CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

MEDICAL REVIEW

HFD-160 Medical Officer's Review

NDA 21-357 (MultiHance)

Letter Date:	August 27, 2004
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium MRI Contrast Agent
Route:	Intravenous as rapid bolus or infusion
Indication:	MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain spine or associated tissues.
Formulation:	[redacted]
Dose:	CNS Adult- 0.1 mmol/kg (0.2 ml/kg)
How Supplied	5, 10, 15 and 20 ml single dose vials

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Executive Summary

I. Recommendations

A. Recommendations on Approvability

Recommendation: Approval

This NDA should be approved for the indication of CNS imaging at a dose of 0.1mmol/kg.

II Summary of Clinical Findings

A. Brief Overview of Clinical Findings

B. Efficacy

- There is a statistically significant difference at the lesion level between pre-dose and paired reads for all of the three primary outcome variables, for all three readers in the re-read of the two US Phase 3 pivotal trials (43,779-9A and 43,779-9,B, Reread MH-105(referred to as study A) in which patients with both tumors and non-tumors were included
- There is a statistically significant difference at the lesion level between pre-dose and post dose reads for all of the three primary outcome variables, for all three readers in the re-read of the single European supportive trial (B19036/020, Reread MH-106 (referred to as study B in which all patients had brain metastases
- These results are consistent with the hypothesis that non-malignant lesions will have a lower score on the post dose than on the pre dose scans because many non malignant lesions do not enhance, are not seen on the post dose scans and therefore receive an imputed score of 0 for all 3 visualization variables.
- Reanalysis of the data has shown that in MH-105, data for patients with tumors, there is a statistically significant difference in favor of the post dose scans for all 3 readers for all three visualization variables between pre dose

and post dose at the lesion level. For patients with non-tumor lesions, in MH-105, the statistically significant difference at the lesion level between pre-dose and paired reads for all of the three primary outcome variables, for all three readers, can be accepted as proof of efficacy.

- Efficacy has been demonstrated.

C. Safety

- A safety update has been submitted for completed and ongoing clinical trials and for post marketing surveillance
- The incidence of adverse events, serious adverse events and deaths, found in the safety update, is comparable to the incidence with other MRI contrast agents and with the incidence seen in the previous review cycle
- [redacted]

D. Dosing

- The results demonstrate superiority of the 0.1 mmol/kg dose over the [redacted] dose for at Approval should be granted for the 0.1mmol/kg dose.

E. Special populations

- The serum half-life is increased in renally compromised and dialysis patients. There is no toxicity associated with this increased half-life.
- [redacted]

Clinical Review

I Introduction and Background

A. Drug

1. Name

A. Generic: gadobenate dimeglumine

B. Trade : MultiHance, MultiHance Multipack

Reviewer's Comment: MultiHance Multipack is the same drug substance at the same concentration as MultiHance. MultiHance is supplied in 5, 10, 15 and 20 ml single dose vials. MultiHance Multipack is supplied in 50 ml and 100 ml rubber stoppered glass bottles. The concentration is ——— *' in both cases. Dosing is the same. The use of the name MultiHance Multipack may mislead some people to believe that the drug in the glass bottles is different than the drug in the single dose vials. The difference in packaging can be handled in the "how supplied" section of the label. The sponsor has made a business decision to make MultiHance available in multi-dose bottles. There is no medical advantage in using this type of packaging. In fact there is a greater risk of contamination with the multi-dose bottles. In this review this submission will be regarded as a single NDA for MultiHance*

2. Class: Gadolinium paramagnetic MRI contrast agent

B. State of Armentariun for Indications

There are four other gadolinium based MRI contrast agents approved in the US for CNS imaging:

- Magnevist
- Prohance
- Omniscan
- Optimark

The sponsor has submitted no data that would support a claim of superiority of MultiHance over any of these agents

C. Important Milestones

April 27, 2001

NDA 21-357 and NDA 21-358 for MultiHance and MultiHance Multipack was received. Indications for — CNS ————————

September 13, 2001

Safety Update Received

February 25, 2002

Industry Meeting Sponsor requests to efficacy update as an amendment before PDUFA date of 2/27/02

February 26,2002

Efficacy amendment received

May 24, 2002

The agency in the action letter of May 24, 2002 informed the sponsor that the application was approvable for the CNS indication. It was stated in the action letter that in order to correct the deficiencies in the submission, at least one robust efficacy study in adults with CNS disease, a placebo controlled cardiac safety study in patients at higher than the indicated dose to study QT effects, a drug interaction study, a preclinical cardiovascular study at doses up to the MTD and a reanalysis of previously submitted data would be required.

August 28,2002

Industry Meeting with Bracco to discuss safety and efficacy concerns raised in the action letter of May 24, 2002 and sponsor's action plan. At that meeting the division stated that it is not clear that a blinded re-read alone could resolve the study design flaws discussed in the action letter. The division reiterated that its request is for new studies (meeting minutes 8/28/02 industry meeting p7-8)

September 18, 2002

Action plan to address deficiencies discussed in the action letter of May 24, 2002 submitted by sponsor in response to the meeting of 8/28/02

November 15, 2002

Additional comments faxed to sponsor

The division stated: "the potential for bias exists when visualization is scored from a paired image set. We recommend that the post dose images are evaluated separately for the visualization endpoints.....a paired read may be carried out for secondary analysis" The studies should be able to demonstrate a clinically significant increase from each pre-contrast visualization score. A 15% average increase, as stated in the current protocol needs to be justified.

December 3, 2002

Internal meeting to prior to industry T-con of 12/11/02

December 11, 2002

Industry T-con: The division stated " you need to show clinically and statistically significant improvement from the unenhanced to the enhanced image sets improvement in each of the co-primary endpoints

October 10, 2003

Complete Response to Action Letter of May 24, 2002 is submitted

April 14, 2004

In action letter dated April 14, 2004 the application is found Approvable for intravenous use in magnetic resonance imaging (MRI) of the central nervous system (CNS). The letter made the following points:

- A pre vs. paired read comparison was not the prospectively chosen primary outcome variable and may be appropriate for a visualization [redacted] endpoint
- MH-105 was the only study with both malignant and non malignant lesions
- Study MH 105 incorporated T1, T2 and proton density PD) images while study MH 106 included T1 and T2 images only
- At least one adequate and well controlled study in adults with a variety of CNS diseases is needed to support a visualization claim
- In study B9036/36 80 pediatric patients were studied. Only 29 pediatric patients with known CNS tumor were submitted for reread under study MH 112

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July 9, 2004

Type A Industry Meeting.

The sponsor and their consultants made the following points;

- Proton density images are not used in routine clinical practice for MRI evaluation of metastatic CNS lesions
- The proportion of spinal exams to cranial exams in MH-105 was comparable to the proportion seen in clinical practice.
- Non- malignant lesions do not enhance and may not be seen on post dose T1 images at all. If the lesion was not seen it would receive an imputed score of 0 for all 3 visualization endpoints. In a Pre vs. post read these non-visualized non-enhancing lesions would bring down the overall post-dose score so that a statistically significant difference in scores between pre dose and post dose reads would not be seen. This problem was not realized by the sponsor until the studies had been performed and analyzed. On the other hand if there were a statistically significant difference were seen, at the lesion level between pre and paired reads, this would prove that the enhanced images were making a non-negligible contribution to the visualization endpoints. FDA agreed to consider sponsor's presentation and to provide a response to the sponsor

July 24, 2004

A letter was sent by FDA to the sponsor making the following points:

- We find that the spectrum of disease for adult CNS (brain and spine) imaging is adequate
- We agree that when lesions do not enhance, the lack of enhancement may be of clinical value and should not necessarily be considered a drug failure.
- If the pre vs. post and pre vs. paired analysis of tumor only patients and the pre vs. paired sub-analysis of MH-105 non-tumor patients shows efficacy for the three visualization endpoints the sponsor may submit labeling to be negotiated for the general CNS anatomic/structural delineation indication.

August 27, 2004

Complete response to action letter of April 14, 2004 Submitted

This complete response is the subject of this review.

D. Other Relevant Information"

MultiHance has been approved in Austria, Belgium, Czech Republic, Germany, Denmark, Ireland, France, Greece, Italy, Israel, Luxembourg, The Netherlands, Portugal, Sweden, and the United Kingdom. Approximately [redacted] single dose vials have been sold (safety update, this submission) . No country has withdrawn approval.

E. Important Issues with Related Agents

No reports of Torsade de Pointes arrhythmias have been made of any Gadolinium based MRI contrast agent including MultiHance

II Clinically relevant Findings from other Disciplines

A. Pharmacology-toxicology (see Pharm-Tox review)

Three complementary pre-clinical pharmacology-toxicology cardiovascular safety studies were conducted primarily to address the concern of the risk of QT prolongation associated with MultiHance. These studies were reviewed during cycle 2 and showed no clear evidence that QT prolongation was associated with MultiHance

III Pharmacokinetics

A. Pharmacokinetics

1. Distribution half –life 0.09-0.6 hr
2. Elimination half-life 1.2-2 hr
3. Elimination route 78-96% Urine, 0- 7.2% feces
4. Hepatic impairment had no effect on pharmacokinetics
5. Renal impairment increased serum half-life

6. MultiHance is dialyzable
7. Drug-drug interactions were not studied.

B. Pharmacodynamics

MultiHance is a paramagnetic gadolinium based MRI contrast agent whose efficacy is based on its ability to increase signal intensity on T1 weighted MRI images and on its ability to leak out through the damaged blood-brain barrier associated with specific types of lesions in the brain.

IV Description of Clinical Data and Sources

A. Overall Data

Data from the previous submission has been reviewed in the previous medical officer reviews.

1. No new clinical trials were reported in this submission.
2. A reanalysis of efficacy data with separate analyses of tumor and non tumor patients, who received MultiHance in MH 105 was submitted.
3. A safety update containing safety data from newly exposed subjects from January 1, 2003 through June 30, 2004 has been submitted. Cumulative safety data through June 30, 2004 has been reanalyzed.

B. Pivotal Clinical Trials:

43,779-9A, 43,779-9B - Re-read as MH-105 (referred to as study A in the label)

B19036/020 reread as MH-106

No new efficacy data has been submitted in this submission The resubmission consists of a reanalysis of data from MH-105.

C. Postmarketing Experience Update

MultiHance has been approved in 16 foreign countries, Austria, Belgium, Czech Republic, Germany, Denmark, Ireland, France, Greece, Italy, Israel, Luxembourg, The Netherlands, Portugal, Sweden, and the United Kingdom. Approximately [redacted] single dose vials have been sold, which is a good estimate of the number of patients who have been dosed. No country has withdrawn approval. There have been no reported cases of Torsade de Pointes arrhythmias associated with MultiHance

V Clinical Review Methods

A. Overview of Material Consulted in Review

Four volumes containing the sponsor's reanalysis of efficacy data from study MH-105 and safety update. Previous MO reviews and team leader summaries were also considered as references. The second cycle MO review is attached as an appendix.

VI Integrated review of Efficacy

A. Summary of Conclusions

The MH-105 data was reanalyzed separately for tumor and non-tumor patients

On a by lesion analysis the 0.1mmol/kg dose shows a statistically significant improvement in scores from pre dose to post dose for tumors for all three readers for all three visualization endpoints.

On a by lesion analysis the 0.1mmol/kg dose shows a statistically significant **decrease** in scores from pre dose to post dose for non-tumors for all three readers for all three visualization endpoints (as noted in the previous review, see appendix 1)

On a by lesion analysis the 0.1mmol/kg dose shows a statistically significant cant improvement in scores from pre dose to pre dose + post

dose for tumors and non-tumors for all three readers for all three visualization endpoints.

On a by lesion analysis the 0.05mmol/kg dose produces results that are inconsistent from reader to reader

The condition specified in the FDA letter to the sponsor of July 24, 2004 for the demonstration of efficacy have been satisfied for the 0.1 mmol/kg dose.

Efficacy has been demonstrated for the 0.1 mmol/kg dose, but not for the 0.05mmol/kg dose

B. Detailed review of Trials by Indication

1. Sponsor's Proposed Indication:

MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain spine or associated tissues.

2. Pivotal Trials For proposed Indication

Table 1. Pivotal Clinical Trials CNS Indication

Study	location	Imaged organ	Patients		Number of studies
			ITT*	Safety**	
43,779-9A, 43,779-9,B Re-read as MH-105	USA	CNS (Tumor & Non-tumor)	277	276	2
B19036/020 reread as MH-106	Europe	CNS (Brain Metastases)	154	150	1

*Scheduled to receive MultiHance

** Received MultiHance

As seen in table 1, Study MH-105 included patients with both tumor and non tumor lesions. Study MH-106 included only patients with brain metastases. The prospectively determined endpoints for both studies was a comparison of the pre dose to post dose scans for scores for three visualization endpoints as determined by three independent blinded readers. A statistically significant difference in favor of the post dose scans was seen for all three endpoints for all three readers in study MH- 106. No further analysis of MH-106 is required. The results of study MH-105 were inconsistent. For most readers and most visualization endpoints the differences between pre dose scans and post dose scans were not statistically significant. In some instances statistically significant differences in favor of the post dose scans were found and in other cases statistically significant differences in favor of the pre dose scans were found (see previous MO review attached). MH-105 did showstatistically significant differences between pre dose and paired reads, for all visualization endpoints and for all readers in favor of the paired read.

At the industry meeting of July 9, 2004, the sponsor's consultants argued that these inconsistent results could be explained by the fact that non-tumor lesions often do not enhance. Lesions that do not enhance may not be seen by the reader at all on the post contrast scans and would therefore receive an imputed score of 0 for all three visualization variables. These imputed 0 scores would bring down the scores for the post contrast scan sets, thus producing these inconsistent results.

In a letter to the sponsor dated July 24, 2004 FDA expressed agreement with the sponsor's argument. As a means to resolve this problem, FDA proposed a reanalysis of the MH-105 data with tumor patients and non tumor patients analyzed separately. If it could be demonstrated that there were statistically significant differences between both pre and post and pre and paired scan sets for tumors and between pre and paired sets for non tumor lesions labeling could proceed. The results of such an analysis are presented below in tables prepared by the statistical reviewer from data supplied by the sponsor.

The Tables below were prepared by the statistics reviewer from data from the sponsor's reanalysis of the data from MH-105. Table 2 shows the number of tumor and non-tumor patients in MH-105

Table 2 Number of Tumor and Non-Tumor Patients in MH-105		
	Number Classified as Tumor Subjects (Number of Subjects with Image Data)	**Number Classified as Non-tumor Subjects (Number of Subjects with Image Data)**
MultiHance 0.05 mmol/kg	70 (65)	70 (59)
MultiHance 0.1 mmol/kg	69 (65)	67 (61)
Omniscan 0.1 mmol/kg	62 (57)	72 (63)

Source: Sponsor Attachment B, pages 14 to 24, from September 3, 2004 request for information submission and Statistical Reviewer's listing.

Study **MH-105**: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of **Predose to Postdose** Image Sets in **Tumor Patients** for the 0.05 mmol/kg dose (N=65) and 0.1 mmol/kg dose (N=65) of MultiHance

Table 3	**By Lesion Analysis Pre-Dose vs. Post Dose MH-105 Tumor Patients**					
	Border Delineation		**Internal Morphology**		**Contrast Enhancement**	
	0.05 mmol/kg	**0.1 mmol/kg**	**0.05 mmol/kg**	**0.1 mmol/kg**	**0.05mmol/kg**	**0.1 mmol/kg**
Reader 1						
Number of Lesions[1]	119	132	119	132	119	132
Number of Patients[2]	61	64	61	64	61	64
Predose Mean (s.d.)	1.6 (1.2)	1.5 (1.1)	1.7 (1.2)	1.7 (1.1)	1.9 (1.3)	1.9 (1.2)
Postdose Mean (s.d.)	2.3 (1.3)	2.2 (1.5)	2.2 (1.3)	2.2 (1.4)	2.4 (1.4)	2.4 (1.5)
Mean Change (s.d.)	0.6 (1.9)	0.7 (1.9)	0.5 (1.8)	0.5 (1.8)	0.5 (2.0)	0.5 (2.0)
p-value[3]	**<0.001**	**<0.001**	**0.003**	**<0.001**	**0.006**	**0.003**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Reader 2						
Number of Lesions[1]	153	136	153	136	153	136
Number of Patients[2]	58	56	58	56	58	56
Predose Mean (s.d.)	1.6 (1.2)	1.5 (1.1)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.3)
Postdose Mean (s.d.)	2.0 (1.5)	2.3 (1.5)	2.1 (1.6)	2.4 (1.6)	2.0 (1.6)	2.4 (1.6)
Mean Change (s.d.)	0.4 (2.2)	0.7 (2.1)	0.5 (2.3)	0.7 (2.1)	0.3 (2.2)	0.7 (2.2)
p-value[3]	**0.039**	**<0.001**	**0.014**	**<0.001**	**0.092**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**NO**	**YES**
Reader 3						
Number of Lesions[1]	115	100	115	100	115	100
Number of Patients[2]	59	56	59	56	59	56
Predose Mean (s.d.)	1.8 (1.1)	1.6 (1.2)	1.9 (1.2)	1.7 (1.2)	2.2 (1.3)	1.9(1.3)
Postdose Mean (s.d.)	2.0 (1.6)	2.8 (1.4)	2.1 (1.6)	2.9 (1.4)	2.1 (1.6)	2.9 (1.4)
Mean Change (s.d.)	0.2 (2.1)	1.2 (2.0)	0.2 (2.1)	1.2 (2.1)	-0.1 (2.3)	1.0 (2.1)
p-value[3]	**0.213**	**<0.001**	**0.352**	**<0.001**	**0.716**	**<0.001**
Statistically significant	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**

Source: Sponsor Tables A and B, pages 008 and 009 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.

Table 3 Demonstrates that in a by lesion analysis for tumor patients there is a statistically significant difference in favor of the post dose scans for all readers for all endpoints for

the 0.1 mmol/kg dose. This result is consistent with the hypothesis that since tumors enhance, a statistically significant difference can be seen on the post dose scan.

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Table 4 Demonstrates that in a by lesion analysis for tumor patients there is a statistically significant difference in favor of the pre-dose + post dose scans for all readers for all endpoints the 0.1 mmol/kg dose. For the 0.05 mmol /kg dose the difference is not statistically significant for contrast enhancement for reader 3.

Study **MH-105**: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of **Predose to Predose + Postdose (Paired)** Image Sets in **Tumor Patients** for the 0.05 mmol/kg dose (N=65) and 0.1 mmol/kg dose (N=65) of MultiHance

Table 4	**By Lesion Analysis Pre-Dose vs. Pre-dose + Post Dose (PAIRED) MH-105 Tumor Patients**					
	Border Delineation		**Internal Morphology**		**Contrast Enhancement**	
	MultiHance 0.05 mmol/kg	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**
Reader 1						
Number of Lesions[1]	122	127	122	127	122	127
Number of Patients[2]	61	60	61	60	61	60
Predose Mean (s.d.)	1.6 (1.2)	1.6 (1.0)	1.7 (1.2)	1.8 (1.1)	1.9 (1.3)	2.0 (1.2)
Predose + Postdose Mean (s.d.)	2.6 (0.9)	2.6 (1.1)	2.7 (1.0)	2.7 (1.1)	2.8 (1.0)	2.8 (1.1)
Mean Change (s.d.)	1.0 (1.3)	1.1 (1.5)	1.0 (1.4)	1.0 (1.4)	0.9 (1.4)	0.8 (1.6)
p-value[3]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Reader 2						
Number of Lesions[1]	154	127	154	127	154	127
Number of Patients[2]	57	56	57	56	56	56
Predose Mean (s.d.)	1.6 (1.2)	1.6 (1.1)	1.7 (1.2)	1.8 (1.2)	1.7 (1.2)	1.8 (1.2)
Predose + Postdose Mean (s.d.)	2.3 (1.3)	2.7 (1.3)	2.5 (1.3)	2.8 (1.3)	2.4 (1.3)	2.7 (1.3)
Mean Change (s.d.)	0.8 (1.8)	1.0 (1.7)	0.8 (1.8)	1.1 (1.8)	0.7 (1.8)	0.9 (1.8)
p-value[3]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Reader 3						
Number of Lesions[1]	115	109	115	109	115	109
Number of Patients[2]	58	59	58	59	58	59
Predose Mean (s.d.)	1.8 (1.1)	1.5 (1.2)	1.9 (1.2)	1.6 (1.3)	2.2 (1.3)	1.7 (1.4)
Predose + Postdose Mean (s.d.)	2.2 (1.4)	3.0 (1.1)	2.3 (1.4)	3.0 (1.1)	2.4 (1.4)	3.2 (1.0)
Mean Change (s.d.)	0.4 (1.8)	1.5 (1.6)	0.4 (1.8)	1.5 (1.7)	0.2 (2.1)	1.5 (1.7)
p-value[3]	**0.025**	**<0.001**	**0.046**	**<0.001**	**0.241**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**NO**	**YES**

Source: Sponsor Tables E and F, pages 011 and 012 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
3 p-value based on paired t-test for the change from predose to postdose.

Study **MH-105**: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of **Predose to Predose + Postdose** Image Sets in **Non-Tumor Patients** for the 0.05 mmol/kg dose (N=59) and 0.1 mmol/kg dose (N=61) of MultiHance

Table5	**By Lesion Analysis Pre-Dose vs. Pre-dose + Post Dose (PAIRED) MH-105 Non-Tumor Patients**					
	Border Delineation		**Internal Morphology**		**Contrast Enhancement**	
	MultiHance 0.05 mmol/kg	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**
Reader 1						
Number of Lesions[1]	196	268	196	268	196	268
Number of Patients[2]	51	58	51	58	51	58
Predose Mean (s.d.)	1.5 (1.0)	1.5 (1.1)	1.7 (1.1)	1.6 (1.1)	2.0 (1.2)	1.9 (1.3)
Predose + Postdose Mean (s.d.)	2.1 (0.8)	2.2 (0.7)	2.2 (0.8)	2.3 (0.7)	2.4 (0.9)	2.5 (0.7)
Mean Change (s.d.)	0.6 (1.8)	0.7 (1.2)	0.6 (1.3)	0.7 (1.2)	0.5 (1.4)	0.6 (1.5)
p-value[3]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Reader 2						
Number of Lesions[1]	222	257	222	257	222	257
Number of Patients[2]	50	54	50	54	50	54
Predose Mean (s.d.)	1.5 (1.0)	1.7 (1.0)	1.6 (1.0)	1.7 (1.0)	1.6 (1.0)	1.8 (1.0)
Predose + Postdose Mean (s.d.)	2.1 (0.9)	2.0 (0.9)	2.1 (1.0)	2.1 (1.0)	2.1 (0.9)	2.1 (1.0)
Mean Change (s.d.)	0.5 (1.2)	0.3 (1.2)	0.6 (1.3)	0.4 (1.3)	0.5 (1.3)	0.3 (1.3)
p-value[3]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statistically significant	**YES**	**YES**	**YES**	**YES**	**YES**	**YES**
Reader 3						
Number of Lesions[1]	139	190	139	190	139	190
Number of Patients[2]	48	50	48	50	48	50
Predose Mean (s.d.)	1.9 (1.1)	1.8 (1.2)	2.0 (1.1)	1.8 (1.3)	2.3 (1.2)	2.2 (1.4)
Predose + Postdose Mean (s.d.)	2.1 (1.1)	2.1 (1.0)	2.1 (1.1)	2.1 (1.0)	2.5 (1.2)	2.6 (1.1)
Mean Change (s.d.)	0.2 (1.5)	0.4 (1.6)	0.1 (1.5)	0.3 (1.7)	0.1 (1.8)	0.4 (2.0)
p-value[3]	**0.203**	**0.003**	**0.412**	**0.012**	**0.343**	**0.003**
Statistically significant	**NO**	**YES**	**NO**	**YES**	**NO**	**YES**

Source: Sponsor Tables I and J, pages 014 and 015 from the July 30, 2004 response to July 23, 2004 letter and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.

Table 5 shows a statistically significant difference between pre dose and paired scores for all readers and for all endpoints for the 0.1 mmol/kg dose. For the 0.05 mmol/kg dose the results are inconsistent between readers with readers 1 and 2 finding statistically significant differences for all three endpoints and reader 3 finding differences that are not statistically significant for all three endpoints

Study **MH-105**: Lesion Border Delineation, Visualization of Lesion Internal Morphology, Lesion Contrast Enhancement
All Lesions Analyses, Comparison of **Predose to Postdose** Image Sets in **Non-Tumor Patients** for the 0.05 mmol/kg dose (N=59) and 0.1 mmol/kg dose (N=61) of MultiHance

Table 6	**By Lesion Analysis Pre-Dose vs. Post Dose MH-105 Non-Tumor Patients**					
	Border Delineation		**Internal Morphology**		**Contrast Enhancement**	
	MultiHance 0.05 mmol/kg	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**	**MultiHance 0.05 mmol/kg**	**MultiHance 0.1 mmol/kg**
Reader 1						
Number of Lesions[1]	178	231	178	231	178	231
Number of Patients[2]	55	58	55	58	55	58
Predose Mean (s.d.)	1.7 (1.0)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	2.1 (1.1)	2.2 (1.1)
Postdose Mean (s.d.)	1.4 (1.2)	1.5 (1.3)	1.5 (1.3)	1.6 (1.3)	1.7 (1.4)	1.8 (1.4)
Mean Change (s.d.)	-0.3 (1.5)	-0.3 (1.7)	-0.3 (1.6)	-0.2 (1.7)	-0.4 (1.9)	-0.4 (2.0)
p-value[3]	**0.022**	**0.021**	**0.006**	**0.036**	**0.003**	**0.001**
Statistically significant	**YES***	**YES***	**YES***	**YES***	**YES***	**YES***
Reader 2						
Number of Lesions[1]	202	245	202	245	202	245
Number of Patients[2]	53	56	53	56	53	56
Predose Mean (s.d.)	1.7 (0.9)	1.8 (0.9)	1.8 (1.0)	1.8 (0.9)	1.8 (0.9)	1.9 (1.0)
Postdose Mean (s.d.)	1.4 (1.3)	1.3 (1.3)	1.4 (1.4)	1.3 (1.3)	1.4 (1.4)	1.4 (1.4)
Mean Change (s.d.)	-0.3 (1.7)	-0.5 (1.7)	-0.3 (1.8)	-0.5 (1.8)	-0.3 (1.8)	-0.5 (1.8)
p-value[3]	**0.005**	**<0.001**	**0.009**	**<0.001**	**0.017**	**<0.001**
Statistically significant	**YES***	**YES***	**YES***	**YES***	**YES***	**YES***
Reader 3						
Number of Lesions[1]	130	171	130	171	130	171
Number of Patients[2]	45	51	45	51	45	51
Predose Mean (s.d.)	2.0 (1.0)	2.0 (1.2)	2.2 (1.0)	2.0 (1.2)	2.5 (1.1)	2.4 (1.3)
Postdose Mean (s.d.)	1.2 (1.4)	1.2 (1.4)	1.2 (1.4)	1.3 (1.4)	1.4 (1.5)	1.4 (1.5)
Mean Change (s.d.)	-0.8 (1.8)	-0.7 (2.1)	-0.9 (1.8)	-0.7 (2.1)	-1.1 (2.1)	-1.0 (2.4)
p-value[3]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Statistically significant	**YES***	**YES***	**YES***	**YES***	**YES***	**YES***

Source: Sponsor Attachment D, Tables 22.1.2 22.2.2 and 22.3.2, pages 54 to 62, from the September 3, 2004 request for information submission and Statistical Reviewer's analyses.
1 Number of lesions used in the "All Lesions" analysis.
2 Number of patients from the Statistical Reviewer's analyses.
* Pre-dose has a higher score than post dose

Table 6 shows that the mean scores are consistently higher on the **pre** dose than on the post dose scans for non-tumor Patients (the differences in means between post and pre are negative). These differences are statistically significant. This result is consistent with the sponsor's hypothesis that non-tumor lesions will have lower scores on post dose scans since if they do not enhance, they will not be seen at all

.VII Integrated review of Safety

A. Brief Statement of Conclusions

Previous safety data has been reviewed in previous medical officer reviews.

There are no remaining safety issues to be resolved from the previous analysis

This review concentrates on new safety data submitted by the sponsor in the safety update.

This new safety data raises no new safety issues.

Safety has been demonstrated.

B. Description of Patient Exposure

Safety data in the sponsor's previous submissions was based on a review of data from 2892 adult subjects and 110 pediatric subjects in the Europe-US-China database, and 1218 adult subjects in the Japanese database who have received MultiHance. The sponsor analyzed the Japanese database of 1218 subjects separately.

Since the previous submission there have been 4 newly completed clinical trials with a total of 90 new subjects who have received MultiHance. The sponsor's safety update is based on the 2892 adult subjects in the previous Europe-US-China database, 110 pediatric patients in the old database and the 90 newly reported patients in the newly completed clinical trials for a total of 2982 adult subjects (2863 patients, 119 healthy volunteers). There were no new pediatric patients reported.

1. Subject exposure, deaths and serious adverse events

Table 7 Study Population Exposed to MultiHance (US, Europe, China)				
	Adult Subjects		Peds. database	Total
	Previous adult database	New adult database		
Completed trials	71	4	2	77
Exposed to MultiHance	2892	90	110	3092
Adverse events	519 (18%)	12(13.3%)	14 (13%)	545 (17.6%)
Deaths	2 (0.06%)	0 (0%)	0 (0%)	2 (0.06%)
SAEs (including deaths)	14 (0.5%)	1(1.1%)	2	27 (0.5%)
Discontinuations for AEs	10 (0.3%)	2(2.2%)	0(0%)	12(0.3%)

There were 127 subjects who received placebo in these completed clinical trials. 35 of these patients experienced adverse events (27.6%) compared to the 18% of patients who received MultiHance.

An additional 883 subjects have been enrolled in 11 ongoing clinical trials as of June 30, 2004. There have been 3 serious adverse events re3ported in this population (0.3%)

Reviewer's comment: In the previous submission, the Patients from Japan were analyzed separately from the patients from the US. Europe and China, for reasons never satisfactorily explained. In this submission the Japanese database is totally ignored. This however raises no safety concerns since the Japanese AE rate was even less than the US-Europe- China AE rate .If the Japanese patients were included there would be 4310 subjects in the safety data base. Deaths and SAEs in the Japanese studies were discussed in the previous MO review (see table 2 below).

Table 8 AEs and SAEs in the Japanese studies N = 1531 (table v p56 v42)				
	Normal subjects		Patients	
	placebo	MultiHance	MultiHance	Magnevist
Subjects	6	22	1196	307
AEs	0	4 (18.2%)	45 (3.8%)	7 (2.3%)
SAEs	0	0	2(0.2%)	1 (0.3%)

The AE rate in the 1218 subjects who received MultiHance was 4% and the SAE rate was 0.2% compared to 17.6% and 0.5% respectively in the US, Europe, China Studies

Post Marketing Data

To date [redacted] single dose units of MultiHance have been sold in countries where MultiHance is approved. 473 patients (0.05%) have reported adverse events, 114 patients (0.01%) have reported serious adverse events and there have been 4 reported patient deaths (0.0004%). The most commonly reported adverse events were nausea vomiting and urticaria. These results are similar to those reported in the previous safety update of October 10 2003 at which time 468,775 patients had been exposed. 265 patients

experienced adverse events (0.05%), 52 patients (0.01%) experienced serious adverse events and there was 1 patient death (0.0002%)

.

Request for Pediatric Waiver/Deferral (vol 1 p79)

The sponsor has performed two pediatric studies , a pediatric pharmacokinetic study and a pediatric safety/efficacy study. There are a total of 110 patients in the pediatric safety database. In contrast, there are 2982 patients in the sponsor's adult safety database.
Reviewer's comment: With such a small pediatric database, any uncommon but serious adverse events, that occurred only in the pediatric population only, would likely be missed

Pharmacokinetic/Safety Study: 43,779-10

Subjects :25

Age range: 2-16 There was only 1 subject below the age of 5

Reviewer's comment: The fact that there was only 1 subject below the age of 5 may be an indication of the difficulty of recruiting very young subjects for this kind of study. Since MultiHance was not approved in the US at the time of the study, if these patients needed a contrast enhanced MRI for clinical reasons they would also had to have am MRI with an approved contrast agent. The risks involved in an additional contrast MRI (in addition to what was needed for clinical management)may carry an unacceptable risk for very young children , from the point of view of their parents.

Only 4 post dose blood samples were obtained from each patient in this study.

Efficacy Study: B10936/036

VIII Conclusions and Recommendations

A. Conclusions

Efficacy has been demonstrated for tumor and non tumor CNS lesions

There have been 90 additional adult patients exposed to MultiHance in completed clinical trials and [——] newly exposed patients identified in post marketing surveillance in countries where MultiHance is approved. The number and nature of adverse events, serious adverse events and deaths is similar to that noted in previous MO reviews. The safety update raises no new safety issues

B. Recommendations

- The NDA should be found to be approved for adults for the CNS imaging indication at a dose of 0.1mmol/kg.
- The appropriate clinical dose in adults is 0.1 mmol/kg
- A pediatric deferral should be granted

Addendum 11/18/04

Labeling has been finalized by the division. This reviewer concurs with the wording of the label

A Phase 4 commitment for a pediatric study of pediatric subjects between ages 2 and 5 will be required. The wording of the phase 4 commitment has been finalized. This reviewer concurs with the requirement for this phase 4 commitment

Appendix 1: Second Cycle MO Review

REVIEW CYCLE #2

Submission Date October 10, 2003

Action: Approvable

Appendix 1 Second Cycle MO review

HFD-160 Medical Officer's Review

NDA 21-357 (MultiHance)

Letter Date:	April 27, 2001
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium MRI Contrast Agent
Route:	Intravenous as rapid bolus or infusion
Indication:	MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults [ ] to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain spine or associated tissues.
Formulation:	
Dose:	CNS Adult- 0.1 mmol/kg (0.2 ml/kg) [ ]
How Supplied	5, 10, 15 and 20 ml single dose vials 50 ml and 100 ml rubber stoppered glass bottles (MultiHance Multipack)

HFD-160 Team:	Medical	Dr. Robert J Yaes MD
	Statistics	Sonia Castillo, MS
	Chemistry	Dr. David Place, PhD
	Biopharm/Tox	Dr. Yanli Oyang, PhD
	Pharmacology	Dr. Young-Moon Choi, PhD
	Microbiology	Dr. Stephen Langille, PhD
	Project Manager	Diane Smith Pharm.D

Table of Contents

Executive Summary

I. Recommendations

B. Recommendations on Approvability

1. This NDA should be found to be approvable for the indication of imaging the brain at a dose of [redacted] in adults, since no clinically significant difference in efficacy between 0.05 mmol/kg 0.1 mmol/kg in any of the studies included in the sponsor's reanalysis.

2. [redacted]

3. Since the vast majority of lesions imaged in these studies were intracranial (there were only 4 patients with spinal lesions in the database), the wording of the indication should be changed to: *MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS to visualize* [redacted] *lesions with abnormal blood brain barrier or abnormal vascularity.* All specific reference to spine or associated tissues should be deleted from the indication.

4. [redacted] For a visualization claim, a statistically and clinically significant difference between pre-dose and post-dose images must be shown for all three visualization endpoints. Flaws in the design of previously submitted clinical studies (e. g. Lack of a standard of truth) can not be resolved by reanalysis of data from those same studies. Protocols for any planned studies should be reviewed by the agency before studies are performed. Study design flaws can not be corrected after the fact.

5. Alternatively, the sponsor may conclude, on the basis of data already obtained that it is unlikely that an additional study would show a clinically significant difference between pre-dose and post-dose images for the three visualization endpoints. [redacted]

6. [redacted]

7. Labeling changes are required to reflect the risks of liver toxicity in hepatically compromised patients and the risk of QTc Prolongation.

II Summary of Clinical Findings

F. Brief Overview of Clinical Findings

G. Efficacy

- There is no statistically significant difference between pre-dose and post-dose scans for any of the three primary outcome variables, for any of the three readers in the re-read of the two US Phase 3 pivotal trials (43,779-9A and 43,779-9,B.)
- A positive result in comparing the pre-dose read to a paired read is insufficient to demonstrate an efficacy when visualization outcome variables are used.
- A positive result in the re-read of the single European supportive trial (B19036/020) is insufficient to support the efficacy claim.
- Efficacy has not been demonstrated.

H. Safety

- No new clinical safety data has been submitted. Reanalysis of previously submitted clinical data alone is insufficient to resolve the safety issues raised in the action letter of May 24, 2002
- [ ] the concern about liver toxicity in liver impaired patients since only a fraction of patients imaged for the CNS indication will have liver impairment. This concern can now be addressed in the labeling.
- The results of the pre-clinical monkey study and the post-marketing experience in Europe reduce the concern about QTc prolongation leading to Torsades. This safety issue can also be addressed in the labeling.

I. Dosing

- There is no statistically significant difference in efficacy between the 0.05 mmol/kg dose and the 0.1 mmol/kg dose of MultiHance for any of the three primary outcome variables in the re-read of the pivotal trials and the

supporting trial in either the comparison of pre-dose to post –dose reads or the comparison of pre dose to paired reads.

- [redacted]

- [redacted]

J. Special populations

- The serum half-life is increased in renally compromised and dialysis patients.
- There is no toxicity associated with this increased half-life.
- MultiHance may lead to increases in LFTs in hepatically compromised patients, particularly patients with cirrhosis. This issue should be addressed in the labeling.

Clinical Review

I Introduction and Background

F. Drug

2. Name

C. Generic: gadobenate dimeglumine

D. Trade : MultiHance, MultiHance Multipack

Reviewer's Comment: MultiHance Multipack is the same drug substance at the same concentration as MultiHance. MultiHance is supplied in 5, 10, 15 and 20 ml single dose vials. MultiHance Multipack is supplied in 50 ml and 100 ml rubber stoppered glass bottles. The concentration is 0.5 mmol/ml in both cases. Dosing is the same. The use of the name MultiHance Multipack may mislead some people to believe that the drug in the glass bottles is different than the drug in the single dose vials. The difference in packaging can be handled in the "how supplied" section of the label. The sponsor has made a business decision to make MultiHance available in multi-dose bottles. There is no medical advantage in using this type of packaging. In fact there is a greater risk of contamination with the multi-dose bottles. In this review this submission will be regarded as a single NDA for MultiHance.

2. Class: Gadolinium paramagnetic MRI contrast agent

G. State of Armentariun for Indications

There are four other gadolinium based MRI contrast agents approved in the US for CNS imaging:

- Magnevist
- Prohance
- Omniscan
- Optimark

The sponsor has submitted no data that would support a claim of superiority of MultiHance over any of these agents

H. Important Milestones

April 27, 2001

NDA 21-357 and NDA 21-358 for MultiHance and MultiHance Multipack was received. Indications for — CNS ————————

September 13, 2001

Safety Update Received

February 25, 2002

Industry Meeting Sponsor requests to efficacy update as an amendment before PDUFA date of 2/27/02

February 26,2002

Efficacy amendment received

May 24, 2002

The agency in the action letter of May 24, 2002 informed the sponsor that the application was approvable for the CNS indication. It was stated in the action letter that in order to correct the deficiencies in the submission, at least one robust efficacy study in adults with CNS disease, a placebo controlled cardiac safety study in patients at higher than the indicated dose to study QT effects, a drug interaction study, a preclinical cardiovascular study at doses up to the MTD and a reanalysis of previously submitted data would be required.

August 28,2002

Industry Meeting with Bracco to discuss safety and efficacy concerns raised in the action letter of May 24, 2002 and sponsor's action plan. At that meeting the division stated that it is not clear that a blinded re-read alone could resolve the study design flaws discussed in the action letter. The division reiterated that its request is for new studies (meeting minutes 8/28/02 industry meeting p7-8)

September 18, 2002

Action plan to address deficiencies discussed in the action letter of May 24, 2002 submitted by sponsor in response to the meeting of 8/28/02

November 15, 2002

Additional comments faxed to sponsor

The division stated: "the potential for bias exists when visualization is scored from a paired image set. We recommend that the post dose images are evaluated separately for the visualization endpoints.....a paired read may be carried out for secondary analysis" The studies should be able to demonstrate a clinically significant increase from each pre-contrast visualization score. A 15% average increase, as stated in the current protocol needs to be justified.

December 3, 2002

Internal meeting to prior to industry T-con of 12/11/02

December 11, 2002 Industry T-con

The division stated " you need to show clinically and statistically significant improvement from the unenhanced to the enhanced image sets improvement in each of the co-primary endpoints

I. Other Relevant Information"

MultiHance has been approved in 16 foreign countries. The first approvals were received in 1998. Countries where MultiHance is approved are Austria, Belgium, Czech Republic, Germany, Denmark, Ireland, France, Greece, Italy, Israel, Luxembourg, The Netherlands, Portugal, Sweden, Portugal and the United Kingdom. Approximately [———] single dose vials have been sold. No country has withdrawn approval. There have been no reported cases of Torsade de Pointes arrhythmias

J. Important Issues with Related Agents

No reports of Torsade de Pointes arrhythmias have been made of any Gadolinium based MRI contrast agent

II Clinically relevant Findings from other Disciplines

A. Pharmacology-toxicology (see Pharm-Tox review)

Data from three new complementary pre-clinical pharmacology-toxicology cardiovascular safety studies were included in the re-submission. These studies were conducted primarily to address the concern of the risk of QT prolongation associated with MultiHance. These studies included:

1. Core battery of Cardiovascular studies in conscious cynomolgus monkeys monitored by telemetry;
2. HERG tail current study in transfected HEK293 cells; and
3. Action potential parameter study in isolated dog Purkinje fibers.

Results:

1. MultiHance at up to 3 mmol/kg (MTD in cynomolgus monkeys, 30 times the proposed human dose) produced no QTc prolongation in the monkeys.
3. MultiHance at up to 50 mmol produced no significant effect on action potential parameters.
4. There were no statistically significant differences between the effects of MultiHance and mannitol at the same osmotic load in the HERG assay.

These studies showed no clear evidence that QT prolongation was associated with MultiHance.

III Pharmacokinetics

C. Pharmacokinetics

8. Distribution half –life 0.09-0.6 hr
9. Elimination half-life 1.2-2 hr
10. Elimination route 78-96% Urine, 0- 7.2% feces
11. Hepatic impairment had no effect on pharmacokinetics
12. Renal impairment increased serum half-life
13. MultiHance is dialyzable
14. Subgroup analysis

No effect by age or sex in adults was seen

There were 110 pediatric patients, 15 patients < 2 years, 69 patients 2-12 years and 26 patients > 12 years. No effect by age or sex in the pediatric population was seen

15. Drug-drug interactions were not studied.
16. The sponsor has reanalyzed adverse event data to determine whether there is a competition between MultiHance and Glyburide, a drug excreted by the liver by the C-MOAT transporter system. The sponsor's hypothesis is that if there was a

drug-drug interaction between MultiHance and Glyburide, the adverse event rate would be *higher* in patients who received both Glyburide and MultiHance than in patients receiving MultiHance alone. The data showed a statistically significantly *lower* rate of adverse events in the Glyburide patients The results of that analysis are therefore inconclusive

D. Pharmacodynamics

MultiHance is a paramagnetic gadolinium based MRI contrast agent whose efficacy is based on its ability to increase signal intensity on T1 weighted MRI images and on its ability to leak out through the damaged blood-brain barrier associated with specific types of lesions in the brain

IV Description of Clinical Data and Sources

D. Overall Data

Data from the previous submission has been reviewed in the previous medical officer review

4. No new clinical trials were reported in this submission.
5. The only new clinical data submitted is efficacy data from a re-read of images from four previously reported clinical trials. Study MH-105 is a re-read of images from studies 43,779-9A and study 43,779-9B, two identical pivotal Phase 3 clinical trials performed in the United States. Study MH-106 is a re-read of images from study B19036/020 which included only patients with brain metastases and which was performed in Europe. Study MH-112 is a re-read of images from the pediatric study B19036/020, which was conducted in Europe
6. No new clinical safety data was submitted although previously submitted data on QTc prolongation was reanalyzed

E. Tables Listing Clinical Trials

Table 1. Clinical trials reviewed in MO review in previous cycle (MO review p 27)					
83 Clinical Studies	location	Imaged Organ	ITT*	Safety**	Number of studies
Studies Re-Read For This Submission					
43,779-9A, 43,779-9,B Re-read as MH-105	USA	CNS	277	276	2
B19036/020 reread as MH-106	Europe	CNS	154	150	1
B19036/036 (Peds) reread as(MH-112)$^{+}$	Europe	CNS	85	85	1
Other Studies					
Other European CNS	Europe	CNS	144	144	14
Japanese CNS	Japan	CNS	381	379	3
US Liver Studies	USA	Liver	317	317	4
European Liver Studies	Europe	Liver	937	935	22
Japanese Liver Studies	Japan	Liver	485	482	5
Other US (pediatric and renal dialysis)	US		56	56	3
Other European (PK, Cardiac, MRA, Breast)	Europe		784	741	20
Other Japan	Japan		352	352	3
Ongoing (MRA, Rheumatoid arthritis)			115	-	5
Total USA			649 16.3%		9 10.8%

*Scheduled to receive MultiHance

** Received MultiHance

Table 2. Clinical Trials Used in the Re-Read for Efficacy in This Submission			
Study	Location	Patients randomized	Dose (mmol/kg) MultiHance (M) Or Omniscan (O)
Re-Read study MH-105 (p019 v25)			
43,779-9A	United States	205	0.05 + 0.01 (M) 0.1 + 0.1 (M) 0.1 +0.2 (O)
43,779-9B	United States	205	0.05 + 0.01 (M) 0.1 + 0.1 (M) 0.1 + 0.2 (O)
Re-read study MH-106 (p196 v2)			
B19036/020	Europe	150	0.05 + 0.05 + 0.1 (M) 0.1 + 0.1 + 0.1 (M)
Re-read study MH-112 (Pediatric) (table 3-53 p223 v24)			
B19036/036	Europe	63	0.1 (M) 0.1 (O)

Reviewer's comment: Patients in all three adult trials received multiple doses of MultiHance with a 15 minute time interval between doses. No patient received just the proposed 0.1 mmol/kg as the only dose. Scans taken after a first dose only were reread. Any safety data obtained more than 15 minutes after the first dose would reflect the toxicity of both doses.

F. Postmarketing Experience

MultiHance has been approved in 16 foreign countries. The first approvals were received in 1998. Countries where MultiHance is approved are Austria, Belgium, Czech Republic, Germany, Denmark, Ireland, France, Greece, Italy, Israel,

Luxembourg, The Netherlands, Portugal, Sweden, and the United Kingdom. Approximately [redacted] single dose vials have been sold. Since most patients receive only a single dose of MultiHance, this is a good estimate of the number of patients who have been dosed No country has withdrawn approval. There have been no reported cases of Torsade de Pointes arrhythmias associated with MultiHance or with any other gadolinium based MRI contrast agent.

G. Literature Review

N/A

V Clinical Review Methods

B. Description of How Review Was Conducted

This review is based primarily on the reread of scans from the previously submitted studies and the reanalysis of previously submitted safety data contained in this re-submission. This material consisted of 44 volumes containing the sponsor's reanalysis of previously submitted safety data, and data from a re-read of three adult and 1 pediatric clinical trials. The previously submitted data has been analyzed in the MO review of the first submission.

C. Overview of material Consulted in Review

Material consulted for this review included

Sponsor's 44 volume resubmission

Medical officer review of previous submission

Clinical team leader's memorandum on previous submission

Minutes of industry meeting August 28, 2002

FDA comments to sponsor dated November 15, 2002

Minutes of T-con dated December 11, 2002

Drafts of reviews by other disciplines, particularly statistics and pharmacology

D. Overview of Methods Used to Evaluate data Quality and Integrity

DSI audited three representative US sites. European and Japanese and Chinese sites were not audited.

There are characteristics of the data that lead this reviewer to question the quality of the data. (p164 v2 note that 107 is a typographical error the number should be 127)

The of the 2892 patients in the US-Europe-China database who received MultiHance, 519/2892 (17.9%) experienced adverse events. 35/127 patients who received placebo (27.6%) experienced adverse events. (p164 v2) This difference is statistically significant, p = 0.003 (see statistics review)

Reviewers comment: An important method in assessing safety risks is to look for an increased incidence of specific adverse events in the treatment group compared the placebo group. When the incidence of adverse events is higher in the placebo group than in the treatment group, such a comparison would be unlikely to add any useful information.

1. The percentage of subjects who experienced at least 1 AE, varies significantly between the US (35.5%), Europe (12.6%), Japan (4%) (tables PPP and VVV p176, p191 v2) and China (7.6%)(tables PPP and VVV p176, p191 v2). These large differences make it difficult to interpret analyses of a combined safety database
2. One numerical error has been found in transcribing data from tables to the text in the safety part of this submission (p164 v2) when this was brought to the sponsor's attention, the sponsor performed a quality check of volume 2 of the submission and found 10 additional similar errors. The other volumes of this submission were not checked.

   Reviewer's comment: while none of these errors had a significant effect on the reviewer's analysis, they do reflect on the care with which this submission was prepared
3. Analyses are not based on the complete safety database. The sponsor has justified not including the Japanese data in the integrated analysis of safety on the basis of the low AE incidence in the Japanese data. The Japanese safety data has been presented and analyzed separately. However there are significant differences in the AE event rate between the US, Europe and China as well. The fact that Chinese data is included in some analyses and not in others makes comparison between different analyses difficult.

5. In tables where different laboratory values are obtained at different time points, the patient database may be different for each lab value and for each time point. For example the number of patients in the database (denominator) for BUN and Creatinine in the MultiHance group at time points 3, 24 and 72 hr post dose is as follows.

Table 3 Number of patients in database* (table UU p131 v2)			
	3 hours	24 hrs	72 hrs
BUN	290	1382	202
Creatinine	282	2114	236

*number of patients at baseline who are within normal limits + number above normal limits + number below normal limits

Reviewer's comment: this type of data is presented in multiple tables of laboratory values. It is not clear, for example, whether the 290 patients with BUN values at 3 hours is a subset of the 1382 patients with values at 24 hours or an entirely different set of patients. With such data it is not possible to follow the changes in laboratory values over time.

E. Were trials Conducted in According to Accepted Ethical Standards

There were no new clinical trials reported in the resubmission.

All studies whose reports were previously submitted for this NDA were conducted in accord with the Declaration of Helsinki

F. Evaluation of Financial Disclosure.

A re-read of MRI images from previously performed clinical trials was performed. There were six blinded readers for trials MH-105 and MH-106. There was a single blinded reader for study MH-112. There were three blinded readers from Italy for study MH-105 and three blinded readers from the United States for study MH-106. Thus scans from the US pivotal study were re-read by European readers and scans from the European study were re-read by US readers. While CVs for all blinded readers have been submitted, financial disclosure forms for these six blinded readers could not be located in the overview Index. Disclosure forms for the readers were included in the electronic case report forms, but these forms refer only to study design

and blinding and not to financial conflict of interest (p.195 and p.226 v.25). There was only a single reader for the pediatric study, MH-112, and no information concerning this reader was provided.

APPEARS THIS WAY
ON ORIGINAL

VI Integrated review of Efficacy

C. Summary of Conclusions

- No statistically significant differences in favor of MultiHance have been found between the scores for the pre dose (non contrast) images and those for the MultiHance images, in the pivotal trials for any of the three primary outcome variables, for any of the three blinded readers
- No statistically significant differences between the scores for the 0.1 mmol/kg dose and the 0.05 ml/kg dose of MultiHance have been found in any of the clinical trials
- Statistically significant differences between pre-dose and post-dose scores have been found in the supporting trial.

D. General Approach to Review of the Efficacy of the Drug

Review of efficacy is based on the data from the re-reads in the re-submission

C Efficacy Deficiencies Identified in the Action Letter of May 24, 2002

1) The two key Phase 3 adult trials (43779-9A and 43779-9B) were not sufficient to establish the proposed dose to visualize lesions. Because of an unknown dose-response relationship to 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.
2) Based on trial design the most critical information is the number of lesions able to be visualized. In study B139036/020 after a single dose of 0.05 mmol/kg and 0.1mmol/kg, the number of lesions was similar
3) In studies 43,779-9A and 9B, in patients that received a single 0.1 mmol/kg, there was no statistically significant increase in the number of lesions seen
4) All studies lacked a standard of truth and study B139036/020 lacked an active comparator

5) Image acquisition and blinded reader methodology is insufficiently documented to support validity of clinical trials data and to determine appropriate acquisition methods
6) The composite [redacted] information score lacks sufficient clarity to document its relevance to the proposed indication
7) The enrolled patients were not appropriate to establish the conditions of use in the clinical setting
8) In order to address these deficiencies , at least one large robust study in adults with CNS disease is required
9) [redacted]

E. Detailed review of Trials by Indication

1. Indication:

MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain spine or associated tissues.

Reviewer's Comment: In the original NDA submission the sponsor sought indications for — CNS [redacted]

D. Efficacy Deficiencies Identified in the Action Letter of May 24, 2002

1. The two key adult trials (43779-9A and 43779-9B) were not sufficient to establish the proposed dose to visualize lesions. Because of an unknown dose-response relationship to 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.

2. Based on trial design the most objective visualization endpoint is the number of lesions able to be visualized. The other endpoints call for subjective scoring by the reader. In study B139036/020 after a single dose of 0.05 mmol/kg and 0.1mmol/kg, the number of lesions was similar
3. In studies 43,779-9A and 9B, The number of lesions visualized with a dose of 0.1 mmol/kg, showed no statistically significant increase over the number of lesions seen with 0.05 mmol/kg
4. All studies lacked a standard of truth and study B139036/020 lacked an active comparator
5. Image acquisition techniques are insufficiently captured to support validity of clinical trials data.
6. The Per-patient score (p38 v25) defined as the weighted average of all per lesion scores for that patient may not be correlated with the clinical outcome. If a diagnosis can be made on the basis of the two or three lesions that are best visualized. The fact that there are 10 or 15 other lesions that are barely visible and have low visualization scores is irrelevant, even though these lesions will lower the per-patient score. In fact if a reader does not see these other lesions at all the per-patient visualization score will be higher than if he does.
7. The enrolled patients were not appropriate to establish the conditions of use in the clinical setting. All patients enrolled in 43,7779-9A and 43779-9-B had evidence of CNS lesions on another imaging study (CT or non-contrast MRI). In usual clinical practice most patients referred for contrast enhanced MRI of the brain would have clinical suspicion of intracranial lesions only. Thus the enriched population in this study would not be representative of the patient population for which MultiHance would be used, and would contain very few negatives (patients without intracranial lesions).
8. In order to address these deficiencies , at least one large robust study in adults with CNS disease is required
9.

Reviewer's Comment:

Each patient in the MultiHance group received 2 doses of MultiHance, either 0.05 mmol/kg + 0.1 mmol/kg or 0.1mmol + 0.1mmol. The doses were given 15 minutes apart and imaging began immediately after each dose.

The patient population in these studies was highly enriched in that all patients entered in this study had to have intracranial lesions seen on another imaging study (CT, MRI, nuclear medicine) There would thus be virtually no negative patients (patients without intracranial lesions) in these studies. In retrospect, a population of all patients referred for a contrast enhanced MRI would more closely the population who would receive MultiHance enhanced scans in clinical practice. Since most of these patients would be referred because of clinical suspicion alone, it is likely that there would be a significant number of negative patients. No new Phase 3 clinical trials of MultiHance have been performed since the previous submission. The only new data submitted comes from a re-read of scans in the two pivotal trials (43779-9A and 43779-9B) and supportive study B19036/020 The data from this re read can address deficiencies in the methodology of the Previous read, but can not address deficiencies in the in the imaging protocol itself (patient population choice of doses, imaging equipment and settings etc.)

Pivotal trials (43,779-9A and 43,779-9B)

Reviewer's comment: The sponsor gives new study numbers to the rereads of the scans from the clinical trials. The reread of the two pivotal trials, 43,779-9A and 43,779-9B is called MH-105

The two pivotal trials 43779-9A and 43779-9B have identical trial design. In each trial patients who had evidence of CNS lesions on other imaging studies (CT, CECT, MRI, CEMRI, angiography, and scintography) were enrolled. These patients were randomized to one of three dosing regimens, receiving two doses of either MultiHance or Omniscan by rapid bolus injection. In each regimen, the second dose was given 15 minutes after the first. Scanning began immediately after each dose was given. The first regimen gave MultiHance 0.05 mmol/kg followed by MultiHance 0.1 mmol/kg. The second dosing regimen gave MultiHance 0.1 mmol/kg followed by MultiHance 0.1 mmol/kg. The third dosing regimen gave Omniscan, 0.1 mmol/kg followed by Omniscan 0.2 mmol/kg. The dosing regimens and the number of patients in each study who received each is shown in table 4. There were 205 patients who completed each of the two pivotal trials for a total of 410 patients.

Reviewer's comment: The sponsor's original reasoning for giving two doses of contrast agent 15 minutes apart was that since the elimination half life for these contrast agents is 1-2 hours, typical for agents eliminated by glomerular filtration, the effect of the two doses 15 minutes apart would be additive. However, since the distribution half-life of MultiHance is 0.085-0.6 hr (5- 36 minutes) additivity might not necessarily occur. Therefore in the analysis of the reread, only scans obtained after the first dose but before the second dose were considered. No such scans were, of course obtained more than 15 minutes after dosing

Table 4 The Three Dosing Regimens For Pivotal Trials 43779-9A and 43779-9B
p. 023 v. 25

MultiHance, N = 276			
Regimen	First Dose	Second dose	PATIENTS (A+B)
1	0.05 mmol/kg	0.1 mmol/kg	140 (71+ 69)
2	0.1 mmol/kg	0.1 mmol/kg	136 (65 +71)
Omniscan, N = 134			
3	0.1 mmol/kg	0.2 mmol/kg	134 (69 + 65)
Total			410 (205 + 205)

Demographics of the 276 MultiHance patients in the pivotal studies (p 17 v 24):

Caucasian 81%

Black 9%

Hispanic 7%

Asian 2%

Other 1%

Reviewer's comment: even for these studies performed in the US, the population was heavily weighted towards Caucasians, and the demographics of the study do not match the demographics of the US population as a whole.

Table 5 Diagnosis by Treatment arm (specified by first dose) p.23 v.25

Diagnosis	MultiHance		Omniscan
	0.05 mmol/kg	0.1 mmol/kg	0.1mmol/kg
Normal parenchyma	5	10	7
1° CNS tumor	14	14	16
Metastases	17	13	15
Benign tumor	38	36	36
Infection	5	4	2
Vascular	6	3	10
Inflammation	6	4	11
Infarct	14	15	19
MS	12	18	14
Post op changes	16	14	10
Spinal lesion	4	4	3
other	1	2	5
Differential Dx	8	11	7
Unknown	10	5	4

Reviewer's comment. Only 22/410 (5%) had a pre-study diagnosis of "normal parenchyma" indicating the highly enriched nature of the population. While the blinded readers were asked to make several subjective ratings of the quality of the images, they were not asked to make a diagnosis which could be compared to a standard of truth. There were only 4 patients with spinal lesions. A larger number would be necessary to justify including spinal lesions in the indication. Intramedullary spinal lesions are rare. Extramedulary intradural lesions and extradural lesions can usually be visualized without contrast.

Re-read of pivotal trials (MH-105):

The re-read was performed by three independent blinded readers with each reader reading all images. Three readings were performed for each patient, pre-dose, post-dose and paired. The three pre-dose images T1 weighted, T2 weighted and proton density were read together for the pre-dose read and the three pre dose image sets plus the post dose T1 images were read together for the post dose read. The images were presented to the readers electronically on a console and their responses were recorded electronically, not on paper case report forms. The sponsor's response emphasizes the differences between the pre-dose and paired reads although the differences between the pre dose and post dose reads were the agreed upon primary outcome variables. Comparisons between the pre-dose read and the paired read and between the pre-dose read and the paired read are included in the submission. There were three primary endpoints:

- Border delineation
- Visualization of internal morphology
- Contrast enhancement

Each endpoint was evaluated for each individual lesion that was seen by the reader and subjectively assigned a value from 1 to 4 going from worst to best. A lesion that was seen on one scan set but not on another would be assigned a score of 0 for the scan set on which it was not seen. The readers were given verbal descriptions corresponding to each score. Lesion tracking was performed by each individual reader to assure that the same lesion was evaluated on the different scan sets. Lesions that were not seen (but were seen on other scan sets) were assigned the value 0 by default. For lesions that were seen, the

readers assigned a value from 1 to 4. Quantitative data was also obtained by each reader. Regions of interest were drawn around lesions and signal intensity was measured inside the lesion and in surrounding normal brain parenchyma. Three scan sets were randomly evaluated, the pre dose scan set (T1, T2, proton density) the post dose enhanced T1 and the paired set, the pre dose scan set plus the enhanced T1)

Supportive Study MH-106 was a reread of study B19036/20 which was a double blind randomized trial in adult5 patients with brain metastases. Patients were randomized to one of two dose regimens each giving 3 consecutive doses of MultiHance. The regimens were:

0.05 +0.05 +0.1 mmol/kg (74 patients)

0.1+0.1+0.1 mmol/kg (75 patients)

The re-read was performed in the same way and with the same primary outcome variables as for MH-105

Pediatric study MH-112 is a re-read of study B19036/036 which was a study in pediatric patients with benign and malignant tumors of the CNS. Scans from 59 patients were re-read by a single neuroradiologist. Of the 59 patients, 26 were in the MultiHance 0.1mmol/kg group and 32 in the Magnevist 0.1mmol/kg group (p 219 v 4)

Pre dose, post dose and paired scan sets were read.

Reviewer's comment: the sponsor has argued in favor of a pre dose read vs. a paired read for the primary outcome variables. For the pre dose read in the pivotal trials, 3 scans would be presented to the reader T1, T2 and proton density. For the paired read the reader is presented with 4 scans T1, T2, proton density and T1 enhanced. The three primary endpoints, Border Delineation, Visualization of Internal Morphology and Contrast Enhancement must be given a single value for each lesion on each set of scans. The readers were not given specific instructions in the training manual as how to do this. In this reviewer's opinion the most likely method would be to choose the scan (say T2) with the best border delineation and assign the border delineation score for the pre dose set based on that scan. When the contrast T1 is added it could have a better worse or the same border delineation as the best pre dose scan. If it is better the score on the paired read will go up compared to the pre-dose read. If it is the same or worse, the score will