



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-357/21-358

Bracco Diagnostics, Inc.
Attention: Melanie Benson
Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225

Dear Ms. Benson:

Please refer to your new drug applications (NDA) dated April 27, 2001, received April 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MultiHance[®] and MultiHance[®] Multipack[™] Pharmacy Bulk Package (gadobenate dimeglumine) Injection.

We acknowledge receipt of your submissions dated July 16 and 30, August 27, September 3, 14, and 15, October 28, and November 12, 2004.

The July 30, 2004, submission constituted a complete response to our April 14, 2004, action letter.

These new drug applications provide for the use of MultiHance[®] and MultiHance[®] Multipack[™] Pharmacy Bulk Package (gadobenate dimeglumine) for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.”

We completed our review of these applications, as amended. They are 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 agreed on November 22, 2004), and the immediate container and carton labels submitted October 28, 2004. Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

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 these submissions “**FPL for approved NDA 21-357**” or “**FPL for approved NDA 21-358**.” Approval of this submission by FDA is not required before the labeling is used.

In addition, submit the content of the labeling in electronic format as required by 21 CFR 314.50(l)(5) and in the format described at the following website: <http://www.fda.gov/oc/datacouncil/spl.html>.

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 waiving the pediatric study requirement for ages less than 2 years. However, as we gain more information from use of MultiHance and studies in other pediatric age groups, we may reconsider the need for pediatric studies in this age group after studying the feasibility and need for doing such studies. We are deferring pediatric studies for ages 2 to 16 years for these applications.

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

1. Deferred pediatric safety and efficacy study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16.
 - a. Protocol Submission: Within 6 months of the date of this letter
 - b. Study Completion: Within 30 months after the agreement of the protocol

Final Report Submission: December 1, 2007

2. Deferred pediatric pharmacokinetic study under PREA for the evaluation of known or suspected CNS disease in pediatric patients age 2 to 5.
 - c. Protocol Submission: Within 6 months of the date of this letter
 - d. Study Completion: Within 30 months after the agreement of the protocol

Final Report Submission: December 1, 2007

Submit final study reports to these NDAs. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated “**Required Pediatric Study Commitments**”.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to Division of Medical Imaging and Radiopharmaceutical Drug Products 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

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).

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.

If you have any questions, call Diane C. Smith, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., MPH
Director
Office of Drug Evaluation III
Center of 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/

Florence Houn
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