

021-520_ORIG_APPROVAL_PKG

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-520

Trade Name: SYMBYAX

Generic Name: Fluoxetine Hydrochloride; Olanzapine

Sponsor: Eli Lilly & Company

Approval Date: December 24, 2003

Indications: For the treatment of depressive episodes associated with bipolar disorder.

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APPLICATION NUMBER:

21-520

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-520

APPROVAL LETTER



NDA 21-520

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated November 4, 2002, received November 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBYAX (olanzapine and fluoxetine HCl) Capsules, 6mg/25mg, 6mg/50mg, 12mg/25mg, and 12mg/50mg. This NDA, which has been granted priority review status, provides for the use of the combination product, SYMBYAX, in the treatment of depressive episodes associated with bipolar disorder.

We acknowledge receipt of your submissions dated:

May 14, 2003

June 24, 2003

July 31, 2003

December 2, 2003

December 15, 2003

Your June 24, 2003 submission constituted a Complete Response to our May 5, 2003 action letter.

We have completed our review of this application as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Proposed Trademark SYMBYAX

We note the resubmission of your proposed trademark, SYMBYAX, for this drug product. It has been reviewed by the Office of Drug Safety / Division of Medical Errors and Technical Support, which has no objections to the proposed trademark.

Request for Phase 4 Commitment:

This section of the action letter lists only that Phase 4 commitment which we requested in our initial approvable letter *and* have elected to retain, as per agreement with your staff on December 23, 2003. Those commitments which we have re-evaluated and decided not to retain are discussed in the discipline-specific sections of this letter.

1. Nonclinical Pharmacology and Toxicology: We have reviewed your response to our request for a Phase 4 commitment to conduct a repeat prenatal/postnatal development study in rats. We retain our request that a repeat study be performed, as a Phase 4 commitment, with appropriately selected doses that will allow reliable assessment of postnatal developmental toxicity parameters and their dose-effect relationships and NOAEL (no adverse effect level).

As agreed, we would expect the study report to be submitted to the Division within three years of the signature date on this letter.

CMC

1. Your proposed expiration date for the drug product, 24 months, is acceptable.
2. Methods validation has been completed and is acceptable.
3. We note that the Eli Lilly(b)(4)-----
(b)(4)-----), which was found to be unacceptable by the FDA's Office of Compliance, has been withdrawn from this application. All facilities involved in the manufacture and control of the drug substance and drug product have now been found acceptable by the Office of Compliance.
4. Please note that a satisfactory inspection (and prior Agency approval) will be needed to add the previously withdrawn(b)(4)----- site or any new alternate site (that would perform the corresponding functions) to NDA 21-520. However, the presently listed sites are acceptable.
5. As noted in our previous action letter, your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application has been granted.

Nonclinical Pharmacology and Toxicology

1. We have reviewed your response concerning the need to conduct a repeat prenatal/postnatal development study in rats, addressing the high postnatal mortality seen with the high-dose combination of olanzapine and fluoxetine, and the developmental disturbances (e.g., testicular degeneration) observed postnatally in the reproductive systems of F₁ males at the low-dose combination. As noted above, we are retaining our request for a Phase 4 commitment to conduct this study.
2. We have reviewed your response concerning the need to address the evaluation (b)(4)---
(b)(4)-----as a Phase 4 commitment. We are withdrawing our req-----this

Clinical Pharmacology and Biopharmaceutics

1. We have reviewed your response to our request that you(bodify your dissolution specifications. We agree with your proposed Q value of)(% dissolved at 30 minutes. Therefore, please adopt the following dissolution metho4)-nd specifications for all strengths of olanzapine/fluoxetine hydrochloride capsules:

Apparatus: USP Apparatus 2 (Paddle) at 50 RPM
Medium: 900 mL of 0.1N hydrochloric acid at 37±0.5°C
Specifications: (b % dissolved at 30 minutes.

2. We have reviewed your response to our request for a postmarketing (Phase 4) commitment to conduct a drug interaction study with the highest strength of olanzapine and fluoxetine HCl capsules and a potent CYP1A2 inhibitor. Based on our review, and on the enclosed agreed-upon labeling, we withdraw our request for this commitment.

Division of Scientific Investigations

Our field investigator has now completed the inspection of all sites involved in the biopharmaceutics studies of olanzapine and fluoxetine HCl capsules. The overall inspection was satisfactory.

Clinical / Statistical / Clinical Safety

We have completed our review of your response to our requests, including our request that you justify the absence of a fluoxetine-only treatment arm. Your response is satisfactory.

Labeling (Package Insert and Container Labeling)

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and the Patient Package Insert) and to the immediate container and carton labels as submitted in your Complete Response of June 24, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, please designate this submission “**FPL for Approved NDA 21-520**”. Approval of this submission by FDA is not required before the labeling is used.

Promotional Materials

Please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MedWatch-to-Manufacturer Program

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Approved Agreed-Upon Labeling)
[The electronic signature page will follow the labeling.]

APPEARS THIS WAY
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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
12/24/03 02:50:32 PM

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/s/

Russell Katz
12/24/03 02:50:32 PM

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APPROVABLE LETTER



NDA 21-520

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated November 4, 2002, received November 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBYAX (olanzapine/fluoxetine hydrochloride) Capsules, ~~6mg/25mg~~ 6mg/25mg, 6mg/50mg, 12mg/25mg, and 12mg/50mg. This NDA, which has been granted priority review status, provides for the use of the combination product, SYMBYAX, in the treatment of depressive episodes associated with bipolar disorder.

We also acknowledge receipt of your amendments dated:

November 21, 2002	December 4, 2002	December 9, 2002
December 16, 2002	December 18, 2002 (2)	December 19, 2002
January 27, 2003	February 3, 2003	February 27, 2003
April 2, 2003	April 11, 2003	April 22, 2003

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments and requests.

Proposed Trademark SYMBYAX

We note the submission of your proposed trademark, SYMBYAX, for this drug product via secure e-mail on March 21, 2003. It has been reviewed by the Office of Drug Safety / Division of Medical Errors and Technical Support, which has no objections to the proposed trademark.

It is CDER policy that proposed proprietary names and their associated labels must be evaluated approximately 90 days prior to the anticipated approval of the NDA. Since the Agency is not yet prepared to approve your application, full evaluation of your trademark will be necessary prior to final approval of the NDA. To this end, please assure that a complete set of mock-up container labels and labeling are provided, featuring the proposed trademark, in your complete response to this letter.

Chemistry, Manufacturing and Controls (CMC):

The following issues have been discussed with Lilly representatives (April 14 and 15, 2003):

1. Please revise the list of excipients in the package insert (lines 22 and 23 as initially submitted) to replace the term _____ with 'pregelatinized starch' and the term _____ with 'dimethicone'.
2. Please revise the storage statement in the labeling (package insert and container labeling) to read, "Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]"

We have made specific changes in the revised labeling (package insert) appended to this letter. Please address these changes in your complete response.

CMC: Categorical Exclusion

We have completed our review of the information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

CMC: Other Issues

The Eli Lilly drug product packaging, labeling and testing facility located in Indianapolis, IN (CFN #1819470) was found to be unacceptable by the FDA's Office of Compliance. A satisfactory inspection will be needed for this site or an alternate site (that can perform the corresponding functions) before NDA 21-520 can be approved.

Nonclinical Pharmacology and Toxicology

We have completed our review of the nonclinical information provided in your NDA. We have made specific changes and comments in the revised labeling appended to this letter. Please address these changes and comments in your complete response.

In addition, we have the following comments and requests for Phase 4 commitments:

1. In the prenatal/postnatal development study in rats, the high-dose combination of olanzapine and fluoxetine resulted in high postnatal mortality. As a result, no postnatal functional or behavioral assessment of offspring could be performed in that group. In addition, a few cases of developmental disturbances were observed postnatally in the reproductive systems of F₁ males (e.g., testicular degeneration) at the low-dose combination. Since the low-dose combination did not provide either a no-effect level or a margin of safety, you need to conduct a repeat study as a Phase 4 commitment. Doses of olanzapine and fluoxetine in combination should be selected in order to address both issues.

Clinical Pharmacology and Biopharmaceutics

1. Please adopt the following dissolution method and specifications for all strengths of olanzapine/fluoxetine hydrochloride capsules:

Apparatus:	USP Apparatus 2 (Paddle) at 50 RPM
Media:	900 mL of 0.1N hydrochloric acid at 37±0.5°C
Specifications:	— dissolved at — minutes. (note change)

2. We request the following postmarketing (Phase 4) commitment:
Since olanzapine is metabolized by CYP1A2 and CYP2D6 (to a lesser extent), the potential for interaction with CYP1A2 inhibitors dosed concurrently with olanzapine/fluoxetine hydrochloride capsules may be of concern. Therefore, we request that you conduct a drug interaction study with the highest strength of olanzapine/fluoxetine hydrochloride capsules and a potent CYP1A2 inhibitor.

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Division of Scientific Investigations

Our field investigator has not yet completed inspection of all sites involved in the biopharmaceutics studies of olanzapine/fluoxetine capsules. Final approval of NDA 21-520 is subject to the satisfactory resolution of DSI's clinical and analytical inspectional findings.

Clinical / Statistical / Clinical Safety

We have completed our review of the clinical, statistical, and clinical safety information provided in your NDA. Our comments concerning the clinical review are incorporated into the revised labeling appended to this letter, as bracketed comments, text insertions [underlined], or deletions [~~strikethrough~~]. Please address these changes specifically in your complete response.

In addition, in order for us to definitively conclude that your studies are adequately designed to document the contribution of olanzapine to the OFC product, you must justify the absence of a fluoxetine-only treatment arm. Toward this end, we request that you submit a comprehensive discussion, including a discussion of any data available, documenting that treatment with fluoxetine does indeed increase the risk of serious manic episodes in this population.

In addition, we have the following comments and requests for clinical safety information:

1. The safety update indicates that there had only been one additional death since the submission of the ISS; however, review of selected serious adverse events identified a second patient who died during the safety update reporting period (HGIE-617-6552). Please explain the discrepancy. Also, please review the serious adverse events for any additional deaths and provide us with your findings.
2. With regard to treatment-emergent mania, there did not appear to be a difference in incidence across the treatment groups in HGGY-1 and -2. However, no information was provided on the time to event for the emergence of mania. Please provide an analysis that compares the time to emergence of mania across the three treatment groups.

3. Please provide table ISS.10.47 broken out by individual study (i.e., one table for HGGY-1 and one table for HGGY-2).
4. Please provide Table HGGYc.12.8 broken out by individual study (i.e., one table for HGGY-1 and one table for HGGY-2).
5. Please recalculate the regression-based correction factor based on the baseline ECGs collected in the olanzapine/fluoxetine hydrochloride development program. Depending on the factor that is calculated, we may request that you recorrect the QT values included in the analyses in the NDA submission.
6. Please explain the inconsistency in number of patients in each treatment group as displayed in Table 11 of the 12/16/02 response for the "Orthostatic Sys BP Decr" and the "Orthostatic Sys BP Low". For these events, the "N" for each treatment group is substantially different (lower) than the "N" for the other PCS vital sign and weight changes. Please provide a corrected table.
7. Please provide the following information in regard to the occurrence of hypotension and bradycardia in the bipolar depression trials:
 - Please provide a narrative for any patient who had a fall in heart rate from baseline associated with a decrease in orthostatic systolic blood pressure of >20 mmHg; what adverse events were associated with these changes in vital signs? What was each patient's outcome?
 - For patients who reported adverse events related to orthostatic hypotension (including, but not limited to, postural hypotension, syncope, hypotension), please provide the details of the associated vital sign changes and each patient's outcome.
 - For patients who reported adverse events related to bradycardia, please describe the associated changes in blood pressure, any associated adverse events, and each patient's outcome.

In the controlled pooled OFC population, compare the subset of patients who were antipsychotic naïve to those who had been previously exposed to antipsychotics and provide the following analyses:

- Calculate mean change in orthostatic systolic and diastolic blood pressures across the treatment groups.
 - Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at any time.
 - Calculate the proportion of patients in each treatment group who met criteria for PCS decrease in orthostatic systolic blood pressure (> 30 mmHg) at endpoint.
 - Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at any time.
 - Calculate the proportion of patients in each treatment group who had a decrease in orthostatic systolic blood pressure of >20 mmHg at endpoint.
8. Please provide a new Table 7 from the 12/16/02 submission "Incidence of Diabetes Mellitus and hyperglycemia in the olanzapine/fluoxetine hydrochloride pooled data" excluding the patients who had pre-existing diabetes mellitus at baseline.
 9. The fluoxetine labeling and proposed olanzapine/fluoxetine hydrochloride labeling includes a statement in the Warnings statement about allergic reactions that says, "Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis have been reported rarely. These events have occurred with dyspnea as the only preceding symptom."

At least two patients treated with olanzapine/fluoxetine hydrochloride have had serious AEs that might qualify as such a pulmonary event.

- Patient HGIE-025-4206 developed pneumonitis after about 10 weeks on olanzapine/fluoxetine hydrochloride therapy. She was discontinued due to persistent dyspnea. Please provide any additional follow-up that describes her response to dechallenge. Also, was any additional work-up performed to investigate the elevated sedimentation rate (e.g., a work-up for connective tissue disease)?
- Patient HGIP-608-6354 developed lung “crackles”, dyspnea on exertion, and a chest x-ray finding that led to hospitalization for work-up of these abnormalities. What was the finding on the chest x-ray that led to the hospitalization? Following the hospitalization, the patient remained on olanzapine/fluoxetine hydrochloride. Did the dyspnea on exertion resolve? Did she require additional work-up? Was any diagnosis made with regard to her pulmonary abnormality?

Did any other patients in the olanzapine/fluoxetine hydrochloride development program develop a pulmonary syndrome or symptoms consistent with the Warnings statement in labeling?

10. Please provide follow-up on the following patients:

- HGHZ-027-2305: Please provide any additional details available regarding this patient’s complicated hospital course. A skin biopsy and the report of a dermatological consultant regarding the diagnosis and etiology of the toxic epidermal necrolysis would be particularly helpful. Also, if an autopsy was conducted, please submit the autopsy report.
- HGIP-007-1334: Please provide any details that might be available of the “allergic reaction” that led the patient to discontinue from the trial.
- HGIE-026-4253: Was there any additional follow-up for this patient after he discontinued for a convulsion?
- HGIE-303-3108: After the patient was treated for the allergic reaction, how much longer was she maintained on olanzapine/fluoxetine hydrochloride? Did she have to stay on prednisone? If so, for how long?
- HGIE-013-1602: The patient was admitted to the hospital with dyspnea after nine months on open label olanzapine/fluoxetine hydrochloride and received a diagnosis of congestive heart failure. The narrative did not describe what diagnostic tests were done to make that diagnosis and the treatment for CHF was not specified. Please provide this information. If CHF treatment was added, did the patient have to stay on it chronically?
- HGGGA-022-2201: Please provide any additional details that are available regarding the patient’s hospitalization for acute MI and pancreatitis. These details should include, but are not limited to, the evidence supporting the diagnosis of acute MI (e.g., cardiac enzymes, echocardiogram results), the peak lipase level associated with the pancreatitis, and the CT scan appearance of the pancreatitis.

Request for Safety Update

In your response to this letter, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b). Please note that your safety update should include the FDA data grouping that was requested subsequent to your submission of the original NDA.

1. The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.

2. Please describe in detail any significant changes or findings in the safety profile.
3. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, please incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the preceding bullet point.
4. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
5. Please present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
6. Please provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, please provide narrative summaries for serious adverse events.
7. Please describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
8. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of olanzapine/fluoxetine hydrochloride. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of olanzapine/fluoxetine hydrochloride. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling (Package Insert and Container Labeling)

1. In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter. We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of SYMBYAX (olanzapine/fluoxetine hydrochloride) in the treatment of depressive episodes associated with bipolar disorder.

Please use the proposed text verbatim. You will see that we have proposed a number of changes to the draft labeling submitted in your November 4, 2002 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff are willing to discuss these proposed changes in detail and to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. We also request that you include a Patient Package Insert (PPI) with the revised labeling. The Information for Patients subsection of PRECAUTIONS has a substantial amount of patient information including: use of Symbyax with alcohol, cautions about cognitive and motor impairment, information about the concomitant use of Symbyax with other fluoxetine and olanzapine containing products, information about heat exposure and dehydration, nursing, orthostatic hypotension, pregnancy, and rash. It is unreasonable to expect a patient to retain this information after discussion with their physician. There could be risk to the patient if the information is not heeded. This PPI should be part of the package insert text, following the HOW SUPPLIED section of the physician labeling.
3. In addition, we have the following comments with respect to the container labeling for the new drug product:
 - Please heighten the contrast on the container labeling for the 12/25 dosage form to improve legibility (label presently shows the dosage strength in black text on a dark turquoise background).
 - Please revise the storage statement on all container labeling to correspond to the wording requested in the package insert.
 - Modify the yellow portion of the letter "X" in the name so that it does not interfere with the readability of the name.
 - Include the dosage form in the established name where it appears on labels and labeling. See below.

SYMBYAX
Olanzapine and Fluoxetine HCl Capsules

- Include the "mg" designation after each dosage strength number to prevent the potential for confusing the "slash" character as a number. For example: Use 12 mg / 25 mg instead of 12 / 25.
- Consider use of a different background color for either the 12 mg / 25 mg or the 6 mg / 50 mg, since the colors are similar. See below.



- Increase the background contrast for 12 mg/25 mg and 6 mg/ 25 mg. See next page.



- The color scheme used for the 6 mg/50 mg does not provide sufficient contrast and decreases the legibility of the product strength and “Each capsule equivalent to...” statement. See image on previous page, right-hand side. Please revise to improve the readability of the text on the labels and labeling.

Promotional Materials

In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Options Under 21 CFR 314.110

Within 10 (ten) days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw this application as provided for under 21 CFR 314.65. Any amendment should respond to all of the comments and requests in this letter, including those incorporated by reference. We will not process a partial reply as a major amendment, nor will the review clock be reactivated, until all deficiencies have been addressed.

Opportunity for Informal Meeting Under 21 CFR 314.102(d)

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Neuropharmacological Drug Products, to discuss what further steps need to be taken before the application may be approved.

This drug product may not be legally marketed until you have been notified in writing that this application has been approved.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

~~/s/~~ {See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Revised Draft Labeling) [The electronic signature page will follow the labeling.]

APPENDS THIS WAY
ON ORIGINAL

32 page(s) of draft labeling has been removed from this portion of the review.

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

/s/

Russell Katz
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