CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-894

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Martin Stogniew, Ph.D.
Executive Vice President, Chief Technology Officer
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Stogniew:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine® (tetrabenazine) Tablets 12.5 and 25 mg.

We also acknowledge receipt of your submission dated January 18, 2008.

The January 18, 2008, submission constituted a complete response to our December 26, 2007, action letter.

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

The attachment to this letter provides a draft of the labeling and Medication Guide that the Agency asks you to adopt for Xenazine. The base document used for the attached draft labeling is the package insert that was attached to the December 26, 2007 approvable letter. Although sections of this proposal are taken verbatim from the labeling proposed by you, other sections have been revised. Please also note that we have embedded throughout the text of the attached draft labeling several "Notes to Sponsor:" requesting that you provide information.

We also ask that when you submit draft labeling in response to this action letter, you provide a highlighted or marked-up copy that shows all changes. Please use the attached label as your base document.

In addition, it will be necessary for you to submit a revised risk management plan. Please be reminded that the provisions in Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) codified at 21 U.S.C. 355-1 (section 505-1 of the Federal Food, Drug, and Cosmetic Act (FFDCA)) go into effect March 25, 2008. As it is likely that your revised risk management plan will come in after this date, please submit your revised risk management plan as a proposed Risk

Evaluation and Mitigation Strategies (REMS). Please consult the Division for assistance in converting your risk management plan to a REMS.

In addition, please note that we will address the six post-approval studies, referenced in your January 18, 2008 submission, in any final approval of this application.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robert Temple
3/18/2008 06:25:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine® (tetrabenazine) Tablets 12.5 and 25 mg.

We also acknowledge receipt of your submissions dated February 9, April 4 and 10, June 12, 13, 26, and 28, July 19, August 1, 2, 6, 15, 17, 20, and 31, September 11 and 26, October 3, 5, 12, and 23, November 6, 13, 16, and 27, and December 11, 2007.

The April 4, 2007, submission constituted a complete response to our March 24, 2006 action letter.

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

1. Submit a revised Risk Minimization Action Plan (RiskMAP) to include an educational program for physicians, patients and families addressing adequate dosing and the risk of depression, suicidality, and other important adverse effects of tetrabenazine. The RiskMAP should be in place before Xenazine® is marketed.

   As part of your revised plan, we ask that you submit a draft of the educational materials that you propose using as part of the plan. You should include a plan for how you will identify tetrabenzine prescribers and potential prescribers, and how you will transmit educational materials to tetrabenazine prescribers and patients.

2. Submit a Medication Guide. We have determined that Xenazine® poses a serious and significant public health concern related to depression and suicidality. This concern requires development and distribution of a Medication Guide under 21 CFR 208 in order to prevent serious adverse effects, inform patients of information concerning risks that could affect their

decision to use or continue to use the drug, and/or assure effective use of the drug. A Medication Guide should be part of final approved labeling.

Submit your proposed Medication Guide with your complete response to this letter. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for every patient who is dispensed Xenazine®. Therefore, the proposed Medication Guide should be provided in a manner that will assure its appropriate distribution to patients and you should include a plan to ensure its distribution. In addition, submit proposed container carton labels for Xenazine that include a prominent and conspicuous instruction to provide the Medication Guide to each patient dispensed the drug. The labels must state how the Medication Guide is provided (e.g., affixed on the container, provided with the product, etc.).

3. Submit a draft package insert revised per the enclosed package insert.

You will note that throughout the Clinical Pharmacology section [redacted] have been removed [redacted] If this conclusion is not supportable, this section will need to be revised accordingly.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please consider the following potential postmarketing commitments in your complete response to this letter.

1. Perform an in vitro metabolism study to characterize the inhibitory effect of tetrabenazine, α-HTBZ, and β-HTBZ on CYP2B6. Please refer to the draft guidance on Drug Interaction Studies (http://www.fda.gov/cder/guidance/6695dft.htm) for information regarding preferred or acceptable substrates. You will need to commit to a date for submission of the final report for this in vitro study. The results of this study will guide the need for further in vivo drug interaction studies.

2. The carcinogenic potential of tetrabenazine has not been adequately assessed. We acknowledge that you have submitted a final report for a 26-week oral carcinogenicity study in P53N5-T heterozygous mice in Amendment 0056 (10/19/07). We also acknowledge that a 2-year carcinogenicity study is ongoing in male rats and a separate 2-year carcinogenicity study in female rats is planned. The 2-year studies may be completed post approval; however, you need to commit to dates for submission of final study reports for these studies.

3. You have not conducted a study of fertility and early embryonic development (to implantation) for tetrabenazine. This study may be conducted post approval but you need to commit to a date for submission of the final study report for this study.

4. You have not adequately responded to our request for in vivo metabolism data in the animal species used in the nonclinical studies of tetrabenazine (most importantly, the reproductive toxicology and carcinogenicity studies). We acknowledge that you have submitted a draft

report for a study that may provide the necessary data ——— tudy no. CAM/35; Amendment 0056, 10/19/07) but submission of a draft report at this stage of development is unacceptable. Although the final report may be submitted post approval, you need to commit to a date for submission of this report.

5. We acknowledge that you have conducted additional histopathology assessments for the 26-week oral toxicity study in rat (Amendment 0031, 2/16/07; Amendment 0031, 4/10/07) and the 9-month oral toxicity study in dog (Amendment 0039, 7/20/07) in order to address concerns regarding the potential for tetrabenazine to produce neurotoxicity, as reported by Satou T et al. (*Exp Toxicol Pathol* 53(4):303-308, 2001). Although you report no additional neuropathology findings in either species, the methodology used in these assessments does not appear to have been sufficiently sensitive to rule out potential neurotoxic effects.

   Based on our review and further internal discussions, we have concluded that a neurotoxicity study of tetrabenazine using methodology and a multiple dose regimen similar to that used by Satou et al. (2001) would provide the best evaluation. Consideration should be given to including a group in which tetrabenazine is administered i.p. as in Satou et al. (2001) in order to facilitate comparisons between studies. Ideally, tetrabenazine should be tested at several dose levels, with the high dose being a maximum tolerated dose.

   This study may be conducted post approval; however, you need to commit to a date for submission of the final study report. We would suggest that you submit a study protocol for review prior to initiation of the study.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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If you have any questions, call Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robert Temple
12/26/2007 06:00:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-894

Prestwick Pharmaceuticals, Inc.
Attention: Benjamin Lewis, Ph.D.
Senior Director, Regulatory Affairs
1825 K Street N.W., Suite 1475
Washington, DC 20006

Dear Dr. Lewis:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 26, 2005, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xenazine (tetrabenazine) Tablets 12.5mg and 25mg.

We acknowledge receipt of your submissions dated:

18-Oct-2005	09-Dec-2005	14-Dec-2005	15-Dec-2005
19-Dec-2005	23-Dec-2005	23-Dec-2005	23-Dec-2005
18-Jan-2006	27-Jan-2006	06-Feb-2006	21-Feb-2006
21-Feb-2006	01-Mar-2006	06-Mar-2006	

We also acknowledge receipt of your submissions dated:

1-Mar-2006	6-Mar-2006	10-Mar-2006	14-Mar-2006
15-Mar-2006	16-Mar-2006		

These latter submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following issues:

CLINICAL

We believe that you have provided substantial evidence of effectiveness for Xenazine as a treatment for chorea in patients with Huntington's Disease (HD).

Specifically, the results of Study 004 are clearly and robustly consistent with this conclusion. Not only is the p-value for the primary contrast extremely small ($p < 0.0001$), but the results clearly favor drug over placebo in 14 of the 15 study sites. In addition, other analyses of the data in this study also document the robustness of this finding. Specifically, we note that upon drug withdrawal at Week 12, patients' chorea scores returned to baseline levels by Week 13, confirming the drug effect seen over the previous 12 weeks. In addition, exploratory analyses document that the responses of patients during the first 11 weeks of Study 007, the open-label extension to Study 004, during which all patients were re-titrated, were essentially identical to the responses seen in the drug treated patients during the titration period in Study 004. This effect in Study 007 was seen in both patients who had previously received active treatment in Study 004 as well as in those who had previously

received placebo. A similar effect was seen for patients enrolled in Study 006, the open-label extension to Study 005. That is, although patients (after their participation in Study 005) were placed back on their best dose in Study 006 (as opposed to being re-titrated, as the patients in Study 007 were), their responses over the first 12 weeks in Study 006 were also essentially identical to those of the drug treated patients in Study 004. Further, although patients were not randomized to fixed dose in Study 004, PK/PD analyses strongly suggest a dose response relationship in that study.

The drug effect seems to be present regardless of the baseline degree of severity of the chorea.

We recognize that the results of the analyses of Study 005 do not meet the usual test for being considered "positive" (p=0.078). However, we note your observation that patients in Group 2 were not treated in compliance with the protocol (that is, placebo was inadvertently substituted for active drug on the morning of Day 3), and we agree that the protocol-specified prospective analysis is therefore inappropriate. We believe that the comparison of Group 1 to Group 3 on Day 3 is an appropriate post hoc analysis under these circumstances, because it is consistent with the rationale for your prospective analysis (that is, it compares patients off drug [Group 1] with patients continuing on treatment [Group 3]). Although the results of this analysis do not achieve nominal statistical significance (p=0.11), the estimate of the treatment effect is essentially identical to that seen in Study 004 (mean between treatment difference of about 3.5 points). In this case, we believe that the absence of statistical significance for this comparison is related to the extremely small sample size (12 patients in Group 1 and only 6 patients in Group 3).

We believe, given the results described above, that the findings establish the effectiveness of Xenazine as a treatment for the chorea of HD, under FDAMA's provision that substantial evidence can consist of the results of a single adequate and well-controlled investigation plus confirmatory evidence. We believe that the statistically strong result of Study 004, its marked internal consistency, as well as the results of Study 005, provide the necessary confirmatory evidence required by this provision of the Act.

Despite the documented effect on chorea, there remain troubling questions about the utility and ultimate approvability, of this application.

In particular, we note that there was a consistent tendency for the results of the analyses of multiple secondary outcomes to favor placebo in Study 004. Specifically, the between-treatment comparisons on the Cognitive Assessment (UHDRS Part 2), the Behavioral Assessment (UHDRS Part 3), the Functional Assessment (UHDRS Part 4), the Independence Scale (UHDRS Part 5), the Functional Capacity (UHDRS Part 6) all numerically favored placebo, and the comparisons on the Cognitive Assessment (UHDRS Part 2) and the Functional Assessment (UHDRS Part 4) actually achieved nominal statistical significance in favor of placebo (p=0.025 and p=0.018, respectively). We also note that there were no patient – rated measures of overall benefit in Study 004. These results, taken together, raise serious questions, not only about the overall utility of Xenazine's effect on chorea, but also, of course, about Xenazine's capacity to cause harm in these patients. We acknowledge that the (negative) effects seen on these secondary measures appear to be numerically small, but we do not have a good understanding of the effects on patient functioning of these sorts of changes. We also do not have data on the consequences of long-term treatment with Xenazine. If overall patient functioning continues to worsen (in the face of reasonable control of the chorea) as a result of chronic treatment, we are not confident that such deterioration could easily be detected clinically (because detailed neuropsychiatric testing may be necessary to detect it). In such a case, clinical deterioration may continue unnoticed; when it does become manifest, the patient's clinical condition would very probably be attributed to progression of the underlying HD.

Beyond the question of these specific ways in which treatment with Xenazine may harm patients, we are concerned with Xenazine's capacity to cause other, serious, adverse events.

In particular, among the numerous adverse events seen in association with the use of tetrabenazine, we note parkinsonism, akathisia, depression, and dysphagia (with associated aspiration pneumonia). Although we acknowledge that the incidence of some of these events in Study 004 is not significantly different from placebo

(e.g., parkinsonism, dysphagia) the incidence of others is substantially greater in the drug-treated patients than in the placebo patients (e.g., depression: 15% vs 0; akathisia: 9% vs 0). Further, it is not clear that other events coded differently from akathisia do not, in fact, represent the same phenomenon (e.g., agitation, anxiety, irritability). All of these events are consistent with the pharmacologic effects of the drug, and the incidence of these events increases with increasing duration of use. We acknowledge, of course, that the long-term safety data were collected in an open-label, uncontrolled setting, and also that these can themselves be manifestations of progressive HD. For these reasons a definitive conclusion about causality clearly can not be made at this time. Nonetheless, we are concerned that these events may be drug-related.

We are particularly concerned about the ability of practitioners to readily identify these events and consider the possibility that they may be drug -related. We would agree that, should these events occur relatively acutely after treatment initiation (or dose increase), the prescriber might consider them drug related (and take the appropriate action). However, to the extent that they might be drug-related, but occur slowly over time, it is less likely that they will be considered potentially drug-related and more likely to be considered related to disease progression. In such a scenario, the possibility that the specific symptom might reach a severe stage (with the possibility that it may become irreversible), or result in a serious outcome even if reversible (e.g., depression leading to suicide), is raised. (In the case of parkinsonism, an article in the literature (Satou T et al. Exp Toxic Pathol 53:303-308, 2001) suggests that there is irreversible damage to the substantia nigra pars compacta in Wistar rats following 7 daily i.p. doses of tetrabenazine.)

Also, in regard to dysphagia specifically, we note the disturbing finding that Dr. Jankovic did not systematically record episodes of dysphagia in many of his patients because he considered it to be a symptom of progression of the underlying HD. Because his experience represents a large portion of the clinical experience submitted in this application, we are concerned that the incidence of dysphagia (which can have devastating clinical consequences) may be significantly underestimated.

For all of these reasons, then, we are not sure Xenazine can be used safely, even with labeling that describes, as accurately as possible, the known risks of its use. Because we are unable to reach a definitive conclusion about the ultimate approvability of the application at this time, we plan to discuss your NDA at a public meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNSAC). We will attempt to arrange this meeting as soon as possible.

CMC

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3. Approval from a CMC standpoint will be contingent on the overall recommendation on establishment from the Office of Compliance.

NON-CLINICAL

Prior to approval, you will need to address the following nonclinical issues:

1. There is a lack of adequate in vivo metabolism data in the animal species used in the definitive nonclinical studies. There is a similar lack of metabolism data in humans. You need to provide additional data identifying and quantitating the major circulating metabolites in animals and humans. These data are needed in order to determine the relevance (and adequacy) of the nonclinical studies to an assessment of human risk. In particular, there is concern that the potential toxicity of the major circulating drug-related material in humans (peak 16) may not have been adequately assessed in animals.

2. The 26-week oral toxicity study is the only definitive toxicity study conducted in rats. Therefore, it is particularly important that you provide the data from this study in a complete and accurate manner. The following deficiencies were identified in the report of the study:

    a. The reporting of clinical signs is incomplete. For example, several instances of convulsions observed in two high-dose animals were not listed in the summary table. Similarly, instances of "lethargy" were noted in the summary table, but not in any individual animal line listing. You need to address the apparent discrepancies between the summary of clinical signs and the individual animal line listings.

    b. The study report did not include a signed Pathologist's Report. In order to document the gross pathology and histopathology findings in the chronic study, you need to provide a copy of this report.

3. You conducted a 14-day oral study of tetrabenazine to assess toxicokinetics and effects on serum prolactin in rats (Covance Study # 7425-114). The toxicokinetics data have been provided, but the serum prolactin data have not. You need to submit a final report of the serum prolactin data. These data are important for the interpretation of the results of the chronic toxicity study in rats.

4. The published findings of Satou et al. (Satou T et al. *Exp Toxicol Pathol* 53(4):303-308, 2001) raise a concern that tetrabenazine may have neurotoxic effects. Therefore, it is particularly important to understand how extensively the brain was examined in the 26-week and 9-month oral toxicity studies in rats and dogs, respectively. The reports of these studies do not provide sufficient detail regarding the methodology used in the microscopic examination of brain. You need to document that the microscopic examination of brain in the chronic studies was conducted using techniques sensitive enough to have detected, if present, neuropathological findings similar to those reported by Satou et al (2001).

5. The equivocal finding in females in the in vivo micronucleus assay in rat needs to be further investigated, particularly considering the lack of carcinogenicity data on tetrabenazine. The in vivo micronucleus assay needs to be repeated exploring a range of doses. Although the equivocal finding was only in females, it is difficult to understand why females would be more sensitive than males based on the available plasma exposure data; therefore, we ask that you include both males and females in the repeat assay.

6. You need to commit to initiating carcinogenicity studies. Your protocol for a 26-week p53 transgenic mouse assay has been reviewed by the Division and the Executive CAC; minutes of the Executive CAC meeting were sent to you on October 27, 2005. You have recently submitted a protocol for a 2-year carcinogenicity study in rats that is currently under review. You need to commit to a timeline for conduct of the studies and submission of final reports of these studies. Final study reports would not be required prior to approval.

CLINIAL PHARMACOLOGY & BIOPHARMACEUTICS

Before approval, we ask you to address the following:

1. Clarify the rotation speed at which the dissolution method was generated (previously requested on 1/2/06). If you have data to support the proposed rotation speed and agreement is reached between us regarding dissolution specifications, the method and agreed upon specifications can be accepted as interim method and specifications. The recommended dissolution method and specifications are as follows:

   Apparatus: USP Apparatus 2 (Paddles)
   Medium: 0.1 M HCl
   Volume: 900 ml
   Rotation Speed: 50 rpm
   Specification: ≥[redacted](Q) in 30 minutes

2. Since the 25 mg tablet is scored, you should demonstrate dissolution similarity (with f2 testing and using the interim dissolution method above) between 2 half-tablets and 1 whole 25 mg tablet.

3. The P16 component, identified as the largest circulating component in the mass balance study, should be characterized. In addition, the extent to which the mono- and bis-dealkyl tetrabenazine metabolites (and other individual metabolites) are circulating should be clarified.

4. You should submit adequately performed *in vitro* metabolism studies to address the potential for inhibition or induction of P450s by TBZ and its metabolites. You should also characterize the *in vitro* metabolism of TBZ and its metabolites as well as the role of PgP in TBZ disposition. Finally, you should adequately address the role for TBZ as a PgP inhibitor *in vitro*. There is currently insufficient information to allow for adequate labeling regarding the potential for drug interactions. Please see our comments below about performing the in vitro drug metabolism studies (communicated to you in an email of 12/21/05).

   1. You have not taken a step-wise approach to understanding the metabolism of TBZ or its metabolites. The preferred first approach would be to directly identify metabolites after incubation with hepatocytes or liver slices. Subsequent studies can also eliminate non CYP oxidative pathways.
   2. The studies to evaluate CYP pathways of TBZ and HTBZ metabolism are methodologically deficient. It is recommended that recombinant enzymes not be used alone, but in combination with other methods (such as use of inhibitors) for identifying drug metabolizing P450 isozymes. In addition, the probes used as controls in the submitted studies are not classical, preferred probes, and you have not provided justification, so it is difficult to understand the acceptability of the reactions.
   3. Studies characterizing the metabolism of TBZ *in vitro* should include measurement of the formation of metabolites (including the oxidative metabolites of TBZ and the oxidative metabolites of HTBZ) to identify the pathways by which they are formed.
   4. You should follow-up the results of the submitted studies with *in vitro* inhibition studies that use well accepted methodology and preferred substrates to confirm lack of involvement of TBZ and its metabolites in inhibition of P450s.
   5. The *in vitro* study of TBZ inhibition of PgP provided from the literature was not conducted with methods that are in agreement with current Agency thinking. The *in vivo* TBZ-digoxin interaction study was performed with a low dose of TBZ, and does not allow for conclusions

about higher doses that will be used clinically. You should perform an adequate *in vitro* inhibition study using preferred methodology to determine the need for further *in vivo* study.

6. The results of adequate *in vitro* drug metabolism studies will guide the need for further *in vivo* drug interaction studies.
7. Since CYP2D6 appears to be involved in the metabolism of TBZ and HTBZ, we recommend genotyping for CYP2D6 in future TBZ clinical trials.
8. The thorough QT study did not assess exposure to TBZ or metabolites outside of the ranges that might be normally observed after administration. The results of the in vitro drug metabolism studies may help guide decisions regarding the need and approach for further metabolically-based evaluation of QT.

Phase 4 Commitments
NON-CLINICAL

We ask that you address the following issues as Phase 4 commitments:

1. Submission of final study reports for the 26-week p53 transgenic mouse assay and the 2-year carcinogenicity study in rats.

2. Conduct of a fertility and early embryonic development (to implantation) study. You should commit to a timeline for conduct of the study and submission of the final study report.

3. The following apparent discrepancies in the report of the pre- and post-natal development study need to be addressed:

   a. the lack of corpora lutea and preimplantation loss data in F1 females. These data need to be submitted if collected.

   b. the number of stillbirths versus early postnatal deaths. You need to specify which pups were determined to be stillborn due only to the lack of milk in the stomach versus those determined to be stillborn by the lack of lung floatation (with or without lack of milk in the stomach); the lack of milk in the stomach alone does not necessarily indicate a stillborn pup. In addition, you need to explain why the summary table (page 39) indicates a dose-related increase in stillbirths, whereas the individual line listings (page 204-207) fail to indicate a stillbirth in any litter.

   c. apparent discrepancies in the data for individual dams, low-dose female B73509, mid-dose female B73526, and high-dose female B73557. You need to provide all data (including pregnancy, litter, and final disposition) for these dams.

Although not needed prior to approval, we ask that you address these issues in a timely manner.

CLINICAL PHARMACOLOGY

We ask that you address the following issues as Phase 4 commitments:

1. Perform an in vivo study of the effect of CYP2D6 inhibition on TBZ disposition using a strong CYP2D6 inhibitor since CYP2D6 inhibition may increase the exposure to the inactive β- HTBZ relative to the active moiety α-HTBZ (based on evaluation of plasma concentrations in Phase III studies).

2. Evaluate the clinical relevance of CYP2D6 inhibition after administration of TBZ in vivo using a sensitive CYP2D6 substrate (such as desipramine) since in vitro studies suggest involvement of CYP2D6.

3. Other *in vivo* drug interaction studies should be guided by the results of the *in vitro* drug metabolism studies, in agreement with the Agency.

4. The discriminatory ability of the interim dissolution method should be determined in order to determine the final dissolution specifications.

In addition, it will be necessary for you to submit draft labeling revised as attached.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). 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.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, 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 bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. 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, provide narrative summaries for serious adverse events.

5. 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.

Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials 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

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If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robert Temple
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