, MD, PhD
Medical Team Leader, HFD-110

Dr. Raymond Lipicky
Division Director, HFD-110

Subject: Olanzapine, NDA# 21255 (IM formulation)
Review of 4 adverse events of sinus pause

Olanzapine is an approved oral antipsychotic agent that belongs to the thienobenzodiazepine class. It is a selective monoaminergic antagonist with high affinity binding to serotonin, dopamine, muscarinic, histamine, and adrenergic (alpha) $_1$ receptors and weak binding affinity to GABA $_A$, BZD, and (beta) adrenergic receptors. The IM formulation is currently under review.

We have been asked to evaluate episodes of sinus pause[1] (either suspected or identified by telemetry) along with orthostatic hypotension and syncope reported in 4 subjects with no known cardiovascular risk factors.

The current package label for the oral formulation includes statements about orthostatic hypotension and syncope (0.6% of phase II-III subjects) in the precautions section. Also, heart arrest (rare) is mentioned in the adverse events associated with the cardiovascular system. The label also states that the drug produces a slight tachycardia, not what one would expect after reviewing the reports of profound bradycardia submitted with this consult. Is there is an explanation (such as a different metabolism) for this phenomenon?

The 4 cases of hypotension, bradycardia, and sinus pause (actually heart arrest) in normal volunteer subjects are discussed below.

[1] Asymptomatic sinus pauses up to 3 sec in duration are relatively common and without clear-cut adverse prognostic implications. Pauses longer than 3 sec are of concern. Hilgard J, et al., Significance of ventricular pauses of three seconds or more detected on twenty four hour Holter recordings. Am J Cardio 55:1005-1008, 1985

Age/sex	Dose	Times of events
47/m	5 mg IM twice	1 hr after 1st dose subject reported nausea and dizziness with bradycardia. 1 hr after the 2nd dose he reported dizziness with hypotension and tachycardia. Sinus pause detected by telemetry 3.5 hrs after 2nd dose. There was associated hypotension and bradycardia.
26/m	10 mg oral	2 hrs post dose reported nausea. Telemetry showed 5 sec sinus pause. Hypotension and bradycardia reported at 3 hours. 4.5 hrs after dose telemetry showed 5 sec sinus pause followed 4 min later by collapse. Recovered.
55/m	5 mg IM	1 hr after dose experienced loss of consciousness while standing. HR was 39 bpm. 6 hrs later experienced another loss of consciousness while standing with hypotension and bradycardia. Telemetry showed 2 sinus pauses up to 6 sec in length.
37/m	5 mg IM	1 hr after dose subject experienced loss of consciousness, extremity shaking, and apnea. There was decreased blood pressure and heart rate was 33 bpm. CPR was initiated. He recovered immediately but was agitated and had bradycardia. There was evidence of a drop in O2 saturation

Our answers to your questions

1) these episodes of sinus pause are occurring in patients as well as normals. These episodes, actually heart arrest in some cases, are cause for great concern and it would not be surprising to find that they can be fatal;
2) we recommend that the sponsor conduct nonclinical studies evaluating the effect of olanzapine on the sinus node and other electrical pathways in the heart;
3) we recommend that human studies be conducted at substantially lower doses, perhaps lowering the dose until there is no effect on heart rate. We recommend that the IM formulation not be approved until further investigations are done.

In summary, these are quite alarming reports of syncope, hypotension, bradycardia, and, especially, sinus pause (heart arrest) in subjects who were considered to be healthy. One should assume that sinus arrest (heart arrest) is also occurring in patients and that it is likely to be the etiology of at least some of the syncopal events. We would recommend that the drug not be approved until (or unless) the sponsor is able to explain the effect of this agent on the electrical properties of the heart, can identify a safe dose in humans, and are able to predict, an thus exclude, patients who are at particular risk for this event.

In addition, it would be prudent for the sponsor to start treatment in-house, keep subjects in-house for at least 12 hours after dosing, as well as begin at much lower doses.

cc
Orig
HFD110 files
HFD-120/HardemanS/DubitskyG

MEMORANDUM OF MEETING MINUTES

Meeting Date: 1-Aug-2000
Time: 9:00 AM
Location: HFD-120 Conference Room
Application: NDA 21-253; Zyprexa (olanzapine) 10 mg intramuscular injection
Type of Meeting: 45 Day Filing / Planning
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Steve Hardeman, R.Ph.

FDA Attendees

HFD-120: Dr. Katz, Dr. Laughren, Dr. Dubitsky, Dr. Fitzgerald, Dr. Seevers, Dr. McLamore
HFD-860: Dr. Zhao
HFD-710: Dr. Jin, Dr. Koti

Background: Lilly submitted NDA 21-253 on June 15, 2000, for the use of olanzapine intramuscular injection in the rapid control of agitation. User fee date is April 16, 2001.

Meeting Objectives:

The purpose of this meeting is to make a threshold determination whether the application is sufficiently complete to permit a substantive review.

Discussion Points (bullet format):

1. **CHEMISTRY**
   Application contains sufficient information required to permit a review. Microbiology consult is pending.
2. **BIOPHARMACEUTICS**
   Application contains sufficient information required to permit a review. OCPB is expecting submission of two additional studies (HGIO and HGJA) NLT 10/15/00.
3. **CLINICAL/STATISTICAL**
   Application contains sufficient information required to permit a clinical review of safety and a statistical review of efficacy. Application will be taken to Advisory 2/2001 to discuss indication. The Division of Scientific Investigations (clinical section) will, under consult from the Division, identify and conduct an inspection of the appropriate clinical trial(s).
4. **PHARMACOLOGY**
   The application contains sufficient information required to permit a review.

Decisions (agreements) reached:
Application will be filed.

Unresolved issues or issues requiring further discussion:
None.

Action Items:
None.

/S/

Minutes Preparer: _____

/S/

Chair Concurrence: _____
(or designated signatory)

/s/

Thomas Laughren
11/18/00 11:59:30 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-253

INFORMATION REQUEST LETTER

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

Dear Dr. Brophy:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) —

We are reviewing the chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. A [ ] specification for the of the non-sterile bulk drug product should be established and [ ] testing is recommended to be performed on each batch.

2. The validation data for the _____ of the drug product vials was not provided.

3. The minimum number of vials for a drug product _____ is not specified.

4. The number of containers tested to validate container closure integrity for the drug product was not specified.

5. [ ]

6. [_____]. Container closure integrity should be demonstrated on units that have been exposed to the maximum sterilization cycle.

Food and Drug Administration
Rockville MD 20857

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Robert H. Seevers
2/27/01 03:04:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB 14 2001

N01-253

Mohammed A. Bari, M.D.
Synergy Clinical Research Center
450 Fourth Avenue, Suite 409
Chula Vista, California 91910

Dear Dr. Bari:

Between October 23 and 27, 2000, Mr. Armando Chavez, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol F1D-MC-HGHW) of the investigational drug Zyprexa — (olanzapine intramuscular), performed for Eli Lilly and Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Chavez during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me at the address listed below.

Sincerely yours,

Antoine El-Hage

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: ————
Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted: None

cc:
HFA-224
HFD-120 Doc.Rm. NDA#21-253
HFD-120 Review Div.Dir.
HFD-120 MO
HFD-120 PM
HFD-45 Reading File
HFD-47 Chron File
HFD-47 GCP File #10270
HFD-47 GCP Reviewer/Lewin
HFD-47 CSO/Hajarian
HFR-PA250 DIB/Kozick
HFR-PA2565 Bimo Monitor/Koller
HFR-PA2540 Field Investigator/Chavez

r/d: CL: 02-13-01
reviewed:AEH:**(2/14/01)**
f/t:mb:**(2/14/01)**

o:\cl\Bari Feb01 NAI.doc

Reviewer's Note to Rev. Div. M.O.

This routine inspection was conducted in support of pending NDA #21-253 and focused on the conduct of protocol F1D-MC-HGHW.

Eighteen (18) subjects were enrolled, seventeen (17) of whom completed the study. One subject discontinued due to consent withdrawal. Records were reviewed for all subjects. No deviations from federal regulations were noted. A Form FDA 483 was not issued.

Data acceptable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-253

INFORMATION REQUEST LETTER

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

Dear Dr. Brophy:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa I.M. (olanzapine for injection) for injection.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. **The tests that you have listed for the color and clarity specification are not official USP test and are subject to change. Please be mindful that once these tests are incorporated into the USP, we request that you amend your specification to adopt the official USP test. This change can be submitted by way of an annual report.**

If you have any questions, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Robert H. Seevers
1/23/01 09:53:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-253

INFORMATION REQUEST LETTER

Eli Lilly and Company
Attention: Gregory T. Brophy, Ph.D.
Director, US Regulatory Affairs
Lilly Coporate Center
Indianapolis, IN 46285-2643

Dear Dr. Brophy:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) —

We also refer to your submissions dated October 16, 2000.

We are reviewing the chemistry section of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Several places in the manufacturing process section you use the term "or equivalent" to describe the equipment to be used. Please be advised that the approval of your application is based on the information that is specified in this application. Please provide a commitment that states that changes made to the application after approval will be submitted per the requirements in the regulations.

2. On pages 74 and 75 of volume 1.3 you use the term "suitable equipment" to describe equipment that is being used in the manufacturing process. Please be advised that the approval of your application is based on the information provided in this application. Accordingly, the information provided should be as specific as possible. Please provide specific information pertaining to the type of equipment that you intend to use.

3. Your manufacturing process indicates that the ——— is ——— with ——— Accordingly, the ———
   the ———

4. On page 76 of volume 1.3 under ———

   Please clearly define how "when necessary" is determined and be specific in the manufacturing process

5. Your specifications for total related substances, compound —— compound —— and largest individual are NMT ——— and —— respectively. Please update these specifications to NMT ——— and ——, for these purity tests.

6. Your specification for the pH of the — is ———. Although the stability data demonstrates a gradual increase in the pH over time, it is not clear why the lower limit of your specification is set so low. Please revise your specification for the pH based on the stability data that you have provided.

7. Your specifications for the color and clarity of solution are "meets Ph. Eur. Requirements for a colorless solution" and "meets Ph. Eur. Requirements for a clear solution" respectively. These are not acceptable specifications as the European Pharmacopoeia is not an acceptable reference. Please provide either a USP reference or a procedure and acceptance criteria for each of these tests.

8. Please provide a table showing which batches were used in each clinical trial.

9. Please provide the specifications and test results for the for Olanzapine for Injection (i.e. bar code, style, dimension and stock/board).

10. Please indicate which batches of the drug product were used in the bioequivalence study.

If you have any questions, call Steven D. Hardeman, R.Ph., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products, (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Robert H. Seevers
12/6/00 12:54:48 PM

Electronic Mail Message

Date: 12/1/00 1:49:54 PM
From: Steve Hardeman (HARDEMANS)
To: Roth_H_John (Roth_H_John@lilly.com)
Subject: Re: NDA 21-253 - Alternative Tradename Proposals

John:

This is OPDRA's official response to my 11/2/00 consult concerning Lilly's proposal IntraMuscular or Injection for the new formulation of Zyprexa.

"OPDRA has no objection to the modifier "IntraMuscular" to be used with Zyprexa.

Jerry Phillips
Associate Director, OPDRA"

Thanks,
Steve

/s/

Steve Hardeman
2/1/01 11:10:01 AM
CSO
Lilly's initial choice for tradename was ——→ OPDRA opposed th
is selection and Lilly proposed "ZYPREXA IntraMuscular."

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA HFD-400

FROM: Division of Neuropharmacological Drug Products HFD-120 (Steven D. Hardeman, R.Ph.)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/2/00		21-253		10/24/00

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zyprexa (olanzapine)	standard	schizophrenia	1/1/01

NAME OF FIRM: Lilly

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY Tradename assessment
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please comment on the sponsor's proposed tradename for their new IM formulation of Zyprexa (olanzapine) for treatment of agitation. Attached is their original proposed labeling and their alternative tradename proposal. The PDUFA due date is 4/16/01. An advisory committee meeting is tentatively planned for February.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Steven D. Hardeman, R.Ph.	☐ MAIL E-mail ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

COPY

October 24, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

GENERAL CORRESPONDENCE

Re: NDA 21-253, Olanzapine for Injection

This is in response to the Agency's concerns with our proposed tradename of ZYPREXA© for the subject NDA, which were communicated by Mr. Steve Hardeman (FDA) to John Roth (Lilly) during their telephone conversations of September 29 and October 12, 2000. Although ZYPREXA remains our preferred tradename for this product, we are responding to the Agency's concerns by providing alternative tradename proposals as suggested by Mr. Hardeman. Our alternative tradename proposals listed in order of decreasing preference are as follows:

1. ZYPREXA® IntraMuscular (Note: As indicated, our intent would be to use an upper case "I" and "M" in "IntraMuscular")
2.

We appreciate your continued cooperation and assistance and ask that you please call Dr. John Roth at (317) 433-3523 or me at (317) 277-3799 if you require any additional information or if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

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