DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

Biovail Technologies, Ltd.
700 Route 202-206 North
Bridgewater, NJ 08807

Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Weet:

Please refer to your new drug application (NDA) dated December 31, 2003, received December 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trade name (tramadol HCL) Extended-Release Tablets.

We acknowledge receipt of your submissions dated February 25, March 31, April 30, August 3, 6(2), 20, 26, and 30, September 1, 8, 9, 17, 23, 28, and 30(2), October 6, 13, 25, and 28(2), and November 11 and 22, 2004, and March 7 and 9, April 26 and 29, June 6 and 10, July 18, 25, and 28(2), August 8, 17, and 23(2), September 1(2) and 8, 2005.

The March 7, 2005, submission constituted a complete response to our October 29, 2004, action letter.

This new drug application provides for the use of TRADENAME ER for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container and carton labels) 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, designate this/these submission(s) "**FPL for approved NDA 21-692**." Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages birth to 16 years until September 30, 2010.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of for the management of moderate to moderately severe chronic pain in pediatric patients ages birth to 16 years.

   Final Report Submission: September 30, 2010

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

In addition, you have agreed to the following interim dissolution specifications:

Time	**Dissolution Specification**
2 hours	(b)(4)
4 hours	----------
8 hours	----------
10 hours	----------
16 hours	----------

In order to validate your proposed in vitro/in vivo correlation (IVIVC), and the associated in vitro dissolution specification, we encourage you to provide the following information:

1. The mathematical models (equations) and the control files that you used for predicting the plasma concentration time profiles for IVIVC; and

2. Evidence that the IVIVC is predictive of alterations in the rate of drug release, i.e., external validation using the (b)(4) ---------- release formulations that would probe the acceptance limits of the IVIVC. Such an external validation could be done with the material from Study

2553 or new lots of product that have release rates/bioavailabilty that are different from the clinically studied product. You are encouraged to seek guidance from the Agency as to what would be an appropriate comparator for this external validation.

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(s) directly to:

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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, call Parinda Jani, Chief, Project Management Staff, at (301) 827-2538.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Bob Rappaport

9/8/2005 06:08:03 PM