CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

APPROVABLE LETTER 2

REVIEW CYCLE #2

Submission Date October 10, 2003

Action: Approvable

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 application (NDA) dated April 27, 2001, received April 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MultiHance® (gadobenate dimeglumine) Injection and MultiHance® (gadobenate dimeglumine) Injection in a pharmacy bulk package.

We acknowledge receipt of your submissions to each application dated September 10 and 19, and November 18, 2002; January 20, October 10, and December 9, 2003; January 16 and February 3, 6, 17, 20, and 27, 2004. Also, we acknowledge the meetings and teleconferences of August 28 and December 11, 2002; January 29 and November 25, 2003; January 14 and 28, and February 18 and 25, 2004.

The October 10, 2003, submission, received on October 14, 2003, constituted a complete response to our May 24, 2002, action letter.

We have completed the review of this application, as amended, and it is approvable for intravenous use in magnetic resonance imaging (MRI) of the central nervous system (CNS) in adults ——— to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. However, before this application may be approved, it will be necessary for you to address the following:

I. CLINICAL ADULT EFFICACY

Originally submitted on April 27, 2001, were two pivotal, adult US trials (43,779-9A and 43,779-9B) that enrolled patients with a variety of CNS lesions. These trials were identically designed as double-blind, randomized, parallel-group, multicenter studies with three arms: a) MultiHance® at sequential doses of 0.05 and 0.1 mmol/kg; b) MultiHance® at sequential doses of 0.1 and 0.1 mmol/kg; and c) Omniscan® at sequential doses of 0.1 and 0.2 mmol/kg. Images from 136 patients (out of a total of 276) acquired following the first dose of MultiHance® (either 0.05 or 0.1 mmol/kg) were blindly re-read under Study MH 105 by three independent readers.

Also, originally submitted, was a third adult trial (B 19036/020), completed in Europe that enrolled only patients with known metastatic CNS disease. This was a double-blind, parallel-group study of 150 patients. These patients were randomized to receive one of two MultiHance® dose sequences: either (0.05 + 0.05 + 0.1 mmol/kg) or (0.1+ 0.1 + 0.1 mmol/kg). Images from 75 patients acquired following the first dose of MultiHance® (either 0.05 or 0.1 mmol/kg) were blindly re-read under Study MH 106 by three independent readers.

Because of concerns about the short dosing interval (approximately 10 minutes) and the lack of dose response in these three adult trials submitted in the original NDA, the blinded readers in the re-read studies, MH 105 and MH 106, were provided only with those images that were acquired following the administration of the first dose of MultiHance® (either 0.05 or 0.1 mmol/kg dose).

Image acquisitions were variable and different combinations of sequences were used for blinded reader evaluations within the trials. Study MH 105 incorporated T1 + T2 + Proton Density sequences in the pre-contrast blinded reader sessions, while Study MH 106, only included T1 + T2 sequences. Proton Density image sequences were not provided to the blinded readers for assessment in this Study MH 106.

A. Primary Efficacy Analyses

The Division views Study MH 105 (adult CNS), the only study in the resubmission that enrolled a population that was not solely oncologic, to be critical in demonstrating effectiveness for your product's claim. For the primary efficacy analyses of pre-drug versus post-drug reads, depending on the reader or the dose, either there was no statistical difference between pre- and post-drug mean scores for the co-primary endpoints of border delineation, internal morphology and contrast enhancement, or mean scores were statistically inferior after the administration of MultiHance®. The statistical significance demonstrated for the co-primary efficacy analyses for Study MH 106 (adult metastatic) does not provide substantial evidence of effectiveness for your claim of visualization of all CNS and spinal lesions (not just those in cancer patients). The statistical significance demonstrated for the secondary efficacy analysis (pre- versus paired reads) for both studies (MH 105 and MH 106) was not prospectively established as a primary measure of success.

B. Target Population

We note that Study MH 105 did not include sufficient numbers of patients with varied neurological diseases for which a contrast MRI would typically be used in clinical practice. Furthermore, Study MH 105 included only four patients categorized with spinal disorders. We also note Study MH 106 only enrolled patients with metastatic CNS tumors.

C. Dose Selection

The re-read results for studies MH 105 and MH 106 did not demonstrate statistically significant differences between the 0.05 mmol/kg and the 0.1 mmol/kg administered doses. Therefore, your proposed dose of 0.1 mmol/kg is not justified over 0.05 mmol/kg.

D. Image Evaluation

Your re-read studies, MH 105 and MH 106, were designed to establish a visualization claim using visualization endpoints via the comparison of a pre-contrast MRI image to the post-contrast MRI image. This design was necessitated by the absence of a truth standard in your original clinical trials. Therefore, the results of the secondary analyses of pre- versus paired reads for studies MH 105 and MH 106 are not supportive of a The pre-drug versus post-drug analysis best demonstrates if MultiHance® provides improved visualization over MRI alone. We also note that the positive results in MH 106 were based upon incomplete image sequences.

To address these deficiencies, at least one adequate and well-controlled study in adults with a variety of CNS diseases is needed to support a visualization claim.

Appropriate patients must be enrolled (such as patients with known disease or in whom it is suspected) and have a well defined need for contrast-enhanced MRI. The study should include sufficient numbers of adult patients with various CNS diseases involving the brain and the spine. The imaging acquisition methodology must include all pre-dose MRI sequences, in accordance with accepted clinical practice within the United States, to show adequate contribution of MultiHance® over baseline imaging. For your proposed visualization indication, you should demonstrate that the MultiHance® enhanced MRI images are superior to the pre-contrast images in an analysis of pre-drug versus post-drug reads. If you wish to continue to pursue the 0.1 mmol/kg dose as the recommended dose, then this new study should be appropriately designed to confirm that the proposed 0.1 mmol/kg dose has statistically and clinically significant superiority over the 0.05 mmol/kg dose.

II. PEDIATRIC SAFETY

While we provided you comments on the design of your adult studies, MH 105 and MH 106, you did not initiate discussions with the Division for re-read Study MH 112, prior to the subgroup reanalysis of pediatric data in your original NDA.

Study B19036/036, conducted in Europe, was originally submitted in the last review cycle to establish the safety and efficacy of MultiHance® in 80 pediatric patients between the ages of 6 months to 16 years. Results from a subset of 29 pediatric tumor patients from the original Study B19036/036 (and defined by presence of a known CNS tumor) were submitted for re-read under Study MH 112.

The images were re-read by a single blinded reader for Study MH 112, which does not provide reproducibility of results. Demographic information, including age and disease site, for the subset of 29 patients included in Study MH 112 was not available. All patients received 0.1 mmol/kg of MultiHance®, so there is no evaluation of what is an appropriate dose for pediatric patients. Investigators did not acquire all standard pre-dose MRI sequences for the patients included in this study.

The application also lacks sufficient safety data in pediatric patients to determine the effect of MultiHance® on the renal and cardiovascular systems. Complete urine analyses and EKG testing were not conducted in pediatric patients. We also note that the pharmacokinetic study of healthy pediatric patients contained only one subject under age 5 years.

Safety monitoring within the trial should additionally include complete urinalysis, blood/serum renal function tests, and complete 12-lead EKGs with hemodynamic monitoring. Prior to initiating such a trial, you are strongly recommended to submit the trial protocol to FDA for review and comments.

We are deferring comments on product labeling until all data to support safety and efficacy are available. Thus, we request that you submit updated draft labeling with your response to this letter.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical 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.

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

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

Within 10 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 314.120. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Medical Imaging and Radiopharmaceutical Drug Products to discuss what further 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 Diane C. Smith, R.Ph., Regulatory Health Project Manager, at (301) 827-7510

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Julie Beitz
4/14/04 12:27:42 PM
Signing for Florence Houn, MD

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

APPROVABLE LETTER 1

REVIEW CYCLE #1

Submission Date August 20, 2001/
February 26, 2002

Action: Approvable

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Rockville MD 20857

NDAs 21-357\21-358

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

Dear Ms. Benson:

Please refer to your new drug application (NDA) dated April 27, 2001, received April 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MultiHance® (gadobenate dimeglumine) Injection and MultiHance® (gadobenate dimeglumine) Injection packaged in a pharmacy bulk package.

We acknowledge receipt of your submissions dated June 15, 22, 27, 28, and 29; July 26; August 7; September 13 and 14; October 24; December 5, 2001; and January 17; February 26; March 7, 8, 12, and 25; April 8, and 18; May 1, 14, and 15, 2002. Also, acknowledged are the teleconferences and meetings of February 25; May 20 and 21, 2002.

We have completed the review of this application, as amended, and it is approvable for intravenous use in magnetic resonance imaging (MRI) contrast enhancement of the central nervous system (CNS) to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated issues. However, before this application may be approved, it will be necessary for you to address the following:

I. SAFETY

Although the application contains safety data from at least 4,000 patients who received a dose of MultiHance®, several critical safety issues were identified and the application lacks sufficient data to establish the safety of MultiHance®.

A. Clinical Safety

1. The application lacks sufficient data to fully assess the risk of MultiHance® on the liver.

   a. MultiHance® is partially excreted through the ATP dependent canalicular multispecific organic anion transporter (cMOAT). In clinical trials it appears that at least three normal volunteers with von Willebrand's disease and one patient with Wilson's disease demonstrated marked increases in bilirubin. This may be the result of competition for the cMOAT. The effect of MultiHance® on other concomitantly administered

medications that have a narrow therapeutic index and that use the same mechanism of elimination is not known.

To resolve this deficiency, appropriate drug interaction studies are needed. Submit protocols for FDA comments prior to initiation of these studies.

b. The stated mechanism of action is hepatocellular uptake. The pre-clinical observations of hepatic necrosis and vacuolization in animals raises concern about the hepatocellular safety of MultiHance® in patients receiving magnetic resonance imaging (MRI), especially those with known liver lesions. We acknowledge that the liver enzyme results in the database are variable, yet some patients with preexisting liver disease had further increases in liver enzymes and bilirubin after exposure to the drug. The submitted safety data of patients with cirrhosis showed that there was a difference in pruritis (2.2% vs. 0.5% in patients with and without cirrhosis, respectively). Laboratory data were not included to evaluate the potential for worsening liver disease.

   To resolve this deficiency, provide a subset analysis of all existing bilirubin and liver enzymes data from the patients with liver disease stratified by disease severity. Additionally, perform non-clinical tri-animal model studies to determine if retention of MultiHance® in the hepatocytes causes liver toxicity.

2. The application lacks sufficient data to fully characterize the safety of MultiHance® on the cardiovascular system.

   Gadolinium is reported to block the cardiac calcium channels and is associated with QT/QTc prolongation. In the submitted studies, most QTc interval monitoring was intermittent. In adults, QTc prolongation was observed across most of the measured time points. The cardiovascular-related adverse events included patients with ventricular arrhythmias and pulmonary vascular-compromise (PVC). Although most QTc prolongations were of < 30 msec magnitude, the frequency of occurrence across the measured time points (ranging from 40-47%) is of concern. Historically, in most drugs that cause malignant ventricular arrhythmias, the magnitude of the change from baseline is not significant. Therefore, the occurrence of most instances of QTc prolongation in the < 30 msec range is not a reassurance. Also, ECG monitoring was not performed in the pediatric Study # B19036/036. Therefore, the cardiovascular safety in pediatric patients cannot be evaluated. Study 43,779-12, of patients on calcium channel blockers did not reveal substantial effects of MultiHance® on QT interval. However, the small sample size of eleven patients is not sufficient to exclude the possible effects of MultiHance® as discussed above.

   To address this deficiency, conduct placebo-controlled studies in patients using higher than indicated doses of MultiHance® (at least 4X) to determine QT effects. We recommend that you submit your proposed protocol. It will be consulted to the Division of Cardio-Renal Drug Products to assess the acceptability in evaluating QT effects.

3. The application lacks sufficient data in adults and pediatric patients to determine

the effect of MultiHance® on the renal system.

To address this deficiency, provide available urinalysis data. These data are especially needed in patients with renal insufficiency, the elderly, and the pediatric population.

Additionally, urine analyses must be added to all ongoing and future studies that may be conducted to address the deficiencies stated in this letter.

4. The application lacks sufficient detail on local adverse events.

   The osmolality and viscosity of this agent is higher than that of currently approved gadolinium agents. These chemical parameters have been associated with serious adverse events (i.e., fascitis, thrombophlebitis, compartment syndrome, amputations, surgical release, infections, etc.).

   To resolve this deficiency, provide additional data and discussion of such events observed in previous and future trials with this product.

5. The application lacks the required case report forms (CRFs) for patients who died during clinical trials.

   To address this deficiency, submit these CRFs and those for cases of serious adverse events in patients who received MultiHance®.

6. The application lacks the required reporting of all patients in the Integrated Safety Summary.

   To address this deficiency, provide summarized data that include (1) Japanese subjects, (2) pediatric subjects, and (3) healthy adult volunteers. Likewise, revise the overall summaries to include all demographics (age, weight, height), method of administration (rapid bolus injection and/or slow infusion), and subanalyses (i.e., adverse events) by imaging indication and location (US versus Europe). Also, provide subset laboratory and adverse event analyses for patient populations; e.g., hepatic (focal or generalized disease), renal, cardiac, and CNS disease. This should consider disease severity.

B. Non-Clinical Safety

Although Pharmacology/Toxicology studies were performed with the proposed 0.5 M formulation, the dose multiples that were studied were low. This assessment is based on a body surface area adjustment and the cumulative maximum human dose of 0.2 mmol/kg originally proposed for CNS imaging.

1. Safety Pharmacology Study:

The dose multiples used for safety pharmacology studies ranged from 0.3 to 3.0 times the maximum human dose, and were inadequate for establishing a clear safety profile for MultiHance®. In most of the studies, only one dose was utilized for safety pharmacology evaluation. Evaluation at various dose levels in the same study is necessary for proper comparison and establishment of a dose-response curve. The identified toxicities of concern were EEG slowing, motor incoordination, convulsions, and death. Adverse effects noted in safety pharmacology studies were attributed to hyperosmolarity. However, most of these studies did not include a hyperosmotic control group to determine if these effects were due to hyperosmolarity. In a few studies where a hyperosmotic control group was included, some of these effects (e.g., slowing of EEG and amplitude) could not be attributed to hyperosmolality as they were not seen with the active control. Additionally, although MultiHance® permeability through a damaged blood brain barrier was low, the dose level tested was too low to assess the risk (i.e., 0.3 x MHD). Also, continuous ECG recording was not performed in these studies and effects on ECG parameters such as QT interval were not reported. Therefore, these studieswere not sufficient to assess potential risk, determine labeling, or risk management approaches for drug effects.

To resolve these deficiencies, conduct a comprehensive safety pharmacology study in monkey because the pharmacokinetic profile is similar to humans. This study must be conducted at various dose levels (at least, three with MTD as the highest dose). The study must include a complete battery of cardiovascular system (including continuous ECG monitoring, QT interval, etc.) and respiratory parameters. A hyperosmotic control group (sucrose/mannitol solution), and at least an Omniscan® control group (to provide a link to the clinical database) must be included for comparison.

Also, conduct *in vitro* electrophysiological studies evaluating effects of MultiHance® on cardiac action potential or potassium channels.

2. Local Tolerance Study:

The local tolerance study histological evaluation at eight days after MultiHance® administration revealed reddening, thickening, inflammatory cell infiltrates, eschare, and larger areas of necrosis. These findings were qualitatively more severe than with the Magnevist® control, and were not produced by the hyperosmolar control. The study did not include an evaluation at earlier time points. These findings suggest that local extravasation or prolonged intravenous exposure to MultiHance® may lead to thrombosis or phlebitis.

To resolve this deficiency, conduct a local tolerance study (intravenous, paravenous, and intramuscular administration) with histological evaluation at earlier time points (e.g., 24 hours) and at later time points, until the local adverse effects are resolved. Also, MultiHance® is proposed for direct bolus or infusion. The study must include the rates of infusion on tolerance.

3. Genotoxicity Study:

In vivo micronucleus assay in rats was carried out using intraperitoneal (5 mmol/kg) rather than the intended intravenous route. Also, the dose level used in this study was inadequate.

In order to resolve this deficiency, an *in vivo* micronucleus assay using the intravenous administration route and higher dose levels of MultiHance® (MTD) must be conducted.

II. CLINICAL EFFICACY

As per your May 21, 2002, letter, MultiHance® was proposed for magnetic resonance imaging (MRI) contrast enhancement of the central nervous system to *"for intravenous use in MRI to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues"*. The revised CNS dose is proposed as one 0.1 mmol/kg intravenous bolus.

The key studies that were submitted to establish the indications and doses were designed as dose escalation studies that contained several design flaws and resulted in a small number of patients who actually received the proposed dose and imaging regimens proposed in the labeling. The complexity of the dosing regimen and the imaging times tended to obscure the individual dose effects. The image information that led to an assessment was not systematically studied in a manner to minimize bias and subjectivity and to allow replication of study outcomes. Additionally, the actual results of the primary and secondary endpoints were not statistically significant. The details of these and related deficiencies are discussed below.

A. Central Nervous System (CNS) Indication - Adults

Two key adult trials (43,779-9A and 43,779-9B) were identically designed as double-blind, randomized, parallel-group, multicenter studies with three arms: a) MultiHance® at sequential doses of 0.05 and 0.1 mmol/kg; b) MultiHance® at sequential doses of 0.1 and 0.1 mmol/kg; and c) Omniscan® at sequential doses of 0.1 and 0.2 mmol/kg.

A third key study in patients with metastatic disease (B19036/020) was a double-blind, parallel group study of 150 adult patients with known metastatic CNS disease. Patients were randomized to receive one of two dose sequences: either (0.05 + 0.05 + 0.1 mmol/kg) or (0.1+ 0.1 + 0.1 mmol/kg). For all three studies, the dosing interval was approximately 10 minutes.

These studies were not sufficient to establish the proposed dose to visualize lesions. Because of the unknown dose response relationship to the liver and cardiac adverse events, it is important to establish the lowest effective dose. Additionally, the application lacks sufficient information to establish the anatomic detection in an appropriate clinical setting.

Detection: Insufficient data were provided on the prospectively defined methodology and imaging techniques used to document lesion identification.

Visualization of lesions is an anatomic indication. Based on the trial design the most critical information is the number of lesions able to be visualized. The relevant data are in Studies 43,779-9A and -9B (N= 276 total) and Study B19036/020 (N= 150 patients).

As noted in your March 12, 2002, amendment, the lesion to background ratio and signal to noise ratios were similar for the first and second doses of all dosing regimens. Since a dose response was not documented, these data suggest that the lower dose 0.05 mmol/kg should be used.

For the number of lesions, the most relevant data were contained in the metastatic disease Study # B139036/020. In these patients after a single dose of 0.05 mmol/kg or a single dose of 0.1 mmol/kg, depending upon the reader, the number of lesions was similar. Also, although you are not requesting a cumulative dose ——— we noted a trend towards more lesions detected after the second dose of 0.1 mmol/kg. This trend, however, was not statistically significant and appears to vary with the imaging sequence.

In Studies 43,779-9A and -9B, in the patients that received a single 0.1 mmol/kg, there was no statistically significant increase in the number of lesions seen before and after this dose of MultiHance®. In fact, there was no statistically significant increase in the number of lesions after the first and second dose of MultiHance® as well. The number of patients with clinically relevant evaluations (baseline numbers of lesions as 0, 1 or 2) was too small to provide a meaningful evaluation.

Moreover, Study B19036/020 lacked an active control and all studies lacked a truth standard to allow for a within patient assessment of the number of lesions. Thus, the studies lacked a method to confirm the location of the lesions (tracking) and the findings could not be confirmed. The data did not include a subset analysis of findings in the intra-cranial or extra-cranial lesions nor did they include intra-axial and extra-axial data for both the brain and spine. How the readers determined the number and the change in number of lesions seen (reported as more, less or the same) is not evaluable.

The major amendment included one new literature article and one new study. Both studies had small sample sizes and used retrospective or descriptive data results. The literature article reported the results of 22 patients in a retrospective analysis of patients with known CNS metastatic lesions. The new clinical study (BBG/701) evaluated cross over descriptive results of 15 patients with known glioblastoma or metastatic CNS lesions. Because of the small sample sizes and study designs, these data were insufficient to establish efficacy.

Imaging technique: Image acquisition and blinded reader methodology is insufficiently documented to support validity of clinical trials' data and to determine appropriate acquisition methods.

Image acquisition methods were variable and different combinations of sequences were used for blinded reader evaluations between and within the trials. There was no uniformity in the comparative analyses between the image reads, and this was reflected in the

inconsistency and variability of the results for the same endpoint. Specifically, in Studies 43,779-9A and –9B, post-contrast T1 images were not evaluated as an unpaired read as they were in the other CNS trials . These variations in the imaging methodology produced different results. The results seemed to be better with contrast when a single sequence of the pre-contrast image (e.g., pre-T1) was compared with the post-contrast T1 image. But, when additional pre-contrast sequences (e.g., T2 and/or proton density) were included with the T1 as part of the pre-contrast set, the use of MultiHance® added very little benefit and the results were significantly inferior from those that had a single pre-contrast sequence. The submitted analyses did not include details confirming the sequences that constituted the pre-contrast images and, at times, sequences that yielded better results appeared to have been chosen. For example, in Study B19036/020, the readers were allowed to randomly use any of the available imaging sequences. It was not possible to determine if the identified sequences were acquired during imaging, which images and the order of images that were entered into the blinded reader methodology, and finally, which images and sequences were used by the blinded reader to make their conclusions. Therefore, we were unable to the interpret results of the studies.

Endpoints:

The composite score of morphology, internal structure, definition of lesion extent, and separation of tumor from edema encompassed several factors that may be assessed in making a decision about an image. These must be tested separately.

Study population: The enrolled patients were not appropriate to establish the conditions of use in the clinical setting of study that are needed for the drug to be effective.

All enrolled patients had a lesion already identified on computed tomography (CT), a pre-enrollment MRI, or conventional angiography. We acknowledge that there are clinical circumstances when patients with lesions on CT may benefit from a MRI, and there are clinical circumstances when a patient with a non-contrast MRI may benefit from a contrast MRI. However, because the clinical indications for the enrolled patients were not identified, it was not possible to determine if the enrolled population was appropriate to represent the intended population of use. We acknowledge the subset analysis of patients with zero or one lesion at baseline (included in the major amendment). This subset was too small to provide sufficient data to support conditions of use.

In order to address these deficiencies, at least one large, robust study in adults with CNS disease is needed. Based on information to date, the 0.05 mmol/kg single or repeat dose must be included in your study. Patients must be enrolled in an appropriate clinical setting and have well-defined need for MRI contrast. For example, the study would include sufficient numbers of stroke patients with

evidence of hemorrhage on CT who require a follow-up MRI for evolution; multiple sclerosis patients who require MRI to evaluate the lesion features including number of lesions; patients suspected of having metastatic CNS disease who have 0 or 1 lesion on non-contrast MRI who need contrast for image features and the number of lesions; and patients who are suspected of having a primary brain tumor and are evaluated for identification of a lesion and evaluation of features.

B.

In order to address these deficiencies, based on the provision of acceptable adult safety and efficacy data, a new dose finding study is needed to determine if a lower dose (or sequential) dosing regimen is effective in children. Likewise, a PK elimination study is needed in younger patients. If the elimination is different in younger patients, then the appropriate dose and regimen must be established for the different age ranges. The study must include at least — patients in the age ranges of [redacted] plus the range of — years. Transmetallation should be included in the evaluation. All pediatric studies must include laboratory evaluations of bilirubin, liver enzymes, comprehensive cardiac monitoring, and complete urinalyses. In addition, because of the safety concerns identified in this letter, a lower dose of 0.05 mmol/kg may be more appropriate.

[redacted]

Additionally, for each pediatric patient in Study # 43,779-10, provide 1) a table of each patient's PK parameters, 2) a table with plasma concentrations versus time data, 3) a table with urinary excretion data, and 4) graphs for concentration versus time. Also, submit a reanalysis of the available adult pharmacokinetic data as a function of age and gender.

III. CHEMISTRY

A. Drug Substance/Final Intermediate

The application lacks certificates of analysis for the following incoming materials used in the synthesis of BOPTA. [redacted]

B. Drug Product

The application lacks adequate information on the Drug Product. The deficiencies are:

1. — manufacturers of glass vials are identified for the drug product packaging. Provide a primary supplier and an order of alternates in order of preference.

2. Concerning the release specification for pH (6.5 - 7.5), evidence to support the broad relaxation of this specification versus its in-process specification [redacted] must be provided.

3. Concerning the tests for pH and color, the European Pharmacopoeial method is cited. Provide full documentation that the method is equivalent or superior to the USP method. Also provide calibration procedures for both methods.

4. Concerning the test and specification for extractable volume, the submission lacks a method describing the procedure. Describe and validate the method.

5. Both gadobenate [redacted]

   Resolve this deficiency by submitting edited versions of both methods and procedures in which the time limitation is prominently noted.

C. Methods Validation

The application lacks adequate information on the Methods Validation. To address this deficiency, provide the following:

1. General to all methods: The validation of methods lack information on the [redacted] Provide detailed information on the use of different operators to evaluate the robustness of all methods.

2. General to all methods: When a method is validated with specified hardware and equipment, such as an identified HPLC column, it is only considered validated with that particular item, not with an "equivalent" substitute. If a major item in the test is changed, the new component must be validated. Resubmit your Methods Validation section in which all instances of "or equivalent" have been deleted.

3. [redacted]

4. [redacted]

   Report the actual quantitation limit.

5. The application lacks adequate information on the HPLC assay determination for impurities in MultiHance®. To address this deficiency, provide the following:

   a. [redacted]

b. [redacted]

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical 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.

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

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

Within 10 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 314.120. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Medical Imaging and Radiopharmaceutical Drug Products to discuss what further 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 Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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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