(capsule vs. aqueous solution for injection), strength (50 mg, vs. 529 mg/mL), and indications of use (Hodgkin's disease vs. a contrast agent for MRI of Central Nervous System). Additionally, Matulane may be given in daily divided doses whereas Multihance will usually only be administered as a one-time dose. Moreover, the conditions of use (radiology department vs. inpatient or outpatient settings) may also decrease the potential for confusion. Overall, the product characteristics will reduce the potential for medication errors between Multihance and Matulane.

2. Label and Labeling comments:

DMETS made several recommendations in ODS Consult # 01-0140, concerning the label and labeling of Mutihance. We provide those recommendations below for your convenience.

A. CONTAINER LABELS AND CARTON LABELING

1.

2.

3.

4.

B. PHARMACY BULK BOTTLE LABELS and BULK CARTON LABELS

1.

2

3.

C. INSERT LABELING

1.

2.

In summary, DMETS has no objection to the use of the proprietary name, Multihance. However, we do not recommend using the term Multipack on the pharmacy bulk package carton. We recommend implementation of the labeling revisions outlined in number 2 above to ensure the safe use of this product. DDMAC finds the proprietary name acceptable from a promotional perspective.

We consider this a final review. If the approval of the NDAs is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDAs approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Linda Wisniewski
2/10/04 10:30:17 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/10/04 10:35:52 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/10/04 01:39:19 PM
DRUG SAFETY OFFICE REVIEWER

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS, HFD-160

FILING MEETING MINUTES

FDA PARTICIPANTS:

Sally Loewke, M.D., Acting Division Director, HFD-160
Zili Li, M.D., Clinical Team Leader, HFD-160
Robert Yaes, M.D., Clinical Reviewer, HFD-160
Tong Li, M.D., Clinical Reviewer, HFD-160
Yanli Ouyang, Ph.D., Pharm/Tox Reviewer, HFD-160
Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader, HFD-160
Young Moon Choi, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader, HFD-870
Sonia Castillo, Ph.D. Statistical Reviewer, HFD-175
Michael Welch, Ph.D., Biometrics Team Leader, HFD-175
Patricia A. Stewart, Acting Chief Project Manager, HFD-160
Diane C. Smith, R.Ph., Regulatory Health Project Manager, HFD-160

Agenda:

This was the filing meeting for MultiHance (NDAs 21-357 & 21-358). This is a second cycle submission. Each discipline was asked whether the application should be filed. Here are the responses from each disclipine.

Clinical

Clinical recommended filing the application.

Pharmacology/Toxicology

Pharmacology/Toxicology recommended filing the application.

Clinical Pharmacology

Clinical Pharmacology did not have any issues to be addressed by the sponsor in this submission. However, there were some issues with the original NDA that have been resolved successfully prior to this new filing. Clinical Pharmacology will be available to assist the Clinical team, if needed.

Biometrics

Biometrics recommended filing the application

Chemistry

The Chemisty team was not present, but did recommend filing the submission.

Discussion:

- The clinical team noted that in the Agency's May 24, 2002, Approvable Letter, the Agency requested that the sponsor perform at least 1 new robust study. The Agency noted a response to the sponsor's meeting question dated November 18, 2002, stating that a re read is an alternative to the request to the action letter dated May 24, 2002. The sponsor has not done a new study, but has submitted a re-read. The adequacy of the re-read is a review issue and will be addressed in the 74-day letter. The clinical team also noted that the Agency recommended that the sponsor perform a new QTc study. The sponsor has responded by performing a re read of the ECG data.
- Statistics noted that the re-read utilized a comparison of pre versus post images however, this is not considered as a fatal flaw in trial design and will be dealt with in the review. Stats also noted that Study MH-105 did not show a difference between pre and post contrast images with respect to the primary endpoints, this is still a review issue, and will be noted in the 74-day letter
- The Pharm/Tox team noted that the sponsor did submit a new-pre-clinical QTc study that will be reviewed by the team.
- Clinical Pharmacology did not have any issues to be addressed by the sponsor. The sponsor has done the renal and hepatic insufficiency studies as requested in the original NDA, and no new data is in the current submission.

Action Items:

1. Dr. Loewke will discuss with ODE 3 the issue of whether the office concurs with the review team that the NDA is fileable inspite of the sponsor not performing a new robust study.
2. The PM will forward some statistical comments to the sponsor by the close of business addressing the image re-reads.

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/s/

Diane Smith
12/15/03 12:40:12 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-358& 21-358

Bracco Diagnostics, Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
107 College Road East
Princeton, NJ 08540

Dear Ms. Benson:

We acknowledge receipt on October 14, 2003 of your October 10, 2003 resubmission to your new drug application for MultiHance® (gadobenate dimeglumine) injection.

We consider this a complete, class 2 response to our May 24, 2002 action letter. Therefore, the user fee goal date is April 10, 2004.

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

Sincerely,

{See appended electronic signature page}

Patricia Stewart, Acting Chief Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation 160
Center for Drug Evaluation and Research

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/s/

Patricia Stewart
12/4/03 06:09:45 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 19, 2003

To: Melanie Benson	**From:** Diane C. Smith
Company: Bracco Diagnostics	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (609) 514-2539	**Fax number:** (301) 480-6036
Phone number: (609) 514-2254	**Phone number:** (301)827-7510

Subject: Statistical comments to sponsor 111903

Total no. of pages including cover: 2

Comments:

Document to be mailed: • YES ☑ NO

COMMENTS TO SPONSOR
NDA 21-357 & 21-358 MultiHance
November 19, 2003

These comments were drafted while reviewing your NDA resubmission dated October 10, 2003.
Please provide the following requested information by C.O.B. December 10, 2003.

1. We understand that the evaluation of the combined pre- and post-contrast images is what is done in a clinical setting. However, for image technical characteristics, to determine the added benefit of contrast compared to baseline, a pre-contrast versus post-contrast comparison should be the primary analysis, as indicated in your protocol. Please describe the possible reasons that your pre-contrast versus pre- plus post-contrast comparison shows a difference while the pre- versus post-contrast comparison does not show any difference.

2. Please provide primary and secondary efficacy analyses for each of the two studies (43,779-9A and 43,779-9B) included in Study MH-105.

3. Please provide the location in the application of the analysis describing the number of additional lesions seen on the post-contrast image compared to the pre-contrast image. If this is not in the application, please provide for study MH-105, for each of the two studies in study MH-105 (43,779-9A and 43,779-9B), and for study MH-106.

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/s/

Diane Smith
11/19/03 03:27:59 PM
CSO

ADDENDUM TO
DIVISION DIRECTOR'S MEMO TO THE FILE

NDA:	21,357 (Single dose) 21,358 (Pharmacy bulk pack)
DRUG:	MultiHance (Gadobenate dimeglumine) Injection
ROUTE:	Intravenous
MODALITY:	Magnetic Resonance Imaging (MRI)
INDICATION:	Contrast enhancement in CNS
CATEGORY:	1S - original
SPONSOR:	Bracco Diagnostics, Inc.
SUBMITTED:	April 30, 2001
AMMENDMENT:	February 27, 2002 (Major)
PDUFA:	February 28, 2002 (10 month) extended to May 27, 2002
COMPLETED:	May 20, 2002
ATTACHMENT:	Division Director Memo to the File dated February 10, 2002

Background: Bracco Diagnostics submitted an NDA for MultiHance (gadobenate dimeglumine) Injection to enhance magnetic resonance imaging (MRI) of the brain [redacted] The original submission was received April 30, 2001. In February, the review concluded that the application was not approvable. After an end-of -review meeting with the sponsor on February 25, 2002,a major amendment was received on February 26, 2002. This was accepted and extended the PDUFA due date to May 27, 2002. During the extension, several other amendments were received to clarify data. This addendum addresses the additional data and their effect on the regulatory action.

The following list summarizes the February, 2002 assessments:

Microbiology-	Approval of section
Chemistry -	Approvable with minor deficiencies.
Pharmacokinetics -	Approvable with minor deficiencies.
Pharmcology-toxicology-	Not approvable

[redacted]

Several studies did not identify a NOAEL or did not establish the margin of safety because the studied dose multiples were less than the proposed for human dose. The following new studies were requested: Safety pharmacology and special studies of the blood brain barrier, in vitro electrophysiologic study of the cardiac action potential, expanded acute, reproductivity (segment II), in vivo micronucleus study, in vivo study of coagulation parameters, extensive local tolerance to evaluate potential thrombosis, in vivo stability of Gadolinium complex, and clarification on EEG and pancreatic findings.

Clinical - Not approvable

For the proposed indications (CNS , the study design did not confirm the dose effects, the basis of the image interpretations, did not establish the conditions of an appropriate clinical setting, and a confounded image acquisition and blinded reader methodology, and did not comprehensively track lesions.

The study, however, did not establish the features used to make this distinction. To resolve these deficiencies for CNS one large robust study was needed; ;

Clinical safety deficiencies included insufficient subsetting of foreign and US data, insufficient data on QTc intervals and arrhythmias, insufficient data on liver effects, the need for select case report forms, etc. Most of the clinical safety concerns were related to insufficient data and could be addressed by additional information about the existing database or by increased monitoring in future studies.

In response to the teleconference and meeting with the sponsor, additional clinical and pharmacology-toxicology data were submitted in the major amendment. These have been reviewed extensively. Some of the above deficiencies have been resolved; others have not. Specifically, the pharmacology-toxicology reviewers recommend the section as approvable with new studies and labeling. The clinical efficacy recommendation remains not-approvable with the need for one CNS studies with modified dosing recommendations. Based on the new data, however, the concern for effect of MultiHance excretion on bilirubin excretion and possibly liver toxicity has markedly increased.

In considering these recommendations, I agree partially. From an efficacy perspective, since CNS needs only one new confirmatory study, it is considered approvable. Any dose finding background studies would be in preparation for the definitive study.

I. PHARMACOLOGY-TOXICOLOGY:

The following lists the requests identified in the draft action letter of February, 2002. Based on the new data, some of these are resolved. At the end of each section there is a statement to clarify the current action. I agree with the recommendations. Dr Kokate's review and Dr. Laniyonu's team leader comments discuss the assessments. I do not have

any additional comments. [Note as of, May 21, 2002 the sponsor submitted a revision of the dosing recommendations to a maximum of 0.1 mmol/kg. the recommendations are still based on 0.2 mmol/kg.]

1. A comprehensive safety pharmacology study in larger species with pharmacokinetics that are similar to humans. This study must be conducted at various dose levels (with high dose-multiples based on body surface area). The study must include a complete battery of CVS (including continuous ECG monitoring, QT interval etc.), CNS (including EEG), renal, and respiratory parameters. This study must be conducted in unanesthetized animals with a hyperosmotic control group (sucrose/mannitol solution), Magnevist®, and Optimark or Omniscan for comparison purpose. **Still needed.**

2. A safety pharmacology study to evaluate effects of MultiHance® on blood brain barrier (BBB) permeability in BBB damaged animals at clinically equivalent and higher dose levels. **Resolved**

3. An *in vitro* electrophysiological studies evaluating effects on cardiac action potential or potassium channels for MultiHance®. **Still needed.**

4. A systematic expanded acute dose study in a large animal with a pharmacokinetic profile that is more consistent with that of humans. This study must be carried out at various dose levels (at least three and higher dose multiples) and hyperosmotic mannitol/sucrose solution and Magnevist® must be included as comparative controls. Various toxicity parameters must be evaluated 72-hours post-dosing and also after 7/14-days recovery period. **Resolved.**

5. A Segment II reproductive toxicity study in rats using 0.5 M formulation of MultiHance® and at dose levels where maternal toxicity is observed. **Resolved, but discuss in labeling when otherwise approvable.**

6. Conduct an in vivo micronucleus assay using intravenous administration route and higher dose levels of MultiHance®. **Still needed.**

7. Conduct an in vivo study, using clinically equivalent and higher doses of the 0.5 M MultiHance®, to determine the effects of the drug on coagulation parameters and bleeding time. **Resolved**

8. Conduct a more extensive 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 evaluate the rates of infusion on local tolerance. **Still needed.**

9. Provide data to document your conclusion that gadolinium impurities resulted in retention of radioactivity in the bone and that these impurities and retention of radioactivity are not concerns for the to-be-marketed-drug. **Resolved**

10. Provide more information on the EEG flattening effect and describe the activity of the rats during this time. **Resolved but discuss in labeling when otherwise approvable.**

11. Provide data about pancreatic function in the animals in the study. **Resolved.**

II. SAFETY

At the conclusion of the February, 2002 review, the data showed that MultiHance was lipophilic and was engulfed by hepatocytes. This engulfment was the basis of the proposed ability of the drug to [redacted] lesions. Also, there were vacuolizations in the testes and pancreas (other gadolinium products did not have vacuolization in these organs). The clinical studies showed increased bilirubin and liver enzymes in some patients. Additional data on the NDA patients and monitoring in future studies were requested.
In response to the February inquiries, the sponsor submitted literature on the liver and more details on the liver enzymes. In one patient with Wilson's disease the bilirubin and liver enzymes increased 8 fold. In 3 normal volunteers with von Willebrand's disease, the bilirubin levels increased. As discuss further in the clinical section of this memo, the data suggested a predominantly bilirubin excretion defect. In a submitted article[1] MultiHance is eliminated by an ATP dependent, canalicular, multispecific organic anion transporter (cMOAT). This transporter is the same one that is used to eliminate bilirubin. It is additionally used to eliminate organic anions and some highly protein bound drugs (e.g., methotrexate). Based upon the review team discussions with the clinical pharmacology working group on these products, MultiHance may be either binding to cMOAT, a substrate of cMOAT, or an inhibitor of cMOAT. Based on the available data, MultiHance is most apt to be an inhibitor of CMOAT for bilirubin. (See attached e-mails.)

[redacted] Based upon these findings it appears that the competition for the cMOAT resulted in decreased excretion of bilirubin in favor of the gadolinium. In von Willebrand's disease[2] the deficiency in vWF factor results in many patients have a baseline hemolysis. The addition of MultiHance may increase the bilirubin levels. In Wilson's disease, copper is eliminated by the same transferase, therefore, both the bilirubin and copper levels could be adversely effected.

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[1] Von Willebrand's disease occurs presents as three types. Type 1 and 2 are autosomal dominant (1-3% of the population). Type 3 is autosomal recessive (occurs 1/billion births). Most patients have easy bruising and bleeding, but they may not be diagnosed until trauma or surgery. Cecil Textbook of Medicine, 21st Edition,2000, Page 1008-9.

MultiHance may effect other hereditary disorders of bilirubin metabolism; e.g., Dubin Johnson's, Gilbert's, Crigler-Najjar, and Rotor's syndromes. In infants who may have difficulty with bilirubin excretion, the use of MultiHance could dramatically increase the serum levels.

What is less clear is the effect of MultiHance on the increased production of liver enzymes. In patients with isolated effects on bilirubin metabolism alone, the liver enzymes should not increase. In biliary obstruction, the alkaline phosphatase (ALP) and aspartate amino transferase (AST) levels may increase. In a small single dose, and two multidose dog studies increased liver enzymes and histopathologic findings of vacuolization, inflammatory infiltrates and liver necrosis. The sponsor hypothesized that the liver toxicity is related to dose levels and chronic dosing. Mechanistically, the transporter abnormalities are not apt to be related to the liver toxicity.

Clinical safety results: The NDA database revealed variable results in liver enzymes. Some patients had increases and others decrease. The following table summarizes the number of patients with normal baseline bilirubin or liver enzymes that increased 3, 24 and 72 hours after MultiHance. Of these, the 4 outliers are those with vonWillibrand's disease or Wilson's disease described above.

Table 1: Percent of Patients with Normal Baseline that Increased After MultiHance			
Parameter	3 hours	24 hours	72 hours
Total Bilirubin	6 (2%)	8 (1%)	2 (0.5%)
Alkaline phosphatase	2 (1%)	28 (2%)	3 (2%)
AST	3 (1%)	46 (2%)	7 (5%)
ALT	1 (0.5%)	57 (2%)	7 (4%)
*Derived from data tables Vol.9, page 98-108			

In the database of all patients, of those that were elevated at baseline, some became normal after MultiHance. The following table shows the percent of patients whose laboratory values were high at baseline and remained high after dosing.

Table 2: Percent of Patients with High Values Before and After MultiHance			
Parameter	3 hours	24 hours	72 hours
Total Bilirubin	15 (89%)	56 (95%)	32 (89%)
Alkaline phosphatase	64 (90%)	347 (87%)	73 (95%)
AST	50 (86%)	377 (78%)	75 (84%)
ALT	71 (92%)	447 (89%)	44 (88%)
*Derived from data tables Vol.9, page 98-108			

The major amendment included a summary of adverse events in patients with cirrhosis. These patients had a higher reporting rate of pruritis (2.2% versus 0.5%). These data did not include laboratory findings to determine if patients with substantial liver compromise may have more liver enzyme changes.

III. Clinical Efficacy

A. Central Nervous System (CNS) Imaging

As noted in my February 10, 2002 memo, the studies 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. Eligible patients had at least one lesion already identified on a pre-enrollment imaging study.

Study B19036/020 was conducted in patients with metastatic disease as a double-blind, parallel group study of 150 adult patients with known metastatic CNS disease were randomized to receive one of two dose sequences: a) 0.05 + 0.05 + 0.1 or b) 0.1 + 0.1 + 0.1 mmol/kg. Regardless of study, the dosing interval was approximately 10 minutes. Imaging occurred about 5 minutes after dosing.

Although there were variations in protocol design, all eligible patients had known disease on a pre-enrollment imaging study. The type of information that was sought in follow-up MRI studies was not identified. Likewise, the potential loss of information (and thereby, the risk of an incorrect ————) was not evaluated. Also, not evaluated is the relevance of the results in patients in different CNS disease populations; e.g., stroke, primary brain tumor, metastatic disease, demyelinating disease. The primary endpoints were subjective evaluations of the level of ———— (43,779-9A and B) or the ———— (B19036/039). Secondary endpoints were the number of lesions. Also, because of the short dosing interval, the contribution of the preceding doses could not be eliminated. The number of patients with the proposed dosing regimen (0.1+0.1) were small.

In response to the deficiencies, the sponsor submitted one small study (n=15), one ~~literature~~ article (n=13), a metanalysis of the existing data that was submitted to the EMEA, and refocused narratives on the existing database.

The proposed indication is revised to be consistent with that of other gadolinium agents approved for CNS imaging (i.e., for use in MRI to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues).

The following table summarizes the number of patients available for evaluation for the single dose and the cumulative 1st and 2nd doses. The shaded areas represent the proposed single and cumulative dosing groups.

Table 3: Dosing regimens in the Key Studies*					
	Single Dose – 1st Period		Cumulative 1st & 2nd		
Study	0.05	0.1	0.1	0.15	0.2
B19036/20 Metastatic disease	X (N=68	X (N=69)	X (N=68)		X (N=69)
43,779-9A & 9B	X (n=130)	X (N=140)		X (N=140)	X (N=135)
*Derived from Dr. Li's review page 33 & 40 and Bracco's March 12, 2002 amendment					

The following table describes the technical features of lesion to background ratio, and the percent enhancement of signal intensity. These technical features are expected to result in increased lesion detection As shown below, for the single doses, the lesion to background results are comparable to baseline, but with a tighter standard deviation. The cumulative doses are comparable to each other. For the percent enhancement of signal intensity, the results are comparable again. These data were in the original application and do not show a difference between the 0.05 and 0.1 single doses, or between either cumulative dose. The sponsor acknowledged this in the major amendment.

Table 4: Technical Features Before and After MultiHance*					
B19036/20 Metastatic disease	Before Any Dose	Single Dose		Cumulative 1st and 2nd Dose	
		0.5	0.1	0.1	0.2
Lesion to background ratio	43.3 ±31.8	0.40 ±0.09	0.43 ±0.31	0.62 ±0.33	0.64 ±0.40
% enhancement of signal intensity	46.7 ±40.0	70.4 ±42.8	74.5 ±53.7	94.4 ±54.5	88.2 ±60.3
*Derived from Dr. Li's review page 36 and Bracco's March 12, 2002 amendment					

In light of the above findings, the sponsor asserts that the number of lesions increased supports the 0.1 + 0.1 regimen. In all patients, there is a trend towards increasing numbers of lesions after higher cumulative doses. For both doses for patients with one lesion at baseline (n= 25-37 patients, depending upon the reader), for 3 of the 4 readers, the percent increase after the 1st injection is comparable (24-27%). This suggests that the higher dose may be more useful, however, the sample size is not sufficient for confirmation. Additionally, the clinical setting of known lesions is not appropriate to confirm the results.

Study 43,779-9A and 9B compared the 0.05 +0.1 regimen (combined 0.15) to the 0.1+0.1 (combined 0.2) regimens. These data show similarity in the two regimens. 0.2. (See Dr.

Li's review page 43 for details.) Within this study the numbers of patients with malignant brain disease and multiple sclerosis were small (44 and 43, respectively). There is a suggestion that the 3 fold increase from 0.05 to 0.15 may identify more than the 2 fold increase from 0.1 to 0.2. However, these data are not confirmed.

In addition to the above, as noted in Dr. Li's original review, the composite endpoint of the level of ——— findings was identified as problematic in a pre-NDA meeting. These endpoints do not separate the features that guided the blinded readers' decisions. In the major amendment, the sponsor withdrew this from the current proposed use.

Overall, these 3 studies suggest that all 3 doses and regimens are able to detect lesions and allow the blinded readers to make interpretations of some type. The lack of dose response is apt to be related to the small sample size and the low dose multiples in the single and cumulative dosing regimen (i.e., 2 fold and 2 to 3 fold depending upon the comparison). Although the endpoints and methodologies are problematic, the similarity in the results of the approved Omniscan treatment group, [3] (see Dr. Li's original review page 10-12) reveal the proof of concept. This concept is consistent with that of other approved gadolinium contrast agents in the brain. However, because of the design flaws identified in the medical and team leader reviews, the appropriate dose, dosing regimen, imaging sequences and timing have not been confirmed and labeling cannot be developed. At least one large, robust study in adults with CNS disease is needed. This study should prospectively document the dose and dosing regimen in patients who have a clinical indication to identify additional lesions; e.g., metastatic disease patients with zero or one lesion at baseline. Based on the safety and efficacy data identified at this time, the single dose of 0.05 mmol/kg should be studied further.

In this study, patients must be enrolled in an appropriate clinical setting, and have well-defined need for MR contrast. For example, stroke patients with evidence of hemorrhage on CT who require a follow-up MR for evolution; multiple sclerosis patients who require MR to evaluate the lesion features including numbers; patients suspected of having metastatic CNS disease who have 0 or 1 lesion on non-contrast MR 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. In this context, the term "features" includes the following: homogeneity, ring patterns, margins, and technical information to confirm ischemia, edema or tissue.

This should be a cross over study with an approved imaging agent (preferably with Omniscan to justify reliance on the existing NDA database). If it is not a cross over, then a standard of truth is needed to confirm the findings.

[3] One literature study of 22 patients and one new clinical study of 15 patients.

ADM-9

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

C. Miscellaneous

Financial disclosure: Bracco certified that there were not any financial agreements that would bias the application.

ASSESSMENT:

Efficacy: MultiHance has been submitted to provide contrast enhancement in the CNS

MultiHance appears to detect CNS lesions in a range of single and cumulative doses. This hypothesis is shown in 4 studies (the pooled 43,779-9A and 9B, the metastatic disease study, ———————— \. The data, however, do not establish the most appropriate dose for labeling. Moreover, the pharmacodynamic effect of increasing the dose suggests that the 0.05 + 0.1 mmol/kg dose that is not requested may be performing better than the requested regimen. Therefore, one large new study is needed to establish the dosing regimen.

Safety: At the conclusion of the preliminary review several pre-clinical studies and new data were needed to clarify critical areas such as the effect of QTc interval, liver effects, and the potential for thrombosis. Several of the pharmacology-toxicology deficiencies have been resolved. However, the major amendment provided data on the mechanism of liver effects.

MultiHance is excreted by the same transporter (cMOAT) used by bilirubin, organic anions, and some protein bound drugs. This accounts for increases in bilirubin that were identified in NDA patients with baseline hemolysis (von Willebrand's) and with Wilson's Disease. This adverse event can be addressed in labeling by a contraindication/strong warning. Of concern is the potential effect of MultiHance in patients with these disorders who may have concomitant medications that use this pathway as well. New drug-drug interaction studies are needed in an appropriate animal model to determine if specific drugs should be included in the labeling.

MultiHance is engulfed by hepatocytes. In dog studies, high doses were associated with liver infiltrates and necrosis (in 28 day studies). The NDA database did not reveal significant elevations of liver enzymes except in the one patient with Wilson's disease that had the elevated bilirubin. In this patient, the liver enzymes increase 8 fold. At this point, the data point to a primary bilirubin excretion concern. Additional animal studies in a cMOAT deficient model should be done to evaluate the potential of liver toxicity in this disorder. Also, the sponsor is requested to provide a detailed laboratory analysis in all patients with liver disease. This should be analyzed by the degree of liver disease.

Pediatric use has not been established because of the preceding deficiencies in the adult data and the lack of sufficient data in the pediatric study suffers from similar design flaws. Moreover, because of the competitive elimination route with bilirubin, the risk in infants in increased. Further study of the dosing regimen and safety profiles are needed.

ACTION: Not approvable

Letter comments:

1. CNS - one new study
2.
3. Special studies in cMOAT deficient animals for drug-drug interactions and liver toxicity
4. Provide laboratory analysis of liver enzymes in all patient with liver disease. Subset by disease severity
5. Modify the pharmacology-toxicology requests as noted in this memo.
6. Provide other safety data as noted in the original review

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/s/

Patricia Love
5/24/02 05:32:03 PM
MEDICAL OFFICER

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*** TX REPORT ***
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 15, 2002

TO: MS. MELANIE BENSON Director, U.S. Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Bracco Diagnostics	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (609) 514-2539	**Fax number:** (301) 480-6036
Phone number: (609) 514-2254	**Phone number:** (301) 827-7510

Subject: NDAs 21-357 & 21-358: MultiHance

Total no. of pages including cover: 2

COMMENTS: Please find attached the CLINICAL comments to NDAs 21-357 & 21-358: MultiHance. Please provide an official response to the NDAs by 3:30 p.m. (EST), today, May 15, 2002. Thank you.

CLINICAL COMMENTS TO THE SPONSOR

NDA 21-357 & 21-358 **May 15, 2002**

1. Please identify the subjects and provide a table with the number of subjects with an abnormal increase in bilirubin with concomitant increase in one or more liver enzymes.

For example:

		LIVER ENZYME/S ELEVATION			
		2 fold	4 fold	6 fold	8 fold
Bilirubin (value in units)	# of subjects				

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	3468
CONNECTION TEL	916095142539
SUBADDRESS	
CONNECTION ID	
ST. TIME	05/14 08:41
USAGE T	00'26
PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 14, 2002

TO: MS. MELANIE BENSON Director, U.S. Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Bracco Diagnostics	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (609) 514-2539	**Fax number:** (301) 480-6036
Phone number: (609) 514-2254	**Phone number:** (301) 827-7510

Subject: NDAs 21-357 & 21-358: MultiHance

Total no. of pages including cover: 2

COMMENTS: Please find attached the CLINICAL comments to NDAs 21-357 & 21-358: MultiHance. Please provide an official response to the NDAs by 3:30 p.m. (EST), today, May 14, 2002. Thank you.

CLINICAL COMMENTS TO THE SPONSOR

NDA 21-357 & 21-358 **May 14, 2002**

1. Where in the submission we can locate the following:

   For all patients with elevated bilirubin and any liver enzymes, a by patient evaluation of the increases.

   This could be a narrative, a 2 X 2 table, or representation.

Nguyen, Thuy M

From: Raman, Ramesh
Sent: Thursday, May 09, 2002 4:51 PM
Nguyen, Thuy M
Cc: Li, Roger; Love, Patricia Y
Subject: Multihance Telephone Conversation with Sponsor

I had two conversations on the phone with Dr. [redacted] today. Both calls were initiated by Dr. Spinozzi. The first call lasted a few minutes (~ less than 10 minutes- 9:50am to 10:02 am) and the second follow-up call lasted ~ 40 minutes (1:00pm to 1:40pm). The main focus of the conversation was on Multihance. Dr. Spinozzi wanted to highlight the important sections within the several recent submissions particularly with respect to the case report forms. He stated that he wanted to point out the main items within these submissions that he thought were relevant with respect to the recent developments and changes that the company is proposing. I wrote these down and have shared this information with Dr. Li. These specific areas that Dr. Spinozzi identified were as follows:

April 18, 2002 submission- Attachments 2-4, pages 9, 21 and another corresponding page for dynamic imaging (similar to the one on page 9)
May 1st document- Attachment with pages 58-81, page 70; and tables 5,6, and 7 on enhancement pattern. These, identified pages, according to Dr. Spinozzi, were the ones that were copied and attached to the monitors during the blinded reader evaluations.

Thank you.

Ramesh

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 18, 2002

TO: MS. MELANIE BENSON Director, U.S. Regulatory Affairs	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Bracco Diagnostics	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (609) 514-2539	**Fax number:** (301) 480-6036
Phone number: (609) 514-2254	**Phone number:** (301) 827-7510

Subject: NDAs 21-357 & 21-358: MultiHance

Total no. of pages including cover: 2

COMMENTS: Please find attached the CLINICAL comments to NDAs 21-357 & 21-358: MultiHance. Please provide an official response to the NDAs A.S.A.P. or by Monday, April 22, 2002. Thank you.

CLINICAL COMMENTS TO THE SPONSOR

NDA 21-357 & 21-358 **April 18, 2002**

1. Please provide the prospective imaging criteria sheet(s) used by the blinded readers for [redacted] lesions [redacted] and/or classification of lesions [redacted] for both the CNS [redacted] trials. These were the sheets you described at the industry meeting in February 2002.

Appears This Way
On Original

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

/s/

Thuy Nguyen
4/18/02 10:30:23 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-02
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

APPLICANT'S NAME AND ADDRESS

Bracco Diagnostics Inc.
PO Box 5225
Princeton, NJ 08543-5225

3. PRODUCT NAME
MultiHance (gadobenate dimeglumine)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATIC
☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER *(Include Area Code)*
(709) 514-2254

5. USER FEE I.D. NUMBER
4097

6. LICENSE NUMBER / NDA NUMBER
NDA 21-357

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, on reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Melanie Benson Director, US Regulatory Affairs	April 2, 2001

FORM FDA 3397 (5/98)

USER FEE ID # 4097

CHASE MANHATTAN BANK DELAWARE
1201 Market Street
Wilmington, DE 19801

62-2
31

Bracco Diagnostics Inc.
P.O. Box 5225
Princeton, NJ 08543-5225

VENDOR #	CHECK DATE	CHECK NO.
[redacted]	03/27/01	086426

*Void after 120 days

PAY ***Three hundred nine thousand six hundred forty seven and 00/100 Dollars***

CHECK AMOUNT
$309,647.00

TO THE ORDER OF
FOOD AND DRUG ADMINISTRATION
PO Box 360909
Pittsburgh, PA 15251-6909

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Bracco Diagnostics Inc.
PO Box 5225
Princeton, NJ 08543-5225

2. TELEPHONE NUMBER *(Include Area Code)*

(709) 514-2254

3. PRODUCT NAME
MultiHance (gadobenate dimeglumine) Multidose

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO NDA 21-357
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER
4107

6. LICENSE NUMBER / NDA NUMBER
NDA 21-358

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, on reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
M Benson	Melanie Benson Director, US Regulatory Affairs	April 2, 2001

FORM FDA 3397 (5/98)

USER Fee ID # 4097

Bracco Diagnostics Inc.
P.O. Box 5225
Princeton, NJ 08543-5225

CHASE MANHATTAN BANK DELAWARE
1201 Market Street
Wilmington, DE 19801

62-26
311

VENDOR #	CHECK DATE	CHECK NO.
	03/30/01	086430

Void after 120 days

PAY ***One hundred fifty four thousand eight hundred twenty three and 00/100 Dollars***

CHECK AMOUNT
$154,823.00

TO THE ORDER OF FOOD AND DRUG ADMINISTRATION
PO Box 360909
Pittsburgh, PA 15251-6909

Appears This Way
On Original

MEMORANDUM OF TELECON

DATE: February 27, 2002

APPLICATION NUMBER: NDA 21-357 and 21-358, Multihance (gadobenate dimeglumine injection)

BETWEEN:

Name: Melanie Benson, Director, US Regulatory Affairs
Andrew Betournay, Group Regulatory Affairs Director
Phone: 609-514-2254
Representing: Bracco Diagnostics Inc.

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Patricia Y. Love, M.D., M.B.A., Division Director
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The major amendment submitted after the sponsor was informed the application was to receive a non approvable action.

During a teleconference regarding another product, Bracco asked impromptu questions about Multihance and whether the major amendment was accepted for review.

The sponsor was informed that the Agency has decided to accept the major amendment in this review cycle and has extended the review clock 3 months past the original PDUFA date. The Agency explained that this did not necessarily mean that the non-approvable decision would be changed, only that the FDA is committing to review the additional information.

The sponsor stated that the amendment contains 1) all supporting literature articles2) information the blinded readers used which was on the view box and not on the CRF 3) toxicology study with a subset evaluation and 4) the submission prepared for the UK.

The sponsor stressed the importance of the product to the company and asked that they be informed whom to call to check on the review's progress. The Agency said Kaye Cho would let them know who would be the project manager. Also, the Agency said that a subset analysis may be necessary. The sponsor said they are willing to do whatever is necessary to move forward with this product.

Patricia A. Stewart
Regulatory Project Manager

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

/s/

Patricia Stewart
3/19/02 03:30:27 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

JAN 10 2002

Dear [redacted]

On November 5, Mr. Mike M. Rashti and H. W. Ju, M.D., representing the Food and Drug Administration (FDA) met with you to review your conduct of clinical studies of the investigational drug MultiHance® (gadobenate dimeglumine injection), for which you are a contract research organization for the sponsor Bracco Diagnostics, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to ensure the proper conduct of clinical studies for submission to FDA, and the protection of the rights and welfare of human subjects.

This inspection focused on the following three studies:

[redacted]

Protocol # 43,779-9A: "A Clinical Comparison of the Safety and Efficacy of MultiHance (Gadobenate Dimeglumine Injection) and Omniscan (Gadodiamide Injection) in Magnetic Resonance Imaging in Patients Highly Suspected of Having Lesions of the Central Nervous System,"

Protocol # 43,779-9B: "A Clinical Comparison of the Safety and Efficacy of MultiHance (Gadobenate Dimeglumine Injection) and Omniscan (Gadodiamide Injection) in Magnetic Resonance Imaging in Patients Highly Suspected of Having Lesions of the Central Nervous System."

The above studies are designed to evaluate the efficacy of MultiHance using as a contrast enhancing agent in the evaluation of [redacted] CNS lesions.

From our evaluation of the inspection report, the documents submitted with the report, and your oral responses to the inspectional observations, we conclude that you did adhere to pertinent Federal regulations and /or good clinical investigational practices governing sponsor responsibilities for the conduct of clinical investigations and the protection of human subject.

We appreciate the cooperation shown Mr. Rashti and Dr. Ju during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-160 Doc. Rm. NDA 21-357/358, IND#43,779
HFD-160 Review Div. Dir.
HFD-160 MO LI
HFD-160 PM MOORE
HFD-46/Reading File
HFD-46/Chron File
HFD-46/CIB File 10522
HFD-46/CIB Reviewer/JU
HFR-PA150 DIB EAGAN
HFR-PA150 BIMO MONITOR RASHTI
HFR-PA1530 FIELD INVESTIGATOR RASHTI

FEI:

Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-W warning letter
_____6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted: None

Drafted/hwj/12/21/01
Reviewed/JRM:12/27/01
Final:jau:1/3/02

Note to Review Division and DSI Recommendation:

This inspection was covered by the Inspection of
No deficiency was noted. The data appear acceptable for use in support of the application.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 10 2002

Ms. Melanie Benson
Director, US Regulatory Affairs
Bracco Diagnostics Inc.
107 College Road
Princeton, New Jersey 08540

Dear Ms. Benson:

Between November 5 and 9, 2001, Mr. Mike M. Rashti and H. W. Ju, M.D., representing the Food and Drug Administration (FDA) met with you to review clinical studies of the investigational drug MultiHance® (gadobenate dimeglumine injection), for which _____ is a Contract Research Organization for the sponsor Bracco Diagnostics, Inc. _____ hosted the inspection. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections, designed to ensure the proper conduct of clinical studies for submission to FDA, and the protection of the rights and welfare of human subjects.

This inspection focused on the following four studies:

_____

_____

Protocol # 43,779-9A: "A Clinical Comparison of the Safety and Efficacy of MultiHance (Gadobenate Dimeglumine Injection) and Omniscan (Gadodiamide Injection) in Magnetic Resonance Imaging in Patients Highly Suspected of Having Lesions of the Central Nervous System,"

Protocol # 43,779-9B: "A Clinical Comparison of the Safety and Efficacy of MultiHance (Gadobenate Dimeglumine Injection) and Omniscan (Gadodiamide Injection) in Magnetic Resonance Imaging in Patients Highly Suspected of Having Lesions of the Central Nervous System,"

_____

_____

The above studies are designed to evaluate the efficacy of MultiHance using as a contrast enhancing agent in the evaluation _____ CNS lesions.

From our evaluation of the inspection report, the documents submitted with the report, and your oral responses to the inspectional observations, we conclude that you did adhere to pertinent Federal regulations and /or good clinical investigational practices governing sponsor responsibilities for the conduct of clinical investigations and the protection of human subject.

We appreciate the cooperation shown Mr. Rashti and Dr. Ju during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-160 Doc. Rm. NDA 21-357/358, IND#43,779
HFD-160 Review Div. Dir.
HFD-160 MO LI
HFD-160 PM MOORE
HFD-46/Reading File
HFD-46/Chron File
HFD-46/CIB File 10522
HFD-46/CIB Reviewer/JU
HFR-PA150 DIB EAGAN
HFR-PA150 BIMO MONITOR RASHTI
HFR-PA1530 FIELD INVESTIGATOR RASHTI

FEI: [redacted]

Field Classification: NAI
Headquarters Classification:
__X__1)NAI
_____2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-W warning letter
_____6)OAI NIDPOE letter

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted: None

O:\ju\benson.doc
drafted/hwj/12/21/01
reviewed/JRM/1/7/02
final:jau/1/8/02

Note to Review Division and DSI Recommendation:
The case report forms (CRFs), Data Transmittal Forms (DTFs), electronic case report forms (eCRFs) and screen shots from randomly selected subjects for the above 4 studies were compared with the sites original CRFs and the data listings, no discrepancy was noted. The data appear acceptable for use in support of drug claims.

ADM-10

3 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

_____

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-400)

DATE RECEIVED: 06/27/01	**DUE DATE:** 01/07/02	**DMETS CONSULT #:** 01-0140

TO: Patricia Y. Love, MD
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

THROUGH: James Moore
Project Manager
HFD-160

PRODUCT NAME: Multihance (gadobenate dimeglumine injection) **NDA #** 21-357,21-358	**NDA Sponsor:** Bracco Diagnostics, Inc.

SAFETY EVALUATOR: Marci Lee, Pharm.D.

SUMMARY: In response to a consult from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, Multihance, to determine the potential for confusion with approved proprietary and generic names as well as pending names.

DMETS RECOMMENDATION: DMETS has no objection to the use of the proprietary name, Multihance. However, we do not recommend the use of "Multipack" in the tradename for the pharmacy bulk bottle. DMETS recommends revising the labels and labeling as outlined in section III of this review. DMETS recommends consulting the USAN Council for evaluation of the established name, gadobenate dimeglumine.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 10, 2001

NDA NUMBER: 21-357, 21-358

NAME OF DRUG: Multihance (gadobenate dimeglumine injection)

NDA HOLDER: Bracco Diagnostics, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products for assessment of the proposed proprietary drug name, Multihance, regarding potential name confusion with other proprietary and/or generic drug names.

PRODUCT INFORMATION
Multihance contains 529 mg of gadobenate dimeglumine per milliliter and is indicated for intravenous use in adults [redacted] as an adjunct to magnetic resonance imaging (MRI) of the central nervous system (brain, spine, and surrounding structures).
The recommended dosage for Multihance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion or bolus injection. [redacted] Imaging can be started up to 20 minutes after the injection of Multihance. Multihance will be available as 5 mL, 10 mL, 15 mL and 20 mL single dose vials as well as 50 mL and 100 mL pharmacy bulk bottles (Multihance Multipack).

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names, which sound or look similar to *Multihance* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[iv]. The Saegis[vi] Pharma-In-Use database was

[i] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2001).
[ii] Facts and Comparisons, 2001, Facts and Comparisons, St. Louis, MO.
[iii] The Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 1998-2001, and online version of the FDA Orange Book.
[iv] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=ki4gp0.1.1
[vi] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, *Multihance*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Four proprietary names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Multihance. These products are listed in the table, along with the dosage forms available and usual FDA-approved dosage.

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other**
Multihance	**gadobenate dimeglumine injection**	**0.1 mmol/kg (0.2 mL/kg) administered as a rapid infusion or bolus injection**	
ProHance	gadoteridol injection 279.3 mg/mL	0.1 mmol/kg (0.2 mL/kg) administered as a rapid infusion or bolus injection	Sound-alike
Multitrace	Combination of chromium, copper, iodine, manganese, selenium and zinc. 1 mL single dose vial 10 mL multi dose vial	Intravenous nutritional therapy component. Single dose is 1 mL.	Sound-alike and Look-alike
Ellence	epirubicin injection 2 mg/mL	The recommended starting dose of epirubicin is 100 to 120 mg/m^2 by IV infusion and is given in repeated 3- to 4-week cycles. The total dose of epirubicin may be given on day 1 of each cycle or divided equally and given on days 1 and 8 of each cycle.	Sound-alike
Lumenhance	manganese chloride tetrahydrate	*Currently not available in the United States.*	Sound-alike

* Frequently used, not all inclusive

2. DDMAC did not object to the use of the name, Multihance.
3. The expert panel recommended review of the established name, gadobenate dimeglumine.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology

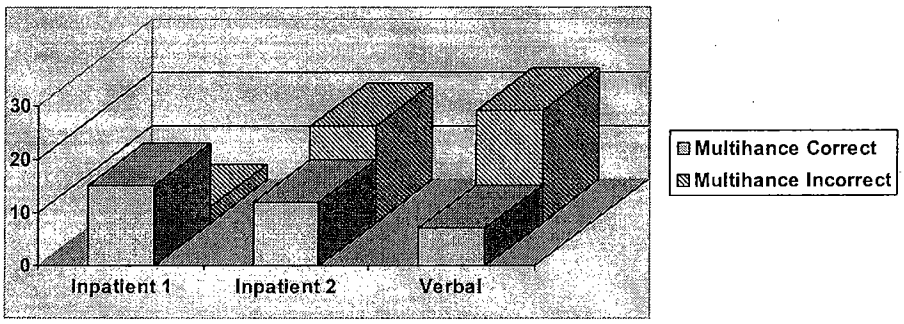
Three separate studies were conducted within FDA to determine the degree of confusion potential of Multihance with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 113 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. Two DMETS staff members wrote an inpatient order, each consisting of a combination of marketed and unapproved drug products and prescription for Multihance. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each participant was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	**VERBAL PRESCRIPTION**
Multihance	
Inpatient 1: Multihance 10 mL IV now	*Verbal:* Multihance 10 mL IV now Dispense 10 mL
Inpatient 2: Multihance 10 mL IV now	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Multihance" response	Other response
Written: Inpatient 1	36	18 (50%)	15 (83%)	3 (17%)
Written Inpatient 2	38	30 (79%)	12 (40%)	18 (60%)
Verbal:	39	28 (72%)	7 (25%)	21 (75%)
Total:	113	76 (67%)	34 (45%)	42 (55%)



Among the two written prescription studies, 21 of 48 (44 %) participants interpreted the name incorrectly. Incorrect interpretations included *Multinance, Multivance, Multiharce, Murtiharce, Multinarce, Muliharce,* and *Multisource.*

Among the verbal prescription study participants for Multihance, 21 of 28 (75 %) participants interpreted the name incorrectly. However, none of the incorrect responses were marketed products and all of the incorrect responses were phonetically equivalent to Multihance. Most participants interpreted the name as *Multihans and Multihands.* Other incorrect responses were *Multihants, Multihand* and *Multihanse.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Multihance, the primary concerns raised by the expert panel were related to look-alike and sound-alike names that already exist in the US marketplace. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Multihance could be confused with ProHance, Multitrace or Ellence. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names.

ProHance was identified to have potential for sound-alike confusion with Multihance. Although these names share the "-hance" ending, their similarity is minimized by the different beginning sounds, "Pro-" and "Multi-". The sound-alike similarity is further decreased because these names have a different number of syllables. However, both products are used for imaging studies of the central nervous system ———, while ProHance is also used for breast, musculoskeletal and soft tissue. Multihance and ProHance have the same sponsor, which may result in look-alike similarity for packaging and label design. ProHance is available as 5 mL, 10 mL, 15 mL, and 20 mL vials and 10 mL or 17 mL prefilled syringes. There is some overlap in the volumes available for Multihance, which may increase potential for confusion. The usual dosing for both products is 0.1 mmol/kg, further increasing likelihood for confusion. ProHance is also stored at room temperature, like Multihance and these products would likely be stored near each other because they are both imaging agents. Finally, they share the same prescribers and patient population. Although many factors overlap for these products, the sound-alike similarity is minimal.

Multitrace (actual name is Multitrace-5) was identified to look and sound similar to Multihance. However, there is little overlap in the clinical context of use between these products. Multitrace is a component of intravenous nutritional therapy. It is likely ordered with total parenteral nutrition (TPN). Depending on how a pharmacy is organized it is possible that Multitrace and Multihance could be near each other on shelf. However, it is more likely that Multitrace is stored with the other ingredients used to make the TPN solutions and Multihance is stored with other radiological products. In many institutions, the TPN solutions are made by a facility outside of the pharmacy department, which may further decrease the likelihood for confusion.

multitrace multihance multitrace multihance

Sound-alike similarity was identified with Ellence, which is an antineoplastic agent used as adjuvant therapy following primary resection of primary breast cancer. Ellence is available as 50 mg/25 mL or 200 mg/100 mL. The recommended starting dose of epirubicin is 100 to 120 mg/m^2 by IV infusion and is given in repeated 3- to 4-week cycles, unlike Multihance. The total dose of epirubicin may be given on day 1 of each cycle or divided equally and given on days 1 and 8 of each cycle. Ellence is typically administered as part of a regimen with cyclophosphamide and 5-fluorouracil, decreasing the likelihood for confusion with Multihance. In an effort to decrease medication errors, some institutions prohibit verbal orders for antineoplastic agents, which may also help to decrease the risk for confusion in this case.

The expert panel also recommended evaluation of the confusion potential for the established name of Multihance, gadobenate dimeglumine injection. There may be potential for confusion between gadobenate dimeglumine and gadopentetate dimeglumine (Magnevist). Both agents are used for imaging studies and have the same dosing, storage, prescribers and patient population. The indications for use of gadobenate dimeglumine and gadopentetate dimeglumine are also similar. They are both available in 5 mL, 10 mL, 15 mL and 20 mL single dose vials as well as a 100 mL pharmacy bulk bottle. While the proprietary names, Magnevist and Multihance are not similar, their established names and clinical context of use are almost identical and may contribute to medication errors. Finally, gadopentetate is likely to be familiar to practitioners because it has been marketed in the US since 1988.

Since Multihance is currently marketed in Sweden, Germany, Austria, Belgium, Italy and the Netherlands, we searched for any reports of confusion with Magnevist. A search of the FDA Adverse Event Reporting System *(AERS)* database was conducted for all post-marketing safety reports of medication errors reported for the active ingredient terms "GADOBENATE DIMEGLUMINE" and "GADOPENTETATE DIMEGLUMINE". We used the MedDRA Preferred Term, MEDICATION ERROR in our search to determine if there are any existing problems relating to confusion between these drug products. This search strategy retrieved five medication error reports, all of which were related to GADOPENTETATE DIMEGLUMINE. However, none of the reports described an error that involved a mix-up of gadobenate dimeglumine and gadopentetate dimeglumine.

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Multihance	**Gadobenate dimeglumine injection**	**0.1 mmol/kg (0.2 mL/kg) administered as a rapid infusion or bolus injection**	
Magnevist	Gadopentetate dimeglumine injection	0.1 mmol/kg (0.2 mL/kg) administered as intravenously at a rate of 10 mL per 15 seconds	Sound-alike confusion between **established names**

In addition to gadopentetate dimeglumine, gadodiamide, gadoteridol, and gadoversetamide also use the USAN stem *gado-*, which is used for gadolinium derivatives.

In addition to safety concerns associated with the proprietary and established names, there is potential for confusion related to the packaging of Multihance. Multihance is supplied as 5 mL or 10 mL as a single dose in a 10 mL vial and 15 mL or 20 mL as a single dose in a 20 mL vial. Having different volumes in a single vial size can contribute to medication errors, especially if the vial labels are not adequately differentiated for each dosage strength. One way this happens is at the point of restocking items returned to the pharmacy. While holding a 10 mL vial, you may not notice it actually contains 5 mL and restock the item with the 10 mL/10 mL vials.

The name Multihance Multipack may connote a multidose vial in the minds of some practitioners. This may be error prone since the intention for use of the bulk bottle is for the vial contents to be removed at once (or within eight hours). Unlike other products available in conventional multidose or bulk containers, Multihance contains no preservatives.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft carton labeling, draft container label and draft insert labeling for Multihance and Multihance Multipack, DMETS has identified several areas of possible improvement, in the interest of minimizing potential user error.

A. CONTAINER LABELS and CARTON LABELING

1.

2.

3.

4.

5.

6

B. PHARMACY BULK BOTTLE LABELS and BULK CARTON LABELS

1.

2.

C. INSERT LABELING

1.

2.

3

IV. RECOMMENDATIONS

A. DMETS has no objection to the use of the proprietary name, Multihance. However, we recommend that the name not favor the "Multi-" in the displayed name.
B. DMETS does not recommend the use of "Multipack" in the tradename for the pharmacy bulk bottle.
C. DMETS recommends implementation of the above labeling revisions.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3231.

/S/

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Marci Ann Lee
1/8/02 08:11:37 AM
PHARMACIST

Carol Holquist
1/8/02 08:16:57 AM
PHARMACIST

Jerry Phillips
1/8/02 08:40:10 AM
DIRECTOR

Richard G. Barr, M.D., Ph.D.
Northeastern Ohio Radiology Research/Education Fund
1044 Belmont Avenue
Youngstown, Ohio 44501

Dear Dr. Barr:

Between August 21 and 27, 2001, Ms. Karen M. Kondas representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #43,779-9A) of the investigational drug, gadobenate dimeglumine injection (MultiHance®), performed for Bracco Diagnostics Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent Federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Ms. Kondas during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

FEI: [redacted]
Field Classification: VAI
Headquarters Classification:
__X__1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

If Headquarters classification is a different classification, explain why:
Deficiencies noted: All the citations are related to IRB rather than clinical review.
____inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-160 Doc.Rm. NDAs#21-357 & #21-358
HFD-160 Review Div.Dir.
HFD-160 MO Li
HFD-160 PM Moore
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP/CIB File #10455
HFD-46 GCP/CIB Reviewer Ju
HFD-46 CSO Prager
HFR-CE450 DIB Heppe
HFR-CE450 Bimo Monitor Eastham
HFR-CE4525 Field Investigator Kondas
r/d: hwj/09/10/01
reviewed:jrm:9/13/01
f/t:jau:9/13/01
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Note to Rev. Div. M.O.

35 subjects were enrolled and 34 subjects completed the study. Six (6) subject's records were completely reviewed. CRFs were compared to the raw data and the adverse event. All adverse events were reported to the sponsor. All of the subjects signed consent forms before enrolling in the study. The data may be used in support of the drug application.