DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

September 28, 2006

Reference Number:

Dear Aripiprazole ANDA Applicant:

This letter is in response to your correspondence dated MM-DD-YYYY. This letter supersedes our previous correspondence dated July 11, 2006. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Aripiprazole Tablets, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg. OGD provides the following comments:

1. The following studies are recommended to establish bioequivalence of Aripiprazole Tablets:

    a. A single-dose fasting *in-vivo* bioequivalence study comparing Aripiprazole Tablets, 10 mg, to the reference listed drug (RLD), Abilify®, (Aripiprazole) Tablets, 10 mg.

    b. A single-dose fed *in-vivo* bioequivalence study comparing Aripiprazole Tablets, 10 mg, to the RLD.

    c. A single-dose fasting *in-vivo* bioequivalence study comparing Aripiprazole Tablets, 5 mg, to the RLD. If adequate exposure is not possible with a 5 mg dose, you may consider using a 10 mg dose (2 x 5 mg).

2. Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers in bioequivalence studies. Although such events have not been reported at doses lower than 30 mg, because of the life-threatening nature of these events, and because the dose response relationship is not known for this event, the following safety precautions are recommended for healthy volunteer studies of aripiprazole at all doses:

    - Study protocols should specify standard procedures to diagnose and treat dystonic reactions should they occur.
    - Subjects younger than 45 years of age should be excluded. There appears to be an inverse linear relationship between age and the incidence of acute dystonic reactions. Adults under 35 years of age were reported to have a 15-

fold higher rate of neuroleptic-induced dystonia compared to a group of patients 60-80 years of age. The occurrence of dystonias appears to be rare at ages of approximately 45 years and higher.

- Protocols should include stringent drug screening procedures to ensure that subjects are free of illicit drugs at the time of administration of each study drug dose.
- The screening interview should include specific questions to exclude subjects with a prior personal or family history of dystonic reactions to medications. Prospective study subjects should also be specifically questioned about prior neuroleptic drug exposures.

3. Aripiprazole has been poorly tolerated by healthy volunteers in some bioequivalence studies, particularly at the 15 and 30 mg dose levels. In several cases, adverse events have resulted in a high incidence of dropouts. Adverse events in aripiprazole studies have included nausea, vomiting, dizziness, syncope, insomnia, headache, fatigue, hypotension, hot flashes, weakness, diaphoresis and confusion. To minimize the occurrence of adverse events, and to ensure the safety of healthy volunteer subjects in clinical trials of aripiprazole, the following is recommended:

   - Subjects should be monitored in-house for at least 3 days after dosing and until adverse events have resolved.
   - Subjects should be kept supine for at least 8 hours starting no longer than 15 minutes after each dose.
   - Subjects should be asked to use the bathroom soon before dosing. Subjects should be encouraged to use urinals or bedpans during the first 8 hours after dosing and at any time after dosing if the subject is experiencing adverse events such as nausea, dizziness or hypotension. If subjects do use the bathroom during the first 8 hours after dosing or while experiencing adverse events such as nausea, dizziness or hypotension, they should be assisted to and from the bathroom by study personnel.
   - At a minimum, routine 12-lead EKG's should be performed at 3-5 hours after dosing and at 8-12 hours after dosing. Continuous EKG monitoring during those time periods may be considered as an alternative.
   - Vital signs monitoring should continue post dosing throughout the period that subjects are housed, commencing no later than 30 minutes following dosing. Vital signs should be monitored frequently (at least every 0.5-1 hour) for at least the first 8 hours after dosing and the first hour after subjects are allowed to rise from the supine position.
   - Prespecified limits should be defined for reporting adverse events related to vital signs (e.g. hypotension, bradycardia, etc.). Vital sign readings that meet these predefined limits should be reported as adverse events, even if they are not performed during a scheduled assessment (e.g. vital signs performed as part of an assessment of an adverse event).
   - The protocol should include standard procedures for the assessment and management of potential adverse events, including vital signs and EKG

monitoring as appropriate for adverse events possibly associated with hypotension.

- Women of childbearing potential should be enrolled only if they are using effective contraceptives. A negative pregnancy test is needed within 24 hours prior to each dose. These subjects should also be informed of the potential teratogenicity of the study drug as part of the informed consent process. Nursing women should also be excluded.
- The protocol should include measures to prevent relative dehydration at the time of dosing, such as encouragement of water intake whenever possible prior to dosing. Consideration should be made to providing a standard meal just prior to the standard fasting period before dosing.
- During the informed consent process, subjects should be advised of the high incidence of adverse events that have occurred in some healthy volunteer studies of aripiprazole.

4. Please measure only the parent compound, aripiprazole.

5. Aripiprazole Tablets, 2 mg, 15 mg, 20 mg and 30 mg, may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 5 mg and 10 mg strengths, (2) acceptable dissolution testing of all strengths, and (3) proportional similarity in the formulations of all strengths.

6. The 2 mg strength of Abilify® is currently not marketed. If you are interested in seeking approval for this strength, please submit a citizen petition requesting the FDA make a determination that this particular strength was not withdrawn for reasons of safety or effectiveness, or check the Federal Register for a previously submitted citizen petition. Submission of the citizen petition to the FDA should be done prior to an ANDA submission.

7. Please note that a new Dissolution Methods Database is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website.

8. Aripiprazole has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a parallel study design due to aripiprazole's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0-t or AUC0-8. Please collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (Cmax) and time to reach peak concentration (tmax).

9. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for

identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

10. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

    a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
    b. SUBJ SEQ PER TRT C1 C2 C3 ……. Cn

    Please separate each field with a blank space and indicate missing values with a period (.).

    Please refer to the Guidance for Industry: “Providing Regulatory Submissions in Electronic Format-ANDAs” for information regarding the proper format at: www.fda.gov/cder/guidance/index.htm (under electronic submissions).

If you have any questions, please call Beth Fabian-Fritsch, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/s/ "Gary Buehler"

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research