DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS HFD-160

Industry Meeting Minutes

MEETING DATE: July 9, 2004

MEETING TIME: 11AM-12:30PM

NDA: 21-357 and 21-358

DRUG: MultiHance

SPONSOR: Bracco Diagnostics, Inc.

TYPE of MEETING: Type A

FDA PARTICIPANTS:

Robert Yaes, M.D., Clinical Reviewer
Ellen Maher, M.C., Clinical Reviewer
Ramesh Raman, M.D., Clinical Team Leader
Zili Li, M.D., Clinical Team Leader
Michael Welch, Ph. D., Biometrics Team Leader
Yanli Ouyang, M.D., Ph.D. Pharmacology/Toxicology Reviewer
Sally Loewke, M.D., Deputy Director
George Mills, M.D., M.B.A., Division Director
Florence Houn, M.D.,MPH, Director, Office of Drug Evaluation III
Kyong Kang, Pharm D., Chief Project Management Staff
Diane C. Smith, R.Ph., Regulatory Health Project Manager

SPONSOR PARTICIPANTS:

Andrew Betournay, M.D., Head, Global Regulatory Affairs
Maurizio Denaro, M.D., Head, Global Research and Development
Usha Halemane, Sr. Director, Head Corporate Biostatistics
J Kris Piper, Vice President, Global Preclinical and Clinical Regulatory Affairs
Alberto Spinazzi, M.D., Group Medical Affairs
Melanie Benson, Director, Regulatory Affairs

NDA 21-357 and 21-358 MultiHance
July 9, 2004

Bracco Consultants/Experts

[redacted]

AGENDA: To obtain clarification and reach agreement with the FDA on the efficacy data deficiency identified in the approvable letter dated April 14, 2004.

DISCUSSION:

After the introduction of the participants, the sponsor's consultants presented a slide presentation on the Methodological, Statistical and Regulatory issues in response to the Agency's approvable letter. (SEE Attachment)

GENERAL

At the conclusion of the slide presentation the sponsor noted that the efficacy for Multihance® is supported by the per patient analysis and by pre vs. paired analyses.

The FDA and sponsor discussed the following issues:

- Scoring of imaging and the impact of scoring "zero" for lesions not seen in the post-drug analyses
- Pre vs. paired, pre vs. paired analyses, and T1 vs T1 analyses, and how scoring impacts these analyses
- The inservice done for the blinded readers
- What imaging sequences are used in practice
- The diagnoses of the patient population studied to support a board indication
- Lesion level vs patient level analyses

Agreement was reached that Proton Density (PD) is not necessary for the analysis involving study MH 106.

The Agency requested that the sponsor provide a list of outstanding items they would like the Agency to look at, i.e., the necessity of Proton Density, the patient population, and the dose. The Agency also noted that in the meeting package, table C, target population, the sponsor provided additional information.

The Agency commended the sponsor and their consultants on the presentation and agreed to provide the sponsor a letter within 2 weeks on how the outstanding issues from today's meeting could be addressed to include the appropriateness of the patient population studied the analytical methodology, the data collected and the necessity of a new study. If a re-read would be needed, the Agency and sponsor would discuss the re-read protocol prior to embarking on the re-read.

The Agency also suggested that within the next few months the sponsor and the Agency meet to discuss how to improve communications.

ACTION ITEMS:

1. The sponsor will submit a hard copy and an electronic copy of the slide presentation.
2. The sponsor will submit a detailed distribution of the patients studied with CNS disease and breakdown of the patients receiving spinal exams.
3. The sponsor will submit a statement confirming that Proton Density is not part of routine clinical practice for CNS metastatic imaging in the U.S.
4. The Agency will provide a letter to the sponsor within 2 weeks of the outstanding issues from the July 9, 2004, meeting to include, the appropriateness of the patient population studied, the analytical methodology, the data collected and the need for a new study.

An Advice Letter was subsequently sent to the sponsor on July 23, 2004, that addressed the deficiencies noted during the meeting, and provided a pathway for the sponsor to correct the outstanding issues. (SEE Attachment)

46 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-357, 21-358

Bracco Diagnostics
Attention: Melanie Benson, M.S.,R.A.C.
Director, US Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225
United States

Dear Ms. Benson:

Please refer to your new drug application (NDA) dated April 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MultiHance® (gadobenate dimeglumine) Injection and MultiHance® (gadobenate dimeglumine) Injection in pharmacy bulk package. Also, please refer to the action letters from the Agency dated May 24, 2002, and April 14, 2004. Finally, please refer to the meeting the Agency had with Bracco Diagnostics, Inc. on July 9, 2004. This letter is in follow up from that meeting regarding the following outstanding matters: the appropriateness of the patient population studied, the analytical methodology, the data collected and the need for a new study.

Regarding the patient population studied and the adequacy of it being representative of central nervous system (CNS) patients presenting for anatomic imaging and whether further studies are needed, the Agency has reviewed your responses of June 10, 2004, (Attachment C) and July 16, 2003. We find that the spectrum of disease for adult CNS (brain and spine) imaging is adequately represented in re-read studies MH 105 and 106, combined.

During the July 9, 2004, meeting Bracco Diagnostics, Inc. presented the Agency with information on the primary analyses done for Study MH 105, involving the pre-drug image versus the post-drug image comparison. The scoring was fundamentally flawed because the lack of enhancement on the post T1 image may still be useful. You stated non-enhancement of certain types of lesions is a finding that should not necessarily penalize drug efficacy assessments. You also stated that the pre- vs. post-drug image analysis and assigning zero scores based on non-enhancement or T2 lesions biased the results and you recommended T1 pre- vs. T1 post-drug image analysis or pre- vs. paired image analysis.

We have reviewed your presented information and agree that when lesions do not enhance with contrast, the lack of lesion enhancement should not necessarily be considered a drug failure, when ultimately the lack of lesion enhancement may be of clinical value. We do not feel the T1 pre- vs T1 post-drug image comparisons provide the best way to evaluate what the drug's overall contribution is to anatomic delineation as a benefit to evaluate CNS patients. In addition, the paired analysis you performed using the currently flawed scoring showed MH 105 winning, suggesting that corrections to scoring must be carefully considered. Moreover, the primary

efficacy analyses in MH 106 using pre- vs. T1 post-drug image comparison as well as the pre- vs. paired reads do demonstrate efficacy for the indication of anatomic/structural delineation for patients in whom there is a suspicion of CNS metastatic malignancy. We find reread study MH 105 is supportive in the pre- vs. paired results and request you conduct a sub-analysis of tumor-only patients (both primary and metastatic) from MH 105 using the pre- vs. post and pre- vs. paired analyses for the same three anatomic endpoints. However, given that there is a preponderance of patients enrolled with tumors in MH 105, we are concerned that the results in the pre vs. paired reading for MH 105 overall are driven by the tumor (primary and metastatic) patients. Therefore, we request you submit a sub-analysis of MH 105 in the non-tumor brain and spine patients (patients without benign, malignant, or metastatic tumors) using the pre- vs. paired results for the three anatomic endpoints.

To move forward, the Agency recommends two options you can pursue. Provided the pre- vs. post and the pre vs. paired MH 105 sub-analysis of tumor-only patients shows efficacy for the three endpoints, you may submit labeling to be negotiated for the indication of anatomic/structural delineation for patients in whom there is a suspicion of CNS malignancy. For the indication of general CNS anatomic/structural delineation, if the pre vs. paired MH 105 sub-analysis of the non-tumor patients shows efficacy for the three endpoints, you may submit labeling to be negotiated. If that sub-analysis leaves outstanding questions about efficacy in the non-tumor population, we can further discuss with you the option of developing a re-read protocol for MH 105 to show superiority of drug in the paired image reading.

Regarding other outstanding issues from the April 14, 2004, action letter, as mentioned, above, the target population is acceptable given the clarification submitted on July 16, 2004. Depending on the results of the analyses, dosing will be determined. Finally, we accept that the absence of the proton density sequence in MH 106 would not significantly impact results in the CNS metastatic tumor patient population.

We thank you very much for the clear and very informative presentations you and your consultants shared with us. These have helped us better understand the unintended consequences of analyses in this class of drug with this type of imaging.

If you have any questions, call Diane C. Smith, Regulatory Health Project Manager, at (301) 827-1607.

Sincerely,
/S/
{See appended electronic signature page}

Florence Houn MD MPH
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Florence Houn
7/23/04 03:23:45 PM

Division Responses re: NDA 21-357 &21-358 MultiHance
Response to Approvable letter dated April 14, 2004Industry Meeting: July 9, 2004

Question 1

In previous documented discussions with FDA, both studies MH-105 and MH 106 were considered pivotal and the agency did "not have a problem with the patient population." Has the FDA changed its position on the patient population, and if so, what caused this change?

Agency Response

The Agency has not revised its position on the patient population. As noted in both approvable letters, the Agency had expressed concern that the population studied for the CNS indication was not adequate to establish the conditions of use in the clinical setting of the study. Both letters requested a new study in a relevant patient population in a clinical setting for which the need for MRI contrast imaging was well defined. Your proposed CNS indication is broad; therefore, clinical trials for such an indication will require representation of a variety of neurological diseases for which contrast MRI would be beneficial. Your re-read study MH 105 (composite of studies 9A and 9B) enrolled a population with a variety of neurologic diseases and thus was considered the study with the greatest potential to support such a broad indication. However, as noted in our letter dated March 7, 2003 , we did not evaluate your re-read protocol from the perspective of whether or not it would address the clinical efficacy deficiencies cited in the first approvable letter, as we anticipated the deficiencies were too great to be overcome by this re-read. We did, however, provide you with comments on the technical aspects of the re-read protocol in the unlikely event that the results of MH 105 may have been overwhelmingly favorable to cause us to re-consider our effectiveness conclusions. With the primary efficacy results of MH 105 also being negative, there is no substantial evidence for efficacy.

Question 2

Considering that omitting proton density images in one of the pivotal trials was a reflection of clinical practice and not an attempt to bias the study in favor of contrast enhanced imaging, and that the Agency was fully aware of the image acquisition methods used in this study when it acknowledged that MH-106 would be considered one of the pivotal studies, doe the Agency accept the data that were generated as valid for the use of MULTIHANCE in the study population?

Agency Response

In the US it is accepted clinical practice for radiologists to read T1, T2 and proton density images together for non-contrast MRI imaging. In studies that are considered pivotal for drug approval in the US, US clinical practice should be followed. The absence of proton density images may have prejudiced the reading in favor of the post dose set. In fact the absence of proton density images in the pre dose set in MH-106 may partially explain the contradictory results between the two studies in the comparison between pre dose and post dose image sets

Question 3

Considering:

- *a. the FDA Draft Guidance Document for Industry titled: "Guidance for Industry: Medical Imaging Drug and Biological Products. Part 3: Design, Analysis, and Interpretation of Clinical Studies",*
- *b. the nature of clinical CNS imaging and routine clinical practice,*
- *c. the indication being sought,*
- *d. that MULTIHANCE-enhanced MRI is not proposed to replace unenhanced MRI,*
- *e. the primary end-points and analyses requested by the FDA, i.e., the comparison between pre- and post-images and the lesion level analyses, which implied the need for imputation rules and created a situation not appropriate for demonstrating the efficacy of any MRI contrast agent in CNS imaging (in the re-reads or in any future clinical trial), and*
- *f. publicly available documents regarding FDA's review of previously approved MR contrast agents of the same class for the same or similar indication,*

Is the Agency willing to consider accepting the comparison between pre-contrast images and pre-plus post-contrast images as primary data?

Agency Response

The Medical Imaging Guidance, Part 3, Section IV, B, 12, states (example 2) "In a study intended to demonstrate that a contrast agent contributes additional information to images obtained with the device alone, it is often highly desirable to perform an appropriate separate image evaluation of test images as the principal image analysis ..."

The comparison of pre-dose and paired image sets would be acceptable if the endpoint were a ——— endpoint. A ——— end-point, however, must include a standard of truth for comparison. For a visualization endpoint, however only a comparison of the pre-dose and post-dose scans would be appropriate. Since the post-dose image set contains the pre-dose image set, one would expect the post-dose scan set to score equal or better than the pre-dose set regardless of what the images actually show. Admittedly it may be clinical practice to read a paired image set rather than a post-dose image set alone, ———————————— ——— not to score visualization variables.

Question 4

The 0.1mmol/kg MULTIHANCE dose was shown to be statistically non-inferior to the 0.1mmol/kg dose of OMNISCAN, while this could not be demonstrated for the 0.05 mmol/kg dose. In addition, two of the three readers in MH-106 detected significantly more lesions when the 0.1mmol/kg dose was used in patients with CNS metastases. Therefore, the Sponsor at present reaffirms the choice of the 0.1mmol/kg dose as the appropriate dose and would like to discuss the issue of the dose selection further with the Division.

Agency Response

We will be happy to discuss this issue further with you as you have requested. Please note that the cited results can only be considered exploratory. The results were not found to be significant for either the 0.05 mmol/kg dose or the 0.1 mmol/kg dose for the more relevant re-read study MH 105. The comparator for the re-read protocols MH 105 and MH 106 was the baseline non-contrast MRI and an approved agent. Lesion number was not the primary efficacy endpoint but a secondary endpoint. Dose comparisons for the clinically more relevant subset of ≤ 2 lesions at baseline did not reveal any significant differences in results between the 0.05 mmol/kg dose and the 0.1 mmol/kg dose. You have therefore not provided confirmatory evidence for your choice of the 0.1 mmol/kg dose as the best dose for marketing.

Question 5

Considering that the primary analyses requested by the FDA, including the end-points, the comparison between pre-and postdose images, and the lesion level analysis, and the imputation rules we utilized created a situation not previously used for demonstrating the efficacy of any MRI contrast agent, would the Agency consider the sum total of evidence provided as proof of efficacy for MULTIHANCE? We are willing to discuss the possible additions/modifications to the labeling that would address any concerns

No.
The primary analysis was one that was not "requested" by the Agency. The Agency recommended new clinical studies. The Agency did not recommend a re-read as a means to resolve problems and biases of data. Subsequently, when you made the decision to re-read, the Agency continued to clearly share its concerns with such an approach. Discussions and comments on your re-read protocol were about the protocol design only and were not meant to imply that re-reading would resolve biases and adequacy of data collected in the original trails. For three of the approved class agents, as indicated in the label, a pre v/s post comparison was the type of analysis that was for approval. In the fourth, the studies were prospectively designed to provide ——— information for a pre versus paired analysis. Therefore the agency does not agree with such a design (pre versus paired) to support an anatomic indication.

Further, based on the concerns on the design flaws and the population (see response to question 1 above), the Agency cannot consider the sum total of evidence as confirmatory proof of efficacy that can support the sought global anatomic indication. Such compilation of results is exploratory.

Question 6

We seek clarification regarding whether the standard being applied to MULTIHANCE is the same that applied to previously approved products with the identical indication, or is the standard different because MULTIHANCE is not the first product in this therapeutic class or for some other reason? Our question is especially important to us in understanding the FDA's position in view of the fact that the comparator drug in our studies, OMNISCAN, also failed by this analysis approach and the fact that no other currently FDA approved MRI agent has been required to demonstrate efficacy in CNS using the predose versus postdose image evaluation.

Agency Response

It is not the agency's intention to apply different standards to MultiHance than to other MRI imaging agents. Whether comparison of the pre-dose set to the post-dose set or comparison of the pre-dose set to the paired set is appropriate depends on the primary outcome variable chosen for the pivotal clinical trials. For a [redacted] endpoint, comparison of the pre-dose and paired sets would be appropriate. For a visualization endpoint, a comparison of pre dose and post-dose sets would be appropriate

Question 7.

The sponsor has requested a deferral of the pediatric study requirements based on the intent of the Pediatric Rule as discussed in the preamble to the final regulation. Will you agree to this deferral with the Sponsor's commitment to conduct the required study(s)?

Agency Response

The Agency will consider a deferral request. We recommend that you submit an official request for a waiver and a time line in which the study(s) will be performed.

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/s/

Diane Smith
7/8/04 05:52:57 PM
CSO

DIVISION DIRECTOR'S MEMO TO THE FILE

NDA:	21,357 (Single dose) 21,358 (Pharmacy bulk pack)
DRUG:	MultiHance (Gadobenate dimeglumine) Injection
MODALITY:	Magnetic Resonance Imaging (MRI)
INDICATION:	Contrast enhancement in CNS
CATEGORY:	
SPONSOR:	Bracco Diagnostics, Inc.
SUBMITTED:	April 30, 2001 (**First Cycle**)
PDUFA:	February 28, 2002 (10 month)
AMMENDMENT:	February 27, 2002 (**Major Amendment**)
PDUFA:	February 28, 2002 (10 month) **extended** to May 27, 2002
COMPLETED:	May 20, 2002 (**First Cycle**)
ACTION LETTER:	May 24, 2002 (**Approvable** for intravenous use in magnetic resonance imaging (MRI) contrast enhancement of the central nervous system (CNS) to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated issues.)
SUBMITTED:	NDA 21,357 - October 14, 2003 (**Second Cycle**) NDA 21,358 - October 14, 2003 (**Second Cycle**)
PDUFA:	April 14, 2004 (6 months) (**Second Cycle**)
COMPLETED:	

RELATED REVIEWS:

Chemistry:	David Place, PhD.	2/25/04
Clinical Pharmacology:	Young-Moon Choi, Ph.D.	
Pharmacology-toxicology:	Yanli Ouyang, Ph.D.	4/07/04
	Adebayo Laniyonu, Ph.D.	4/06/04
Clinical:	Ramesh Raman, MD	
	Robert Yaes, MD, Ph.D.	
Statistics:	Sonia Castillo, Ph.D.	3/03/04
	Mike Welch, Ph.D.	3/09/04
Project Manager:	Diane Smith, R.Ph.	

The Second Cycle NDA review is directed to Bracco Diagnostics' response to the Approvable Action Letter of May 24, 2002 (attached).

The Approvable Action Letter (attached) lists specific issues that have been the subject of **Discipline reviews.** Bracco Diagnostics has responded to these issues in their response of October 14, 2003. The Agency's review of these responses has been completed by the following:

David Place, Ph.D.	**Chemistry**
Yanli Ouyang, Ph.D.	**Pharmacology-toxicology**

Each of these Discipline reviews **recommends for approval of MultiHance and propose labeling changes.** I have reviewed their reports, agree with their comments, and their proposed label revisions.

The **clinical and statistical Discipline reviews** have been completed by the following:

Clinical:	Ramesh Raman, MD Robert Yaes, MD, Ph.D.
Statistics:	Sonia Castillo, Ph.D. Mike Welch, Ph.D.

These clinical and stastistical **Discipline Reviews** recommend the following:

Approval for safety of MultiHance with label changes

Approvable for efficacy of MultiHance for adult ——— indications

Based on the clinical and statistical reviews, Bracco Diagnostics should proceed to design and initiate new adult ——— clinical trials to accomplish the following:

1. The identification of the appropriate dose for — the adult ——— population.

2. The enrollment of adult ——— subjects with all CNS diseases (brain and spine) represented in adequate populations to support the proposed clinical indication.

3. The studies should be designed to demonstrate congruence between the proposed clinical indication, the primary efficacy variables and with an appropriate pre-specified independent analysis that will support clinical usefulness. The data and imaging should be collected, archived and submitted for a prospectively designed, blinded, independent reader methodology.

4. The clinical trials should be conducted in accordance with the clinical standards of practice in the United States, to replicate the conditions under which a physician would consider administering a contrast agent, such as Multihance.

5. ———

I have reviewed these submitted Discipline reviews, agree with their analyses, comments and regulatory recommendations:

Approval for safety of MultiHance with label changes

Approvable for efficacy of MultiHance for adult ——— indications

From the submitted clinical and statistical reviews incorporated into Dr. Ramesh Raman's review for this NDA review cycle (2), I have drawn the following information, comments and analyses to support the regulatory assessments.

To support the original NDA review cycle (1), please refer to the Division Directors's Memo to File (2/10/02) and the Addendum to the Division Director's Memo to the File (5/20/02).

DRUG:	MultiHance (Gadobenate dimeglumine) Injection
ROUTE:	Intravenous as rapid bolus or infusion
MODALITY:	Magnetic Resonance Imaging (MRI)
INDICATION:	Contrast enhancement in CNS (adults ——— for Central Nervous System (including the spine) in Adult ——— Population ———
PROPOSED 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, and associated tissues."
PROPOSED DOSE:	CNS Adult - 0.1 mmol/kg ——— g
RELATED DRUGS:	Magnevist (approved - 1989) ProHance (approved - 1992) Omniscan (approved - 1993) Optimark (approved - 1999)

Regulatory Background:

Bracco Diagnostics submitted an NDA for MultiHance (gadobenate dimeglumine) Injection to enhance magnetic resonance imaging (MRI) of the brain ———. The original NDA submission was received on April 30, 2001. In February 2002, the NDA 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 amendment was accepted and extended the PDUFA due date to May 27, 2002. In the course of the first cycle review, a Division Director's memo to the file was created on February 10, 2002 and an Addendum to the Division Director's memo to the file was created on May 20, 2002. Subsequent to the completed first cycle NDA review, an Approvable Action Letter for NDA 21,357 and NDA 21,358 was sent to Bracco Diagnostics on May 24, 2002.

Bracco Diagnostics responded to the Approvable Action letter through a meeting with the Division on August 28, 2002. Subsequent to that meeting with the Sponsor, the Division responded with comments on November 15, 2002 and provided additional clarification comments on December 3, 2002. Further clarification comments to the Sponsor were provided in a telecom on December 11, 2002. Bracco Diagnostics responded on January 20, 2003 with reference to their proposed re-reading of images from the previous studies and the Division responded with a follow up letter to the Sponsor on March 7, 2003. In the March 7th letter, the Division noted that as in the action letter of May 2002, that to address the clinical efficacy deficiencies for approval of MultiHance, would require at least one large, robust clinical study in adults. The Division further noted in the March 7th letter that Bracco proposed re-read protocol was not evaluated by the Division, as to whether the protocol would address the clinical efficacy deficiencies.

In follow up to the first cycle safety review, the Division requested a consultation from the Division of Cardio-Renal Drug Products on December 4, 2002 and received the completed consult on January 3, 2003. The Division sent to the Sponsor a Discipline Review Letter on March 10, 2002 regarding the consultation and the noted issues related to MultiHance and possible prolongation of QTc and the possible affect on AV node conduction.

The current re-submission has been modified from the original NDA submission with [redacted] an anatomic (visualization) claim. In this regard, the current focus of this re-submission (and the development program) is on the safety and efficacy for single global CNS and Spine indication in adults [redacted]

It is noted in the reviews that rather than complying with the Approval Action Letter of May 24, 2002 recommendation to proceed with new clinical trials, the sponsor submitted a proposal to the Division for a blinded re-read of the adult CNS studies for a new visualization claim. It is to be noted that this re-read approach was one that was neither recommended nor suggested by the Agency/Division. The proposal for the blinded re-read of existing data was one initiated by the sponsor, who fully understood the risks that the results may not support the sought indication despite its change [redacted] to an anatomic claim. The sponsor was reminded that the agency's recommendation remained for new study/s. The agreement on the proposed blinded re-read protocol was on its design and not on its acceptance as an alternate to new studies to support an indication.

This re-submission is a blinded re-read of old data and does not include new studies, as recommended. Thus, in support of the efficacy indication, no new CNS studies were performed, as recommended in the action letter.

The Agency provided comments for the submitted re-read protocols 105 and 106 that included the original three adult CNS studies. Agreements that were reached under these two re-read protocols were for the adult studies only.

Included in the submitted blinded re-read are a total of three adult studies and one pediatric study:

- The two identical adult pivotal studies, 9A and 9B, conducted in the US, which were combined under re-read protocol 105.
- The third adult study, 020, involving patients with brain metastases conducted in Europe was included in re-read protocol 106.
-

TABLE 1: Efficacy Re-read Database

New Protocol #	Referenced Study #	Patient (N) [1]	Site/s	Pivotal	Population Type [2]
MH-105	43,779-9A & 9B	136	US	Yes	Adult Brain and Spine – All CNS diseases
MH-106	B 19036/020	75	Europe	No	Adult- All known brain mets

Ref: Table 2.1 of Dr. Castillo's review; Review cycle 1 memo (appendix 2)
1 = Those who received the sought 0.1 mmol/kg dose
2 = Compare with Table 2. Note: Total CNS = 240 (adult = 211 [136 from re-read 105+75 from re-read 106] of which 172 (72%) patients (adults = 143 [68 from re-read 105+ 75 from re-read 106] were tumors (primary and or mets) and 4 patients (1.6%) with spine disorder.

TABLE 2: Efficacy Database Compared
Review Cycle 1 v/s Current

COMPARATOR	REVIEW CYCLE 1	CURRENT REVIEW CYCLE
Adult		
Adult Indication		Visualization
Adult population [1]	All CNS and Mets	All CNS and Mets
Adult Patients (N)		
105 (43,779-9A & 9B)	136 (0.1 dose) (276 all doses)	136 (0.1 dose) (276 all doses)
106 (B19036/020)	76 (0.1 dose) (150 all doses)	75 (0.1 dose) (149 all doses)
Adult Dose in mmol/kg	0.1 + 0.1	0.1
Blinded Readers [2] (N)	2 per study	3 per study
Pediatric		

Ref = Review cycle 1 memo; Table 2.1 of Dr. Castillo's review; Sponsor's Vol. 24, pp. 083, 117
1 = Type of patients = Study 105 (Surgical = 9.8%, Infarct = 11.7%, Multiple Sclerosis = 10.7%, Tumor 50.7% (primary 12.4, benign 27.3, mets 11.0) with only 4 spinal disorders; Study 106 = 100% mets.
2 = Three US blinded readers for pivotal US trial 105 and three Italian blinded readers for study 106.

1 + 3 = Note: Total CNS = 240 (adult = 211 [136 from re-read 105+75 from re-read 106] of which 172 (72%) patients (adults = 143 [68 from re-read 105+ 75 from re-read 106] were tumors (primary and or mets) and 4 patients (1.6%) with spine disorder.

Key Blinded, Re-read Protocol Features

The protocol specified primary objective for re-read studies

- 105 (the two pivotal adult US studies similar in design)
- 106 (the adult metastatic tumors study conducted in Europe)

was to compare the two doses (0.05 and 0.1 mmol/kg) of MultiHance given as first, single doses in terms of changes from pre-dose to post-dose for lesions in all the primary endpoints/variables:

- Border Delineation
- Visualization of Internal Morphology
- Contrast Enhancement

All image sets (pre and post), following a randomization, were blindly read and scored on a 5-point scale (0-4) for each of the end-points.

The score that a pre-contrast image received was a composite score given to the entire sequences that comprised that pre-contrast set.

The **pre-contrast image sets** were variable and included the following:

- T1, T2, and PD (Proton Density) - re-read study 105
- T1 and T2 - re-read study 106
-

The **post contrast image set** was a single sequence of T1.

The **primary level of analysis** is the comparison between the pre contrast images (a set of different sequences) and the post contrast images.

The **secondary level of analysis** is the comparison between the pre contrast images and the paired images (paired = pre contrast + post contrast).

The **secondary endpoint/variable** was number of lesions.

Key Protocol and Trial Design Issues

The flaws in the overall study design of the original protocol and those directly related to the re-read protocol are discussed below.

Enrollment bias/enrichment- all enrolled patients were with known disease and had received another imaging study as part of inclusion criteria.

The patient population was underrepresented for the sought claim. Specifically, there were only 4 patients with spine disorders in the pivotal re-read study 105 and over 70% of the patients in the study 105 re-read were tumor patients.

There was no gold standard established in any protocol. Since the re-read protocol was designed to compare the MultiHance images against its own baseline for a visualization claim, the need for a "gold standard or truth standard", or an approved active comparator was not crucial. In this context, such absence of a reference standard does become relevant, particularly when the sponsor claims success based on the positive results in the pre v/s paired comparisons that typically are employed

Approved active comparator.

- Study 105 had an active comparator (Omniscan).
- Study 106 had no active comparator.
- Study 112 had an active comparator (Magnevist).

Image Acquisition Methodology

The lack of consistency in the acquisition of image sequences and the lack of complete representation of the required image sequences in the pre-contrast set of images were fundamental flaws in the clinical trials design with respect to the practice of medicine. As a result, the sponsor has failed to reliably and consistently demonstrate that "the drug" (MultiHance) could provide beneficial information over the "device" (non contrast MRI). Specifically, the results seemed to be better with contrast, when a single sequence of the pre-contrast image (e.g. pre-T1, T2) was compared with the post contrast T1 image (results of re-read 106). But when additional pre-contrast sequences (PD) were included with the T1 as part of the pre-contrast set, MultiHance provided very little additional benefit and the results were significantly inferior from those that had a limited pre-contrast sequence (results of re-read 105).

Based on the previously identified flaws in review Cycle 1 due to the multiple dosing regimen in the adult studies and the lack of a dose response, the submitted re-reads

were carried out only on images that were acquired either immediately following the administration of the sought 0.1 mmol/kg as the first dose or the 0.05 mmol/kg dose, also as the first dose.

The schema for the blinded re-read protocol is attached.

Thus, the change to an anatomic visualization claim, coupled with the small sample sizes in the different dose arms for the MultiHance group, and the parallel comparator study design; automatically restricted the value of the analyses (e.g., pre v/s paired image comparisons) and rendered potential comparative analyses to the approved class agent clinically meaningless. Therefore, **the focus of the analysis of the re-read efficacy results were primarily on the comparisons of the post contrast MRI with the baseline non-contrast MRI (the committed and agreed primary analysis)** and not to the comparator (not meaningful) or the comparisons between the pre and the paired images (agreed as secondary level of analyses and is not congruent with a visualization claim).

Results

The results on the three co-primary variables/endpoints will be discussed, first at the primary level of analyses (pre v/s post) and secondary level of analyses (pre v/s paired). Following that discussion, the results on the secondary endpoint/variable of lesion numbers will be discussed.

The focus of the statistical review was on the pre v/s post images since this was the agreement per protocol.

The results on a secondary level are also discussed in detail in this memo, in regard to the sponsor's emphasis that success was achieved on this level.

Table 3 below provides an overview of the statistics and results for adult studies for all the three co-primary efficacy variables by dose and at both primary and secondary level of analyses.

TABLE 3: RE-SUBMISSION RESULTS [1]
PRIMARY EFFICACY VARIABLES/ENDPOINTS
ADULT — CNS

ALL CO-PRIMARY [2] ENDPOINTS (All Lesions)

STUDY	Primary Level - Pre v/s Post				Secondary Level - Pre v/s Paired			
105 Adult All Lesions	Dose	Patient N	Lesion N [3]	Result	Dose	Patient N	Lesion N [3]	Result
	0.05	140	245-355	NS*	0.05	140	254-318	S*
	0.1	136	271-381	NS*	0.1	136	299-395	S*
106 Adult Mets Only	0.05	74	142-180	S*	0.05	74	149-171	S*
	0.1	75	250-274	S*	0.1	75	245-275	S*

BY DOSE DIFFERENCE- 0.05 v/s 0.1 [A, B]

	Primary Level - Pre v/s Post	Secondary Level - Pre v/s Paired
105	NS**	NS**
106	NS**	NS**

1= Ref = Tables 3.3, 3.5, 3.7 of Dr. Castillo's review; Sponsor's Tables 1-8, 1-9, 1-10, 1-23, 1-24, 1-25, vol. 24, pp.37-39
2= Three Co-primary End-points - Border delineation, Internal Morphology, Contrast Enhancement
3 = Lesion number varied by reader
NS* = Not significant (for all 3 readers, for all primary variables and for all doses)
NS** = No significant differences between doses.
S* = Significant (p-value <0.001 for all 3 readers, for all primary variables and for all doses)
S** = Significant (p-value <0.001 for all primary variables for single blinded reader and single dose studied)
A = 0.1 mmol/kg dose is the sought market dose for both adult — indications.
B =

Outcome Findings of the Re-Read for Efficacy

The re-read results for the pivotal adult CNS study (105), for the primary efficacy analysis (of pre v/s post) were not significant (Table 3) and therefore, the required evidence of effectiveness that Multihance performed better than the device alone that was agreed upon with the Sponsor, was not established.

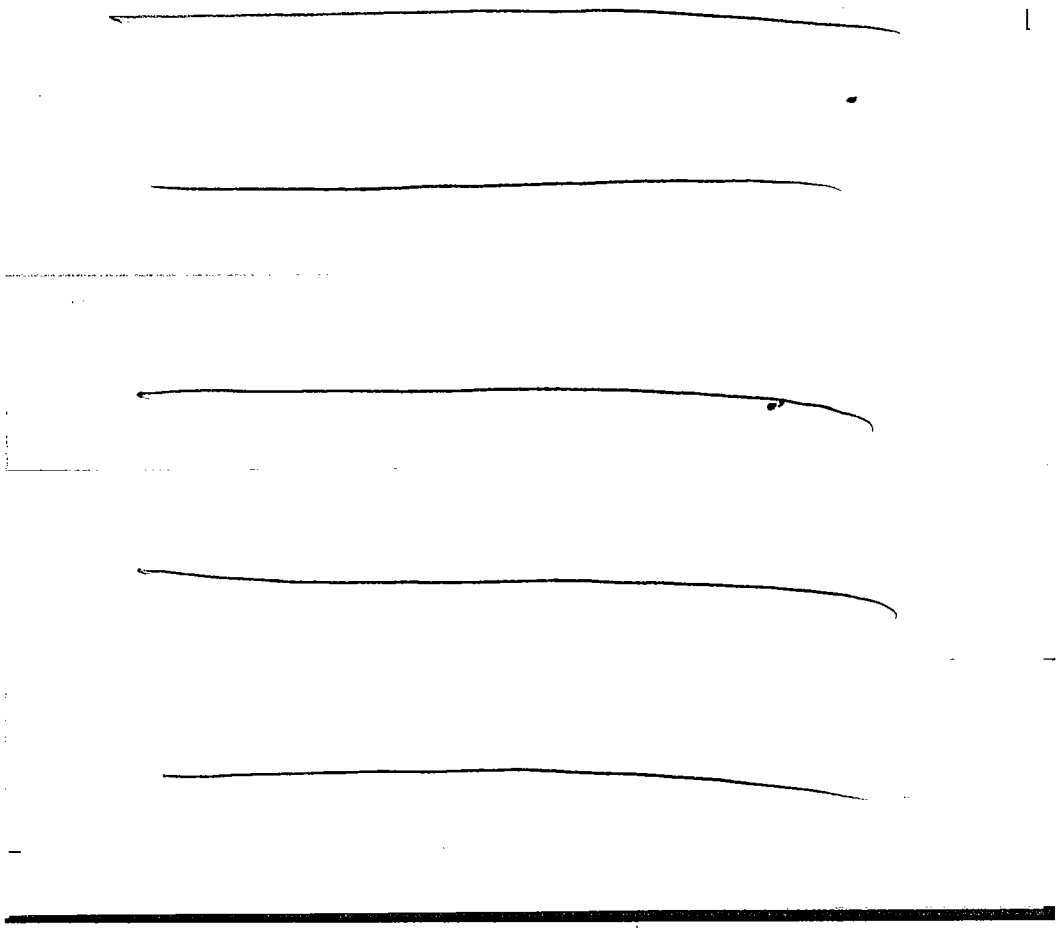
The statistical significance demonstrated for the primary efficacy level for the non-pivotal adult metastatic study and the statistical significance demonstrated for the secondary level of efficacy analysis (pre v/s pair) for all the studies was not what the Sponsor committed to provide in the re-read as the primary measure. In addition, these results are not clinically relevant with respect to the intended market population and were achievable because of intrinsic flaws (lack of required sequences in the pre images and the scoring system [not concordant for a pre v/s pair analysis]). These are discussed below broadly under each category and Table 4 summarizes the limitations of the results.

Value and Limitations of the Re-read Results

TABLE 4: CNS INDICATION - LIMITATIONS OF RE-READ RESULTS

	STUDY 105	STUDY 106
Patient Type	Adult CNS	Adult Mets
US Study Site	Yes	No
Pivotal	Yes	No
CNS Disease Type	70% tumors 30 % others	100% mets
US blinded reader/s	No	Yes
Number of blinded readers	3 European	3 US
Significant Primary Level Results	No	Yes
Significant Secondary Level Results	Yes	Yes
Incomplete Sequences Influencing Primary & Secondary Level Results	No	Yes
Scoring method Influencing Primary Level Results*	N/A	N/A
Scoring method Influencing Secondary Level Results*	Yes	Yes
Differences in Dose Response (0.05 v/s 0.1) at any level for any primary endpoint for any reader	No	No

*= Since Re-read protocol was designed for visualization claim, the scoring methodology did not influence primary level analyses but influenced the secondary level



In this context, the true benefit of a drug over a device is not determinable and therefore, was not demonstrated, a fundamental flaw. The sponsor acknowledges and recognizes that the imaging conditions employed for the two pivotal trials performed under re-read protocol 105 were those employed in clinical practice in the US. Such conditions were not followed for re-read protocols 106 [redacted] As noted, in the single re-read study #105, which was closer to the conditions of clinical practice in the US, the results were not significant in the primary analysis. The analyses with positive results were achieved in studies performed under sub-standard conditions of clinical practice in the US (re-reads 106 [redacted]. In those studies where the conditions were closer to the standard practice of medicine in the US, the primary results were not significant. The positive secondary level results for the pivotal US re-read study 105 were achieved due to the scoring methodology that is discussed below.

The sponsor's arguments that effectiveness was demonstrated for the secondary level of analyses (pre v/s pair) for all studies, requires careful deliberations and considerations. As much as it is the clinical practice to read the non-contrast images with the contrast images, such paired assessments typically are implemented when

which eventually translates to the effective management of patients. Since it was clear from review cycle 1, that without new studies, the existing Multihance program could not deliver such a (lack of truth standard), the focus in crafting the meaningful design for the re-read protocol that could achieve the sought new visualization claim was, therefore on the comparisons between the pre and the post images alone. From these perspectives, the agreed primary level of analyses of pre v/s post would be an approach that would be congruent for a visualization claim. The primary efficacy variables that were analyzed in the re-read were chosen to provide information that would best support a visualization claim by comparing the pre v/s the post and not , that would be best achieved typically via pre v/s paired comparisons. On the contrary, if the primary level of analyses involved pre v/s paired, then different primary variables would be selected and analyzed differently to provide information. Retrospective application of secondary level (pre v/s pair) positive results for a (visualization) claim was not agreed upon and is neither clinically meaningful. In essence, the issue is not whether comparisons between pre v/s post or pre v/s paired images should be used to demonstrate effectiveness, but whether the chosen level of analyses is congruent with the primary efficacy variables and the sought claim. To understand this further and as a response to the sponsor's arguments on their claims of success based on the significance in results between the pre and the paired images, it would be best, at this time, to re-visit and discuss the clinical trials for the approved class agents.

There are currently four approved class agents in the market:

1. Magnevist
2. Prohance
3. Omniscan
4. Optimark

The table below (Table 6) provides an overview and summary of the salient features for each of approved class agents and Multihance. Suffice it to say, when the focus of the claim for three of the class agents, viz., Magnevist, Prohance, and Omniscan were anatomic/visualization, their success were determined primarily on the basis of the comparisons between the pre and the post images. Diagnostic information and lesion

numbers was secondary and additional in nature. The story is slightly different for Optimark. Although the pre v/s paired comparisons rendered an anatomic claim, the studies and the CRF were designed in a manner to provide information not only for the primary visualization endpoints (anatomic features) but also for diagnostic information. These primary visualization endpoints were woven intricately in the blinded CRF to further provide diagnostic information that was directly attributable to the imaging features. Further, all the standard MRI sequences were fully represented and the regions studied were supportive of the sought claim (69.1% brain and 30.9% for spine). Most importantly, the patient population was more representative of the disease spectrum for which such an agent would be used (tumor 28%, degenerative/demyelinating 33%, infection/inflammation 4.6%, other 16%, unknown 6%, etc.). It is beyond the scope of this review to provide further details on the clinical trials for all the agents.

The re-read Multihance protocol did not capture [redacted] the program enrolled predominantly tumors (~ 70% tumors in the adult pivotal US trial and 100% tumors in the supportive adult trial), the program did not have enough spine patients, and the pediatric re-read was on 100% tumors. Therefore, the sponsor's claims on success that a well represented disease population that mimics the class agents were achieved via the pre v/s paired comparisons are baseless and not relevant. On these grounds as well, approval is not justified.

TABLE 6: APPROVED CLASS AGENTS*

	Magnevist	Prohance	Omniscan	Optimark	Multihance NDA Resubmission
Approval date	1989	1992	1993	1999	N/A
Adult CNS (Brain and Spine)	Yes	Yes	Yes	Yes	Yes
CNS (Brain and Spine)	Yes	Yes	Yes	No	Yes
Spine and associated tissues	Yes	Yes	Yes	Yes	Yes
Body [1]	Yes	No	Yes	No	No
Total subjects (N) for CNS Indication	550	NR**	439 adult	394	240
Adult (N) Brain and Spine subjects-core studies	NR**	133	NR**	262	211
Truth Standard &/ Comparator	See note [B]	See note [B]	See note [B]	See note [B]	See note [C]
Analysis Type	Pre v/s post	Pre v/s Post	Pre v/s Post	Pre v/s Pair	Pre v/s Post
Anatomic/Visualization Endpoints	Yes	Yes	Yes	Yes	Yes
Lesion numbers	Yes	No	Yes	Yes	Yes (secondary)

*Ref: Respective Labels; DD memo (Feb 02); Review Cycle 1 memo; Review Optimark NDA
NR**: Not retrievable
1 = Intrathoracic (excluding heart), Abdominal, Retroperitoneal
A =
B = Included histopath for Magnevist for brain tumors · Omniscan. The others had either a cross over image with an approved class agent or CT or histopath or a parallel design with large representative sample size with comparable demographics , with a pre-specified statistical plan.
C = No truth standard. Approved class agent/s was included in the studies. The primary analyses were based on the comparisons between pre contrast and post contrast images with no comparative claims (superiority or non-inferiority).

Fourthly, another reason why there was significance in results at a secondary level and not at a primary level is related to the design of the re-read protocol. The re-read protocol was specifically designed to provide anatomic information (for the sought visualization claim) via a pre v/s post comparison and not for a (typically via a pre v/s paired comparison). Not considered a re-read protocol flaw for an anatomic claim, the blinded reader scoring methodology in the re-read protocol clearly influenced the results when a pre v/s paired (secondary level) image sets were compared. The schema (attached) provides an overview of the blinded re-read methodology and the scoring.

The scoring for each of the end-points was a composite scoring for the all the sequences in the pre-image-sets, i.e., the T1+T2+PD sequences in re-read study 105; and T1+T2 for re-read studies 106 and 112 received a single composite score based on the best score without attribution to the sequence/s that rendered that best score. In the paired reads, if the pre-image-set received a higher score than the post image (T1 only), then the paired read received the score of the pre-set-image. Therefore, the results were driven by the scoring - i.e.- how the best sequence received the highest

score and therefore the score of a post contrast image in a paired read, even if it was lower than the pre contrast image sets, would receive the same score as the pre-image-set. The true lower post contrast score would never be recorded and only when the post contrast image score was higher, would it be recorded to override the overall score that the paired read would receive. With such scoring, in the pre v/s paired comparisons, the results of the paired read would be at least equal to or better than the pre-contrast image sets and would never yield results that would be inferior. Hence, and not surprisingly, the results on the secondary analyses of pre v/s paired read were statistically significant for all readers and all primary endpoints. Once again, despite significance at a secondary level, there was no dose response.

As in the primary level of analyses involving pre v/s post images, there were no differences between the 0.05 dose and the 0.1 dose in the secondary level of analyses for all readers and for all primary efficacy variables. The relevance of the statistically significant results for each of the individual doses whether in the primary level of analyses for the non-pivotal studies or in the secondary level of analyses for pivotal and non-pivotal studies, therefore, has no clinical significance other than to indicate that both doses were effective equally. The proper dose was not identified and the chosen 0.1 mmol/kg dose as the lowest effective dose for the adult indication was not established. The sponsor's argument favoring the higher 0.1 mmol/kg dose is based on the non-inferior comparability in results with the comparator (Omniscan). The protocol was not designed to provide comparative data. The more relevant finding that there were no statistically significant results between the two Multihance doses has not been addressed by the sponsor.

Lesion Numbers

The effects of Multihance on the number of lesions was a secondary endpoint/variable.

Such analyses were presented for the adult indication

The re-submission focused on two clinically relevant aspects in these analyses.

- lesion tracking
- changes in those lesions that were 0 or 1 or 2 at baseline.

The results generally indicated the following:

- Majority of lesions remained the same in number as baseline.

- In the all lesion analyses (Table 7 below), there was no significance in results for re-read study 105, where the number of subjects with lesions were lower post contrast for each blinded reader and each dose.

- However, the results were significant post contrast in re-read study 106 for all readers and for each of the doses, but there were no differences between the two doses for each blinded reader.

TABLE 7: SECONDARY ENDPOINT- LESION NUMBER [1]
PRE v/s POST - ALL LESIONS*

STUDY 105			STUDY 106		
	DOSE			DOSE	
	.05	.1		.05	.1
Reader 1			**Reader 1**		
Number of Lesions	297	363	Number of Lesions	142	250
Pre-contrast (N)	**233**	**286**	**Pre-contrast (N)**	**91**	**120**
Post-contrast (N)	**206**	**250**	**Post-contrast (N)**	**132**	**237**
Reader 2			**Reader 2**		
Number of Lesions	355	381	Number of Lesions	180	274
Pre-contrast (N)	**273**	**299**	**Pre-contrast (N)**	**106**	**145**
Post-contrast (N)	**217**	**232**	**Post-contrast (N)**	**170**	**256**
Reader 3			**Reader 3**		
Number of Lesions	245	271	Number of Lesions	171	259
Pre-contrast (N)	**203**	**206**	**Pre-contrast (N)**	**112**	**127**
Post-contrast (N)	**138**	**166**	**Post-contrast (N)**	**152**	**248**
Significant Results	**No**	**No**	**Significant Results**	**Yes**	**Yes**

*Derived from tables 3.3 and 3.5 from Dr. Castillo's review
1 = Such lesion number analyses as a secondary endpoint

The results for the < 2 baseline lesions (Table 8 below) subset were generally similar to the all lesion analyses. In the majority of subjects, the numbers of lesions were the same as the baseline following contrast administration. The results were better for re-read study 106 (as anticipated since these subjects were all with mets) compared to re-read study 105 and there were more subjects with lesions detected with both doses that were significant but there were no differences between the doses.

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TABLE 8: SECONDARY ENDPOINT – LESION NUMBER [1]

SUBSET: PATIENTS WITH ≤ 2 LESIONS AT BASELINE [A]

		Level of Analyses Performed		RESULTS		
Study/Dose	**Number of Patients****	**Pre vs. Post**	**Pre vs. Paired**	**Baseline = Post (n**)**	**Post > Baseline (n**)**	**Dose Comparison**
Study MH-105						
0.05 mmol/kg	104 - 118	Yes	No*	Majority (67 - 80)	Two of 3 readers (25)	Not Significant
0.1 mmol/kg	98 - 111	Yes	No	Majority (51 - 76)	All readers (21 - 27)	
Study MH-106						
0.05 mmol/kg	66 - 71	Yes	No	Majority (37 - 40)	All readers (24 - 30)	Not Significant
0.1 mmol/kg	59 - 66	Yes	No	Majority (27 - 34)	All readers (30 - 31)	

* Not clinically meaningful
** Varies by reader
A = Derived from tables 3.4 and 3.6 from Dr. Castillo's review
1 = Such lesion number analyses as a secondary endpoin[illegible] 2

These lesion number results were driven by the non-pivotal re-read study 106 (the mets study) and generally, MultiHance, independent of the administered dose, identified a majority of subjects with the same number of lesions at baseline. As with the concerns on the results for primary endpoints/variables discussed above, the results for non-pivotal re-read study 106 were influenced by

- the sequences (lack of complete sequences in the pre-contrast-sets)
- the type of patients (all with mets).

As with the arguments on the improvements in results at a secondary level of analyses (pre v/s paired) for the primary variables, the sponsor claims success for this secondary endpoint of lesion number for re-read study 106 on the secondary level.

[redacted] there would be no such grounds for lesion detection by numbers. As such, assessments on pure lesion numbers do not require the type of imaging features that are typically used to render [redacted] attributes. Therefore, success based on a pre v/s paired analyses for lesion numbers has no merit. Another important issue with respect to lesion numbers is that there was no way to verify if the lesions that increased post contrast were true lesions or artifacts.

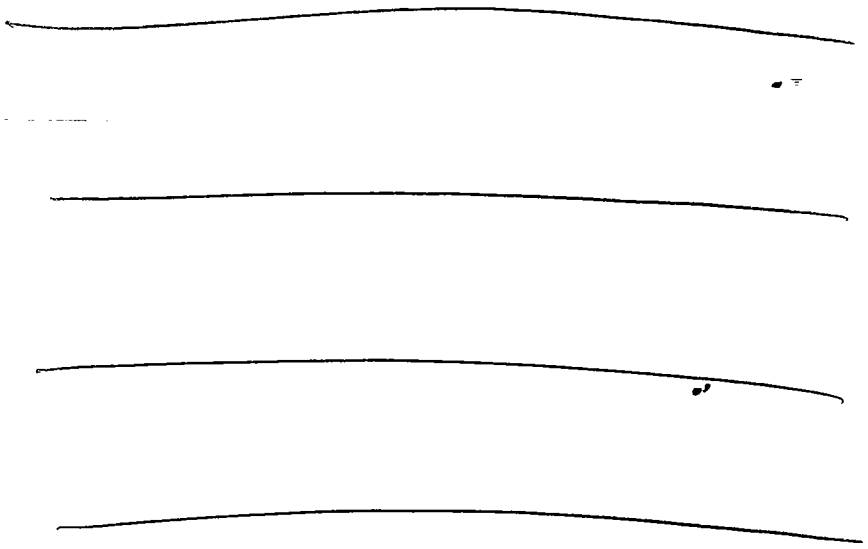
ADM-6

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



General Safety Comments

In conjunction with resolution of safety issues related to all the disciplines and with the available overall clinical safety information, Multihance's magnitude of the previously identified clinical safety issues have been sufficiently lowered, such that the safety profile can be considered less worrisome and any outstanding issues can be addressed in the label.

Since these issues have been discussed in the primary review, the focus of this section will be to discuss how those deficiencies, identified in the action letter, evolved to become outstanding labeling issues.

In the overall decision that Multihance is not ready for approval, any specific clinical label recommendations are premature, but since clinical safety can be considered established at this time, the label changes for safety will be identified.

The recommendations in the May 2002 action letter based on the identified concerns were the following:

> **Liver:** New drug interaction studies and subset analyses of LFTs from patients with liver disease to address the concern on the lack of sufficient data to fully assess the risk of Multihance on the liver.

CVS: New placebo-controlled studies in patients using at least 4x the sought dose to address the concern on the lack of sufficient data to fully characterize the safety of Multihance on the cardiovascular system.

Renal: Recommendation to provide available urinalysis data in patients with renal insufficiency, the elderly and the pediatric population and to collect urine data in all the on-going studies to address the concern on the lack of sufficient data in adult and pediatric patients to determine the effect of Multihance on the renal system.

Local AE: Lack of sufficient information on local adverse events with the recommendation to provide additional data on serious AEs such as fascitis, thrombophlebitis, compartment syndromes, etc.

Death CRF: Case report forms on all patients who died during the clinical trials.

Reporting of all patients in the Integrated safety summary.

In this re-submission, the sponsor has responded to each of these issues.

Liver and Multihance

The basis for the concerns was:

- The PK properties of Multihance and its relation to the cMOAT (canalicular multispecific organic anion transporter), the hepatocellular uptake and the biliary excretion.
- Post Multihance hyperbilirubinemia in three volunteers with underlying von Willebrand's disease and one patient with Wilson's disease.
- Increased pruritus in patients with cirrhosis compared to those without cirrhosis (2.2% v/s 0.5%).

Sponsor's Response

- Justification for not conducting new studies.
- Detailed mechanism of action of Multihance with respect to the hepatocyte uptake and its biliary excretion based on preclinical data.
- The results of the assessments of the possible competition for the cMOAT by bilirubin, Multihance and other drugs.

- Re-analyses of safety results in patients with liver disease.

- Post marketing reports from European and Asian countries where ~ [redacted] units were sold.

Discussion

Although the results were limited by small sample sizes in some of the analyses that questioned the value of such data, partial relevance to the issue, and arduousness in interpretation due to the editorial quality of the submission, overall, there were no new significant findings that would warrant new studies. Based on the on-going discussions with the agency clinical pharmacology discipline that dates back to May 2002, the concerns on the relationship between Multihance and the liver (and the cMOAT [canalicular multispecific organic anion transporter]) that was identified in the action letter may be considered an issue that can be addressed in the label. The basis for such a decision was based primarily on the PK properties (rapid clearance) of Multihance, and its dosing regimen (single dose as a [redacted] imaging agent) which, in combination, was felt that the likelihood of Multihance interacting with those drugs using the same metabolic pathway and causing problems was remote.

Liver & Multihance Label Recommendations:

[redacted]

CVS and Multihance

The basis of the concerns was:

- The known cardiac channel blockade effects of gadolinium.

- Lack to adequate data to fully characterize the noted QT prolongation (most < 30 msecs but at a frequency of 40-47%) or the exclusion of such association based on the data on eleven patients (study 43,779-12) who received calcium channel blockers.

- CVS related AE (arrhythmias).

- No cardiac monitoring in the pivotal pediatric study (see Table 9).

Sponsor's Response

- Justification for not conducting new clinical studies as recommended.

- Comprehensive pre-clinical CVS studies (core CVS studies in monkeys, cardiac electrophysiology studies, HERG tail current [potassium channel], Action potential study in dog Purkinje fibers).

- Re-analyses of QT/QTc from study 43,779-12 using Bazett methodology and individualized corrections methodology (methodology was recently verified by agency's Cardio-Renal division

- Literature search for torsade de pointes and gadolinium.

- Postmarketing experience

Discussion

The re-submission in essence is a re-analyses of old QT data with justification for waiving new clinical studies based on the lack of preclinical signals.

No new clinical CVS/QT studies were performed as requested in the action letter of May 02 or as communicated subsequently in letter by Dr. Houn (March 10, 2003). The latter letter was sent to the sponsor following the feed back (on study 43,779-12) from cardiorenal consultation that re-confirmed the positive findings (Multihance, like gadolinium and some of its class agents, was associated with QT) and additionally caused AV nodal dysfunction. At the time these letters were written, the CVS preclinical studies had not been conducted and the currently presented preclinical results were therefore not available. The results from preclinical comprehensive cardiovascular studies were not concerning and there were no suggestions that Multihance had the tendency to block the relevant ion channels in animals that are traditionally known to cause torsades. The requested calcium channel preclinical studies were not performed and the sponsor has not addressed this known class concern on the association between gadolinium agents and the calcium channels. However, the concern, if Multihance has a strong relationship to the calcium channels can be addressed in two ways:

- the lack of effects of calcium channel blockade in the action potential studies

- the results from the clinical study (study 43779-12- despite its limitations in study design, sample size, and scientific basis of comparability) in which patients with cardiovascular disease who received calcium channel blockers and Multihance did not experience concerning reactions.

Based on these data, the potential for Multihance to block the calcium channel that would result in serious adverse effects is less of a concern. In this context, although the sponsor has not addressed this issue directly, it can be argued that the existent preclinical and clinical data provides information to address this deficiency.

It is to be noted that the Multihance program is the first in its class in which such comprehensive preclinical studies have been conducted. It is re-assuring that the preclinical studies did not identify problems with respect to the potassium channels in the HERG studies (although calcium ion studies were not conducted) and based on the post marketing safety data and Multihance's intended use as a single administration, it is reasonable to infer that the risk of Multihance causing torsades despite causing QT prolongation is probably insignificant. The clinical concern on the effects of Multihance on QT (like the class agents) that has been previously verified by cardiorenal, and on AV conduction, therefore, stands. The requirement for new adult clinical studies is therefore not required, but the label should still reflect the relationship between Multihance and the heart.

CVS & Multihance Label Recommendation (Adults):

Renal and Multihance

The basis for concern was:

As with the other class agents, renal vacuolization (in rats, NOAEL was .5 mmol/kg in the acute and repeat tox studies) was noted with Multihance but in addition, and not seen with the class agents, these changes were also associated with functional abnormalities (electrolyte changes in the repeat tox studies).

Further, since the primary elimination path for Multihance is via the kidney, and renal elimination is prolonged in patients with renal impairment, adequate clinical safety

monitoring that included urinalysis in adults and pediatrics were not preformed (see Table 9).

Sponsor's Response

Integrated analyses of Renal Function Tests.
Integrated Urinalysis Data.
Integrated analyses by degree of renal impairment and age (< 65 years and ≥ 65 years) in 2121 patients
Summary of AEs occurring in renally impaired patients (32 patients [20 received Multihance and 12 received placebo]) and renal dialysis patients (17 [11 received Multihance and 6 received placebo])
Pediatric patient UA information from the PK study in healthy subjects.

Discussion

These responses are discussed in detail by Dr. Yaes. Although no significant findings of concern were identified, interpretations were limited by sample sizes and the inconsistencies in the assessments. The presented data varied with the parameter being measured and the timing of the measurement (table 25, Dr. Yaes' review).

Renal & Multihance Label Recommendation

Concur generally with the proposed language under the precautions section.

Local AEs and Multihance

The basis of the concerns was:

The osmolality and viscosity of Multihance is higher than the approved class agents and these physico-chemical properties were felt to be the cause for serious local reactions- such as fascitis, thrombophlebitis, compartment syndromes, etc. In the current label for Magnevist (with the highest osmolality and viscosity amongst the approved agents), under the precautions sections, these AEs are listed.

Sponsor's response

Narratives summaries of such events (submitted Vol. 2, pp. 157-159).

New analyses of local events by method of drug administration (infusion, bolus and power injector; Vol. 2, pp. 153-157).
Preclinical local tolerance studies (intravenous, perivenous and intramuscular routes).
Postmarketing world wide reporting data (Vol. 2, p 159, Oct 2003)

Discussion

As discussed by Dr. Yaes, the AE rate for Multihance for such events were comparable to the class agents with no significant concerns. The magnitude of the reactions and the type of reactions as presented from the various sources did not raise specific concerns. In the preclinical studies, perivenous injections resulted in greater reactions than the intravenous injections. The power injector has been referenced and included in the amended label under the AE section and deleted from the dosage and administration section of the label (this was negotiated during the review cycle, see correspondence 2/20/04).

Local Reaction Label Recommendation

> In concurrence with the agency pharmacology-toxicology reviewer, and along the lines for Magnevist (although such severe reactions have not been seen to date), given Multihance's higher osmolality and viscosity, precaution to monitor the injection site if extravasation occurs during administration is recommended.

Additional Safety Comments

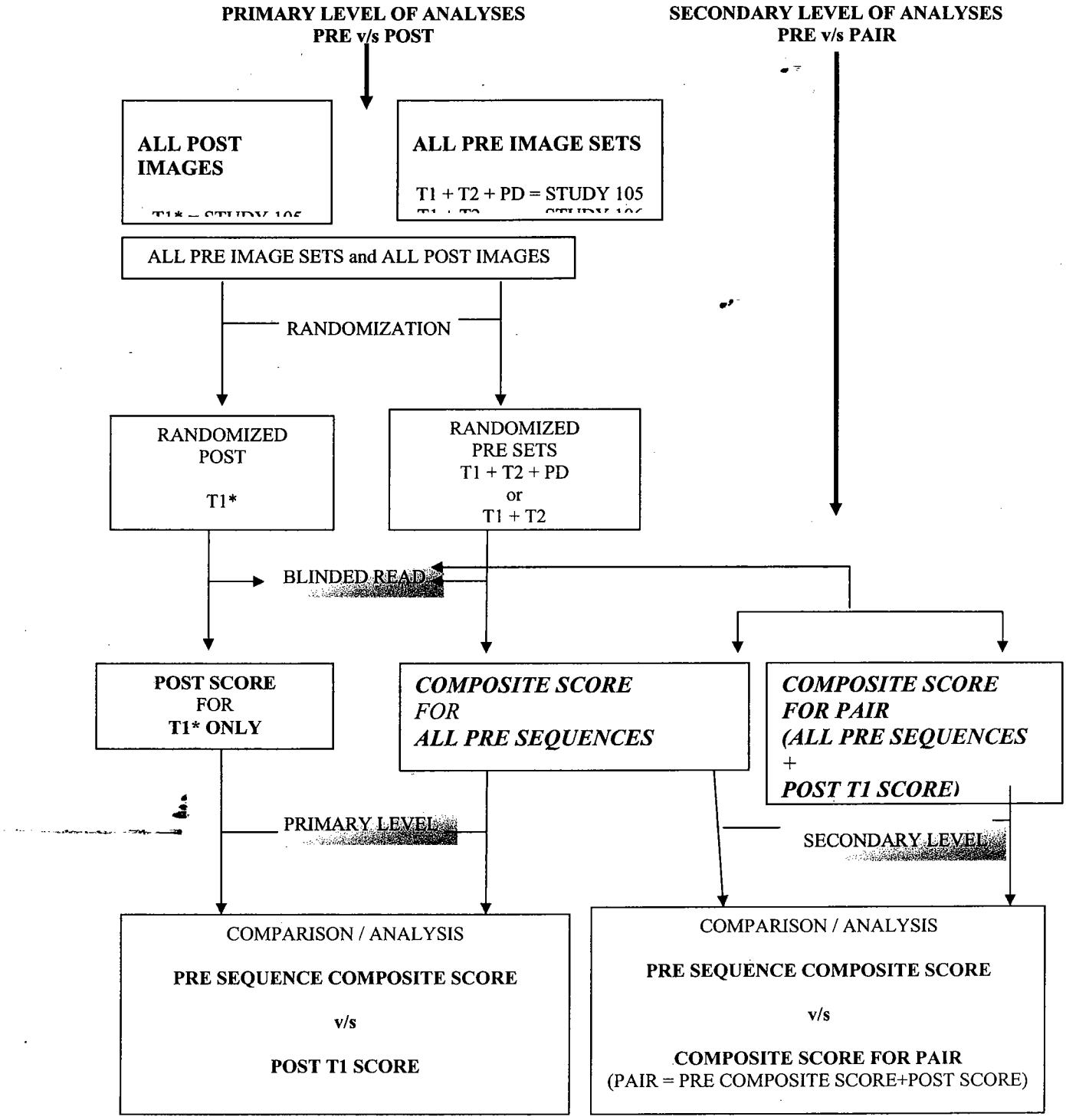
In addition to the information requested in the action letter on the CRFs and to integrate the data from all sources, during the review cycle, the sponsor contacted to provide clarification on the number of deaths, serious AEs, and the AE database. These were provided by the sponsor (see correspondences, Feb 27, 2004).

There were no new deaths or serious AEs or discontinuations since review cycle one and its safety update. (Number of Deaths = 5, Serious AEs = 20, Discontinuations = 10).

Attachment

RE-READ SCHEMA - BLINDED READER METHODOLOGY*

***(Ref = Sponsor's Vol. 24, pp. 092-094)**



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/s/
George Mills
4/9/04 12:18:11 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2004

FROM: Florence Houn MD MPH

SUBJECT: Office Director Memo

TO: NDA 21-357/58 MultiHance (Gadobenate dimeglumine) intravenous injection by Bracco Diagnostics

I am concurring with the Division of Medical Imaging and Radiopharmaceutical's recommendation to issue an approvable letter to Bracco Diagnostics. Bracco is seeking an anatomical delineation claim for MultiHance with MRI of the CNS in adults [redacted] to visualize brain, spine, and associated tissues. The deficiencies from the last action letter of May 24, 2002 have been addressed except for clinical-statistical issues. While many of the safety concerns can now be addressed by labeling, the safety database for pediatric patients (not healthy volunteers, as in the pK studies, who all but one were over the age of 5) is deficient. No EKGs or complete urine analyses were collected in pediatric patients in the phase 3 studies. For adults, the safety issues are resolved as described below. Evidence for efficacy remains inadequate. The effectiveness issues are: 1) only the US trial's population presented as a reanalysis of a subgroup (N=136 of 276 ITT) from the original submission contained a patient population supportive of a broad claim for CNS lesions (albeit not a spinal indication and, of note 50 of the 136 had tumors) and this study's primary efficacy variable failed to show any difference in visualization post-drug versus pre-drug with MRI scans plus no dose-response was seen, 2) the second trial was a reanalysis of a subgroup (N=75 of 150 ITT) of a European study of patients with known metastatic disease to the CNS and this study was a win on the primary efficacy endpoint on visualization but no dose-response was seen, 3) only 4 patients had spinal disorders, a number that is too small to support the spinal indication, 4) [redacted] and 5) we don't know what criteria were used for subgrouping from the original studies and if these criteria for subgrouping introduced bias. Also, the ability to visualize lesions in known diseased patients does not test the drug's ability to detect disease in the intended use population, all comers referred for MRI CNS scans, not just cancer patients with known disease. The populations were used from the original submission when the company was pursuing [redacted] One way forward is to provide us with more data on the ability to better delineate anatomy in a variety of CNS diseases, known and suspected, over MRI alone.

MultiHance is a gadolinium based MRI contrast agent that is renally excreted, like other gadoliniums. It is also minimally hepatically metabolized (from 0.4 to 4% of the drug), unlike other gadolinium agents. Of the gadolinium agents, it is the most hyperosmolar and it has the most viscosity. There were signs of QT prolongation and AVNodal block in the NDA. This cycle, we note that while we have adequate data for safety of the drug on the kidneys in adults, we have no complete urine analysis data in pediatric patients or pediatric healthy volunteers. We do have pK studies in healthy children down to 5 years of age (and one 3.2 year old child) with urine dip sticks and serum creatinine. However, in pediatric patients we would need these complete urine analyses as well as EKG monitoring. Safety related to hepatic interactions with other drugs is now viewed as unlikely given the one time administration of MultiHance and the rapid elimination of the drug. The hyperosmolarity and hyperviscosity of the drug give extra risk when the drug extravasates during administration. This can lead to reactions and inflammation. Magnevist, the second most viscous and hyperosmolar drug has cases postmarketing of severe thrombophlebitis requiring amputation. Labeling will be needed. Regarding QT risk, the class as a whole has these concerns. No

clinical studies were performed despite our recommendations, but the full battery of preclinical information was negative. Because this is a one-time administration drug, we could label this risk and encourage studies to eliminate labeled class risk for specific products.

Dr. Julie Beitz, the deputy office director, will be overseeing the review until the action date on April 14, 2004.

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/s/

Florence Houn
4/8/04 01:52:29 PM
MEDICAL OFFICER

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

Teleconference Meeting Minutes

NDA: **21-357/ 21-358**

DRUG: **MultiHance®**

SPONSOR: **Bracco Diagnostics, Inc.**

DATE: February 18, 2004

FDA ATTENDEES:
Robert Yaes, M.D., Clinical Reviewer
Ramesh Raman, M.D., Clinical Team Leader
Diane C. Smith, R. Ph., Regulatory Health Project Manager

SPONSOR ATTENDEES:
Usha Halemane, Sr. Director, Corporate Biostatistics
Carole Venetianer, Associate Director, for Medical Writing
Melanie Benson, Director, Regulatory Affairs

AGENDA: This is a teleconference requested by the Division, to obtain clarification on the sponsor's October 10, 2003 submission.

DISCUSSION: After a brief introduction of the participants, the discussion was as follows.

The Division requested clarification on the sponsor's label on page 220, volume #1 in the October 10, 2003, submission. The Division noted that in a previous submission, from 2001, the number of patients in the proposed labeling was 1,808, and there was a difference of 1,084 patients in the 2003 submission.
The sponsor noted that a four month safety update had been submitted, to the Division, in which there were 2,637 patients. The sponsor noted that the information for the study update was located in the October 10, 2003, resubmission in volumes 42-44.

DISCUSSION: continued

The Division asked for clarification on the label in the tables in volume number 2, page 156. The Division noted there was a difference in the label from the May 2002 cycle, and the label in the October 2003 submission, specifically with reference to the use of the [redacted]
The sponsor noted the [redacted] was added to the 4 month safety update. The information in the tables was noted that column number 4 contained information on manual versus [redacted] and columns 5 and 6, contained the totals from manual and [redacted]
The data in the submission includes synopsis from the safety update, and information on the additional 1084 patients.

The Division noted that referring to the use of the [redacted] in the safety database in the label maybe more appropriate than in the dosage and administration section, since there was no efficacy data. The sponsor noted that table KKK describes where the [redacted] patients for the CNS indication came from.

ACTION ITEMS:

1. The Division will discuss with upper management on the usage of the [redacted] in the efficacy section of the label for the CNS indication.
2. The sponsor will discuss the usage of the [redacted] in the CNS label with the Clinical Director, and if necessary and will follow up with the Agency.

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/s/

Diane Smith
3/24/04 03:44:45 PM

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

Teleconference Meeting Minutes

NDA: **21-357/21-358**

DRUG: **MultiHance®**

SPONSOR: **Bracco Diagnostics, Inc.**

DATE: January 28, 2004

FDA ATTENDEES:
Robert Yaes, M.D., Clinical Reviewer
Ramesh Raman, M.D., Clinical Team Leader
Sonia Castillo, Ph. D., Biometrics Reviewer
Diane C. Smith, R.Ph., Regulatory Health Project Manager

SPONSOR ATTENDEES:
Usha Halemane, Sr. Director, Head, Corporate Biostatistics
K. Kris Piper, VP Clinical and Preclinical Regulatory Affairs
Alberto Spinazzi, M.D., Senior VP, Group Medical Affairs
Melanie Benson, Director, Regulatory Affairs

AGENDA: This is a teleconference, requested by the Division, to discuss with the sponsor's ~~clinical and statistical~~ teams on the NDA.

DISCUSSION: After an introduction of the participants the discussion was as follows.

It was noted that in the October 10, 2003, submission, in the Safety Data base text there were typographical errors. The computer generated tables had some discrepancies with the text. The Division noted that in Volume #2, page 164, the Adverse Events table showed the incidents of AE's in the MultiHance group was lower than the placebo group, noting possibility of calculation or transcription errors.

The sponsor stated they would follow up on the issue of possible calculation errors, but stated that for the increase in side effects of placebo versus MultiHance, the placebo patient population was only 127, and therefore the percentage shown was correct.

Another typographical error was noted on page 164, (table NNN was mislabeled as LLL). The sponsor will follow up with reviewing the submission for additional typographical errors, and will submit and corrections in the text & table and table & text with the page number and the corrected information to the Division.

Other drugs use the same transporter as MultiHance, the Division asked the sponsor to explain the reasoning why a comparison was not done between other drugs and MultiHance. The sponsor noted that the therapeutic index for the drugs compared was larger than MultiHance or there was no interaction. The comparison was performed and only one drug showed a significant interaction.
The Division noted that in Volume #2, page 19, there was a listing of drugs, and Glyburide was the only drug that an analyses for the transporter was performed. The sponsor confirmed that was correct, and stated that an analyses was done for the other drugs and sited the location of the information in their submission. The Division confirmed that the transporter and safety data provided was from the MultiHance database available, and the information showed no signs and symptoms of adverse events. The sponsor confirmed, and stated there were 4 patients from Japan and no patients in China, and only one clinically significant adverse drug reaction in China. The sponsor concluded that most patients taking Glyburide were from Europe.

The Division asked if the MultiHance QT/QTc re-analyses was the same methodology used in the sponsor's [redacted] submission. The sponsor confirmed that they were identical.

ACTION ITEMS:

1. The sponsor will perform a complete quality check and cross reference the consistency of text to table, and will submit any correction to the Agency by February 6, 2004.
2. The sponsor will review the adverse events information for Glyburide to ensure no reports are missing
3. The sponsor will correct the mislabeled Table in Volume #2. page 164, from LLL to NNN.

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/s/

Diane Smith
2/20/04 05:20:48 PM
CSO

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

Teleconference Meeting Minutes

NDA: **21-357/21-358**

DRUG: **MultiHance**

Sponsor: **Bracco Diagnostics, Inc.**

Date: January 14, 2004

FDA ATTENDEES:

Sonia Castillo, Ph. D., Biometrics Reviewer
Diane C. Smith, R.Ph., Regulatory Health Project Manager

SPONSOR ATTENDEES:

Usha Halemane, Sr. Director, Head, Corporate Biostatistics
Alberto Spinazzi, M.D., Senior VP, Group Medical Affairs
Melanie Benson, Director, Regulatory Affairs

AGENDA:

This is a brief teleconference requested by the Division to receive clarification on table 17A, volume 34, page 70, "Distribution of Changes from Pre-dose in Number of Lesions Detected – Patient Level", in the sponsor's October, 10, 2003 submission.

DISCUSSION:

The Division requested clarification on table 17 A, volume 34, page 70, on how patients who had 2 or fewer lesions at baseline were detected.
The sponsor clarified that the table shows a change from pre-dose to post-dose, based upon lesion tracking. The sponsor also clarified that the lesions seen at contrast were the same lesions seen in the post images plus any additional lesions.

CONCLUSION:

The clarification was acceptable to the Division.

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/s/

Diane Smith
2/13/04 09:04:01 AM
CSO

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

Teleconference Meeting Minutes

NDA: **21-357/358**

DRUG: **MultiHance**

SPONSOR: **Bracco Diagnostics, Inc.**

DATE: November 25, 2003

FDA ATTENDEES:
Zili Li, M.D., Clinical Team Leader
Ramesh Raman, M.D., Clinical Team Leader
Sonia Castillo, Ph.D., Biometrics Reviewer
Michael Welch, Ph.D., Biometrics Team Leader

SPONSOR ATTENDEES:
Alberto Spinazzi, M.D., Senior VP, Group Medical Affairs
Gianpaolo Priovano, M.D., Director, MRI Clinical Development
K. Kris Piper, VP Clinical and Preclinical Regulatory Affairs
Usha Halemane, Sr. Director, Head, Corporate Biostatistics
Liz Bloss, Director, Regulatory Affairs
Melanie Benson, Director, Regulatory Affairs

AGENDA: This is a meeting requested by the Agency to obtain clarification on the blinded readers training for the sponsor's resubmission dated October 10, 2003.

DISCUSSION: After a brief introduction of the participants, the discussion points are as follows.

Clarification of the order in which the pre-dose, post-dose, and paired image sets were evaluated during the blinded read was discussed. The sponsor stated that for study numbers MH-105, MH-106 and MH-112, the pre-dose and post-does image sets were randomized in 1 batch and then read, and a separate reading occurred for the paired images.

The issue of how the paired images were evaluated and rated during the blinded read was discussed. The sponsor stated that a qualitative form was used for the paired image sets, and scoring was based upon what the reader visualized. The sponsor described how the images were displayed, then described the scoring for one of the three primary end points.

In study MH-105 the pre-dose image sets consisted of the T_1, T_2 and proton density (PD) MRI sequences, and the post-dose image sets consisted of the T_1 sequence only. In study MH-106, the metastatic-study, the pre-dose only image set consisted of T_1, and T_2 MRI sequence and no proton density (PD) sequence.

The Division noted that when an anatomical image is rated, it is unclear on how the scoring of delineation is determined. The sponsor stated that the best of the T_1, T_2 or PD images were used. The Division noted that the benefit of the drug over baseline is demonstrated using pre-dose versus post-dose evaluation for the chosen endpoints.

Lesion tracking was discussed and the sponsor stated that the tracking was performed after the paired reads.

The Division requested that the sponsor submit a copy of an example of how the blinded readers scored an image set.

The sponsor was asked the possible reason for there being less lesions detected on the post-dose image set compared to the pre-dose image set in study MH-105 (Table 3-35, page 191 of Volume 24).

The sponsor provided additional clarification their tracking procedure as described in the protocol.

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/s/

Diane Smith
2/12/04 03:41:01 PM
CSO

Diane Smith
2/12/04 03:42:44 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 11, 2004

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: Pharm Tox Comments to sponsor 021104

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

COMMENTS TO THE SPONSOR
NDA 21-357/ 21-358 MultiHance
February 11, 2004

These Pharmacology/Toxicology comments were drafted while reviewing your submission dated October 10, 2003. Please respond by close of business February 17, 2004.

Perivenous local tolerance study

Perivenous local tolerance study was not conducted according to the protocol approved by FDA. The injection volume was 0.2 mL in this study instead of proposed 0.5 mL. Please provide the scientific rationales of choosing 0.2 mL as injection volume.

ECG study

In a letter dated on March 10, 2003, FDA recommended "include a positive control in the revised CVS protocol." No positive control was included in ECG study. According to ICH S7B, positive control should be used to test the sensitivity of the testing system. Please provide the positive control information to verify the sensitivity of the testing system.

Premature ventricular contractions were noted in one monkey at approximately 23 h after administration of high dose MultiHance. Please clarify exact dose and provide detailed information regarding this monkey's PVCs including, but not limited to, PVCs/min, duration of PVCs, and clinical signs et al.

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 2004

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: Chemistry comments to sponsor 011204

Total no. of pages including cover: 2

Comments:

Document to be mailed: • YES ☑ NO

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
HFD-160

COMMENTS TO THE SPONSOR

These Chemistry comments were drafted while reviewing your submission dated October 10, 2003. Please provide the requested information as soon as possible.

Labeling:

There is one deficiency in labeling that is not addressed in the resubmission.

For the package insert, a chemical structure that depicts the bonding of the [redacted] should be used. This coordination complex is displayed elsewhere in the original NDA , but not in the package insert. [redacted] should also be shown.

Please address this issue by providing a draft structure to the NDA files and by committing to use this structure in the final printed labeling.

[redacted]

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/s/

Diane Smith
1/12/04 10:29:32 AM
CSO

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
PDUFA:	February 28, 2002 (10 month)
COMPLETED:	February 10, 2002
RELATED DRUGS:	Magnevist (approved - 1989) ProHance (approved - 1992) Omniscan (approved - 1993) Optimark (approved - 1999)

RELATED REVIEWS:

Chemistry:	David Place, PhD, 01/25/02
Clinical:	Roger Li, MD, 02/08/02; Ramesh Raman, MD, 02/11/02
Clinical Pharmacology:	Hyun Kim. PhD, 01/09/02
Microbiology:	Stephen Langille, PhD, 01/04/02
Pharmacology-toxicology:	Tuschar Kokate, PhD, 02/01/02; Nakissa Sadrieh, PhD, 02/06/02
Statistics:	Shala Farr, MS, 02/05/02
Project Manager:	James, Moore, RPH

BACKGROUND:

Drug Class: Gadolinium chelates are approved to provide contrast in magnetic resonance imaging (MRI). In a magnetic field gadolinium accumulation primarily enhances the T1 weighted imaging sequences. After intravenous injection, gadolinium remains intravascular until it reaches an area of abnormal vascular permeability. In those areas, it enters the intravascular space. As summarized in the following table, all of the 4 approved gadolinium products (Magnevist, ProHance, Omniscan and Optimark) are indicated for contrast to detect lesions associated with abnormal permeability in one or more of the following areas, the central nervous system (CNS), head and neck (spine), liver, or body (i.e., intrathoracic (excluding the heart), abdominal, retroperitoneal].

Table 1: Gadolinium Contrast Drug Approved Indications					
Drug	CNS		Head & Neck (spine)	Body [intrathoracic (excluding the heart), abdominal, retroperitoneal]	Liver
	Adult	Peds (> 2yrs)			
Magnevist	X	X	X	X	
ProHance	X	X	X		
Omniscan	X	X	X	X	
Optimark	X		X		X
Several of these products are used off-label for magnetic resonance angiography					

In the first NDA (Magnevist,)the truth standard included histopathology for the brain tumors. In ProHance and OmniScan and Optimark, patients had either a cross over image with an approved gadolinium comparator or the patients had a CT or histopathologic confirmation of the lesion findings.

Although all of the products are approved for similar uses, there are differences in osmolality, viscosity, and ionicity. Specifically, Magnevist is the only approved product that has the highest osmolality, viscosity and is the only ionic product. Also, based on post market surveillance, it appears that Magnevist has the greatest frequency of significant local adverse events; e.g., thrombosis, phlebitis, fibrosis and associated severe consequences that required surgical intervention including compartment release and partial amputation (in 2 patients). The extent to which these findings were related to the drug or underlying disease was not established. Recently, these events were added to the Magnevist warning section of the labeling. In comparison to Magnevist, MultiHance has a similar osmolality and is ionic. Also, it has a higher viscosity and concentration.

Table 2: Summary of Chemical Characteristics in a Approved Gadolinium Contrast Drugs						
Drug	Osmolality	Viscosity	Ionicity	PH	Density	Concentration (mg/ml)
MultiHance	1970	5.3	Ionic	6.5-7.5	1.22	529
Magnevist	1960	2.9	Ionic	6.5-8.0	1.20	469
OptiMark	1110	2.0	Non-ionic	5.5-7.5	1.16	331
Omniscan	789	1.4	Non-ionic	5.5-7.0	1.14	287
ProHance	630	1.3	Non-ionic	6.5-8.0	1.14	279
*Derived from Dr. Li's summary tables (his review, page 9)						

MultiHance Regulatory History:

Bracco Diagnostics Inc. developed MultiHance (Gadobenate dimeglumine) Injection as a MRI contrast agent. It is approved in at least 16 countries including Germany, France, and the United Kingdom. As of April 2001, MultiHance had not been withdrawn or denied approval in any country.

Like the other approved gadolinium contrast drug, MultiHance crosses abnormally permeable vasculature and is predominantly excreted by the kidney. Unlike the other

approved products, MultiHance appears to be more lipophilic and may be engulfed by hepatocytes. The current NDA is submitted to support the following indications.

"MultiHance 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). [redacted]

One NDA was submitted with 4 vial sizes (5, 10, 15, 20 mL) and one separate NDA was submitted for 2 pharmacy bulk packs (50 and 100 mL). The clinical database included approximately 80 studies of which [redacted] were identified by the sponsor as critical to establish the indications and [redacted] were key clinical pharmacology-biopharmaceutics studies. The pharmacology database included 150 studies.

The MultiHance IND (#43,779) was submitted in 1993. IND was placed on hold because of protocol design and concern about a [redacted] dose. Protocols for key studies in the NDA were last submitted in 1997. Several comments were provided to the sponsor on the design of the CNS [redacted] studies. These addressed the endpoints, truth standards, and use off pre-study MRI's. A pre-NDA and related meetings were held in June - October, 1999. These meetings addressed the statistical plan, reporting of ECGs, animal findings of liver toxicity. During these meetings the sponsor had not determined which studies would be identified as critical and the statistical methodology was still being developed. Full agreement on the database and methodology was not reached before submission.

All disciplines have completed their reviews. Collectively, the application is considered as non-approvable; however, the individual discipline recommendations vary. Microbiology considered their sections as acceptable for approval. Chemistry and clinical pharmacology considered their sections, respectively, as approvable pending resolution of minor deficiencies. However, the clinical, statistical, and pharmacology-toxicology sections were recommended as non-approvable. In considering the collective recommendations, the application is non-approvable. All of the primary reviews and the team leader memoranda to the file (where applicable) comprehensively address the deficiencies and their recommendations. Salient features of the collective assessment are briefly discussed in the following sections.

CHEMISTRY

MultiHance (gadobenate dimeglumine) is provided as a solution of paramagnetic lanthanide metal ion (trivalent gadolinium) racemate mixture bound to BOPTA[1] dimeglumine. The molecular formula is $C_{36}H_{62}GdN_5O_{21}$ with a molecular weight of 1058. The solution contains gadobenate dimeglumine 529 mg per mL in a 0.5 M solution. Its osmolality is 1970 mOsmol/kg (6 x plasma) with a pH of 6.5-7.5. Dr. Place's review notes that MultiHance is manufactured in one combined drug substance and drug product process. His review accepts the method and noted that the approach similar has been used by other manufacturers of approved gadolinium drugs.

The CMC section of the application has been comprehensively reviewed by Dr. Place who recommends approvable pending additional documentation and , or clarifications on the vial suppliers, several matters related to the pH conditions of the drug product, methods validation, HPLC assay for impurities, and labeling. One DMF was submitted and found to be adequate. Pending completion of all inspections, this recommendation has the concurrence of the ONDC Division Director. I agree with their recommendation.

MICROBIOLOGY: MultiHance is a sterile, pyrogen free, ——— sterilized product. Dr. Langille recommends acceptance of this section. I agree with the recommendation.

PHARMACOLOGY-TOXICOLOGY

General: Proposed for market concentration is 0.5 M solution of gadolinium 529 mg per ml. All of the required pharmacology-toxicology studies were performed with this concentration. Also, other studies were completed with a lower concentration of 0.25 M. Regardless of concentration, the majority of the key studies either were completed with a low dose multiple or without an active control. Also, the results of several studies identified toxicity at or below the human dose multiple. Therefore, a no adverse effect level (NOAEL) was not established. Additionally, toxicity was noted in the brain, kidney, liver, and cardiovascular systems. Also, there is suggestive evidence of local perivascular toxicity. Thus, the reviewers reached a non-approvable recommendation for this section of the application. In considering their concerns, I agree with the recommendation. Dr. Nakissa Sadrieh's team leader summary provides a complete summary of the concerns, Dr. Tuschar Kokate's review

[1] Chemical name: (4RS0-[4-carboxy-5-8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-octo(5-)]gadolinate(2-) dihydrogen, compound with 1-deoxy-1-(methylamino-D-glucitol (1:2).

provides comprehensive details of the deficiencies. Salient aspects of their concerns and their relationship to other aspects of the application are discussed below.

Pharmacologic evidence of efficacy: As with other gadolinium contrast agents, MultiHance is primarily an intravascular drug that crosses vascular areas of high or abnormal permeability. When this happens, gadolinium drugs tend to reside in the extrascular space until cleared. Given rapid vasuclar clearance, contrast develops between lesions with normal and abnormal vascular permeability. Such contrast was shown in preclinical studies of the liver, myocardial infarction, and several murine tumor models. In all models contrast was comparable to or greater than that of Magnevist. Perhaps unlike some gadolinium agents, the sponsor states that MultiHance was engulfed by hepatocytes and had increased T-1 weighted contrast for approximately 2 hours.

Safety pharmacology studies: The safety pharmacology studies showed that most NOAELs occurred at low dose multiples of the maximum human dose (0.3 to 3 times the MHD). Also, in most of the studies, only one dose was studied. Therefore, a dose response curve and assessment of the margin of risk could not be made. The identified toxicities of concern are the EEG slowing, convulsions and death. Dr. Kokate noted that these effects were not seen the active hyperosmolar control. Additionally, although MultiHance permeability levels through a damaged blood brain barrier were low, the dose level was too low to assess the risk (i.e., 0.3 x MHD). Also, continuous ECG recording was not performed in these studies and the results of ECG parameters such as QT interval were not reported. Therefore, these studies are not sufficient to assess the potential risk and to determine labeling or risk management approaches for drug effects.

Expanded acute studies: The submission did not include the required expanded acute dose toxicity studies as identified in the ICH guidelines for single dose toxicity studies (such as hematology, clinical chemistry, urinalysis, complete histopathology etc.). Instead the submission included LD_{50} studies. These are not acceptable substitutes in part because they identify the dose at which half the animals die. The goal is to identify the margin of safety for reversible toxicities. Also, in these LD50 studies had a low safety margins for death outcomes. A positive control group was not used; therefore, the effects cannot be attributed to hyperosmolality alone.

Reproductive toxicity studies: In the Segment I repeat dose study in male rats, MultiHance® (3 mmol/kg/day) produced vacuolation in testes and abnormal spermatogenetic cells. This effect was still present at 28-days. The segment I studies in female rats were not dosed high enough to produce maternal toxicity. Therefore, any absence of effect on the fetus can not be established. Segment II studies in rats were not conducted with the proposed for market formulation (0.5 M).

Mutagenicity studies: In vivo micronucleus assay in rats was carried out using intraperitoneal (5 mmol/kg). Although this study was negative, it did not used the

proposed for market route of injection and the dose multiple was low. Therefore, the results are not conclusive.

In order to address the deficiencies above, the studies should be repeated at sufficiently high dose multiples and in accordance with FDA and ICH guidelines.

In addition to the deficiencies in study conduct described above, there were a few toxicology findings that raised safety concerns.

First as noted above, there was vacuolization in the kidney, testes, and pancreas. Typically other gadolinium drugs are associated with kidney vacuolization. However, to our recollection, this is the first one associated with testicular and pancreatic findings. In the testes this appeared to be associated with abnormal spermatogenesis.

Local tolerance: An intramuscular, perivascular injection study was performed with histologic evaluation 8-days after injection. At this time point there was "thickening, inflammatory cell infiltrates, eschare and larger areas of necrosis." According to Dr. Kokate, these findings were greater than the Magnevist control and were not produced by the hyperosmolar control. The study did not include an evaluation at earlier time points. These findings suggest that local extravasation or prolonged intravenous exposure to MultiHance may led to thrombosis or phlebitis. This raises concern because of clinical symptoms seen with Magnevist (see page 1, drug class comments). Because of the similarity of MultiHance and Magnevist chemical profiles, these findings need further study. ***Before approval, additional data are needed to further evaluate the risk of thrombosis. This should include the completion of a more extensive local tolerance study (intravenous, paravenous & intramuscular administration) with histological evaluation at earlier time points (e.g., 24 hours) through the 8 days reported in the submission. Also, MultiHance is proposed for direct bolus or infusion. The study should address the rate of infusion as well.***

In vivo stability of MultiHance. According to Dr. Kokate, approximately 6% of the injected dose was recovered as free gadolinium ion in the feces of rats and dogs. Also, in a radioactive biodistribution study, 2.7% of the injected dose was found in the bone. The sponsor attributed these findings to formulation impurities that reportedly are not present in the proposed for market formulation. However, in the human PK studies, there was evidence of increased urinary zinc level. In one other gadolinium drug, the increased excretion of zinc reflects transmetallation of the gadolinium. As such, the gadolinium is free and the zinc would be bound to the BOPTA. The application does not contain data to document the absence of transmetallation. It is known that free gadolinium is incorporated into the bone. If significant transmetallation occurs, its effects on developing bone of the fetus and pediatric patients would be of concern. ***In order to address the retention of the basis of impurities, provide data to document the presence or absence of***

transmetallation. This should include the study of various conditions that might promote transmetallation

Neurologic findings: There is inconsistency in the CNS toxicities reported in the submission. In single dose studies in rodents, MultiHance was associated with convulsions and death. Also, in rats and pigs, 1.7 to 3.6 x MHD doses caused transient flattening (for 2 min) of EEG in what was apparently a conscious animal. (Dr. Kokate noted that how a conscious animal could have a flat EEG is not clear.) After single dose low dose multiples (0.3 x MHD) studies, Dr. Kokate noted that MultiHance minimally crosses an abnormal blood brain barrier. In discussions with Dr. Kokate, MultiHance is supposed to cross an abnormal blood brain barrier. Therefore, the actual amount of MultiHance in the brain is apt to be a function of the cross sectional area of the abnormal blood brain barrier. Hypothetically, this could be of concern in patients with a large number of CNS lesions. ***Therefore, the sponsor should provide more information on this effect and describe the activity of the rats that had EEG flattening. Also, the sponsor should repeat the abnormal BBB barrier study in animals with larger numbers of lesions or in models with various amounts of BBB abnormalities. Additionally, in patients, a EEG safety study is needed in patients with large numbers of brain lesions.***

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Submitted studies in healthy volunteers, and in small populations of patients with renal impairment, liver impairment, hemodialysis requirements, and pediatric ages. Dr. Kim's review noted that the majority of the ADME data were acceptable. The pharmacokinetic parameters of MultiHance are summarized in table 3. These data show that MultiHance is renally, primarily and that there is minimal liver compensation for renal impairment. Also, in patients with hepatic impairment, the mean percent of gadolinium excreted in the urine decreased from a 97% in healthy volunteers to 80%. Additionally, his review notes two critical concerns about the use of MultiHance in pediatric patients and in those maintained on hemodialysis. Specifically, on page 3, Dr. Kim notes that most patients will receive just one dose, dose adjustment in mild to moderate renal disease is probably not needed. In considering this, based on 5.5 times t ½ to clear the body, MultiHance clearance time is 30-45 hours with 90% eliminated in the first 2 hours. However, as shown in the following table, without dialysis, MultiHance remains in the body at least 42 hours (i.e., the time of the next dialysis). This is 21 times longer than that of patients with normal renal function. The prolonged exposure to the high osmolality and ionicity of MultiHance may lead to unanticipated toxicities. As noted above in the animal repeat dose studies, the brain, liver, and kidney are target organs.

ADM-7

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_____ § 552(b)(5) Draft Labeling

Table 3: MultiHance Mean Pharmacokinetic Parameters *				
	Doses	Terminal elimination t ½ (hours)	Renal	Gd^{+2} Mean cumulative FECAL excretion (mean across studies)
Healthy volunteers (N=54*, across 4 studies)	0.005 to 0.4	2.0	78-96%	1.9% (0 – 7.2%)
Renally Impaired	0.2			
CrCl 130 ≤ 60 mL/min (N=32)		6.1	94%	5.6%
CrCl 10 ≤ 30 mL/min (N=23)		9.5	92%	6.6%
Hemodialysis (N=17)		42.4	72% (in 4 hr dialysate	---
Liver Impaired	0.1	2.06	80%	---
Pediatrics: 2 to 16 years (N = 25)	0.1	1.5	---	---
* Derived from Dr. Kim's review pages 8-9.				

CLINICAL – STATISTICAL

I. Efficacy

Bracco has submitted a large clinical database of 4, 190 patients (4, 075 patients in 78 completed studies and 115 in 5 ongoing studies). Of the 78 studies, the majority were submitted for safety and 6 were identified to establish efficacy. Of these — studies, 3 were completed in for the CNS indication ——————— These —studies have complex dosing and imaging designs that obscure the potential benefit of MultiHance. As a result of the analysis, Drs. Li and Raman consider the application as non-approvable. I agree with this decision. Dr. Li's review contains a comprehensive evaluation and discussion of his evaluation. Dr. Raman's Team-leader memo to the file provides a cogent summary of the trial design complexities, the approaches to the analysis, data results, and recommendations for new studies. Their reviews adequately identify the deficiencies. Because of the complexities, this portion of the memo will identify common elements of the design flaws and the results. Dr. Raman's efficacy summary page 1-9 should be read for details and both reviews provide substantive background information. These data will not be repeated in this memo.

Overall the critical deficiency in both the CNS ——————— studies is a collection of trial design flaws. These flaws resulted in a small sample size of patients that received the proposed for market dose and imaging regimen. Additionally, the trial designs were not sufficiently robust to confirm the blinded readers findings and interpretations. A brief synopsis of the trial designs, the deficiencies and results are provided on the next few pages.

MultiHance is proposed for

> *"....intravenous use in adults ——————— as an adjunct to magnetic resonance imaging (MRI) of the central nervous system (brain, spine and*

surrounding structures).

This proposed indications contain concepts, detection. The

The second portion of the indication (detection) requires data on how many lesions are detected. Currently the gadolinium class labeling states that lesion detection is increased on the basis of abnormal vascular permeability. This leads to the detection of lesions and the ability to identify associated features (border delineation). Although there is historic information that this detection is helpful in triaging patients for additional work-up this anatomic indication

As outlined in Dr. Raman's summary, the CNS studies lack the critical features to establish the lesion detection indication. The critical studies are listed below

A. CNS: Three studies were submitted (43,779-9A, 43,779-9B, and B19036/020))

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 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. Hence, appropriateness of the studied clinical setting is not clear.

Secondary endpoints were the number of lesions.

ADM-8

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Overall, the MultiHance NDA includes safety evaluations were conducted in > 4,000 patients. Of these, 2637 patients (M= 57%, F = 42.3%; mean age = 55.9 years) were studied in the United States or Europe. Of these patients, 1218 received proposed for market formulation , and approximately 937 received the proposed dose and formulation.

In the entire database there were 5 deaths (none in the US population). Of these 4 of the 5 patients died beyond 12 days after the study drug administration. The 5th patient died from a pulmonary embolism at an unclear time. The details all patients were limited to a narrative.

Drs. Li (page 83-105) and Raman (page 10, and 47-53) have adequately summarized the safety deficiencies. Attached on page 17 is a listing of the adverse event profile. Of the 2637 US and European subjects, 502 (19%) had at least one adverse event. Of the 624 patients in the US, 225 (40%) had at least one adverse event. The most commonly involved body system was the body as a whole (14.9%). The common events were headache (5.9%), nausea (3.4%), taste perversion (3.2%), and dizziness (2.4%)
Also, there were 5 deaths, 17 serious events. Preliminarily, the deaths did not appear to be directly related to the study drug and 4/5 occurred 12 –35 days after dosing. However, only narratives were submitted and additional details are needed to confirm this impression. Of the 17 serious events, the sponsor attributes 5 to MultiHance. These were all allergic in nature. After reviewing the 17 serious events and discussing with the reviewers, there are other suspect events. These include acute congestive failure, hemiplegia, chest pain, aphasia, pancreatitis, coronary bypass occlusion within one hour, and hypoxia. Since the case report forms for these patients were not submitted, a full assessment of these events can not be made. However, it is possible that these events may be at least related to the hyperosmotic load. Additional data are needed. (See item 6 below).

Additionally, because of the EEG and neurologic findings in the animal studies, a special, non-imaged, EEG monitoring study is needed in patients with large numbers of CNS lesions.

The following are the list of items to include in the letter. Since the reviewers have addressed these in detail, I will not discuss them further.

1. The integrated safety summary did not include summarized data on (1) Japanese subjects studied in supportive studies, (2) pediatric subjects, and (3) healthy adult volunteers. Likewise revise the overall summaries for demographics (age, weight, height), method of administration (rapid bolus injection and/or slow infusion) and subanalyses (i.e. adverse events) by imaging indication, location (US versus Europe) were not assessed and evaluated. ***These analyses must be submitted.***

2. In the most studies, cardiovascular monitoring was not adequate to evaluate the potential effects of MultiHance on QTc intervals and arrhythmias. In most studies, QTc interval monitoring was intermittent. In the adults, QTc prolongation was observed across most of the measured time points (table S2). The cardiovascular related adverse events included patients with ventricular arrhythmias and PVCs. Although most QTc prolongations were of the <30 msec magnitude, the frequency of its occurrence across the measured time points (ranged from 40-47%) is of concern. (See Raman page 49). Historically, in most drugs that caused malignant ventricular arrhythmias, the magnitude of the change from baseline were not significant. Therefore, the occurrence of most QTc prolongation in the < 30 msec range is not a reassurance. Also, ECG monitoring was not performed in the pediatric patients. ***To address this deficiency, continuous cardiovascular ECG monitoring must be added to all ongoing studies and included in the formal studies that will be conducted to address the clinical deficiencies.***

3. The application did not contain the required case report forms on the patients that died or had serious adverse events. ***These must be submitted.***

4. The application did not contain the results urinalysis data in adults and pediatric patients to determine the effect of MultiHance on the renal system. ***These must be provided if available. Also, these evaluations must be added to future studies***

5. The application lacks sufficient data to fully assess the risk of MultiHance on the liver. The stated mechanism of action of hepatocellular uptake and the pre-clinical observations of hepatic necrosis in animals raise concern about the safety of MutiHance in patients receiving liver MRI. Although the application contains reporting of individual liver function studies, it does not provide sufficient detail to the determine the risk. ***In order to address this deficiency by patient analysis of all liver function studies and associated hepatic or gastrointestinal events is needed.***

6. The database identified 2 cases of thrombosis. However, the MEDRA adverse events method may not capture the consequences of these events. The osmolality and viscosity of this agent is higher than that of the approved gadolinium agents. Since these chemical parameters have been associated with serious adverse (i.e., fasciitis, thrombophlebitis, compartment syndrome, amputations, surgical release, infections, etc). ***Additional case report forms on these patients must be submitted on all patients.***

7. Because of the EEG and neurologic findings in the animal studies, ***a special, non-imaged, EEG monitoring study is needed in patients with large numbers of CNS lesions***

8. Because the repeat dose animal studies suggested decreased cellularity in the bone marrow, ***a detailed subanalysis of all marrow elements is needed.***

MISCELLANEOUS

The division of scientific investigations findings did not identify information that would affect the data integrity.

CONCLUSIONS

Overall, the MultiHance NDA provides the results of a large development program. The interactions between Bracco and the Agency resulted in the resolution of the microbiology and most of the chemistry concerns. On the other hand, the application contains a number of critical safety and efficacy deficiencies. From a safety perspective, the application omitted the required expanded acute safety studies, and most of the studies that were completed used a dose multiple that was too low to establish a safety margin. Moreover, in studies where a no effect level was established, often it was lower than the human maximum dose adjusted by body surface area. The identified toxicities affected the organs of the intended use (brain ——— as well has the kidney, testes, pancreas, bone marrow, and bone. Additionally, the data lacked a comprehensive evaluation of cardiac electrophysiologic effects. In clinical studies, a few patients had adverse events in related areas of neurologic, congestive failure and allergic symptoms.

From an efficacy perspective, — the CNS ——— studies had similar deficiencies that included a complex dosing regimen with an inadequate dosing / imaging interval to allow for a full assessment of dose effects. Also, the complex scheme resulted in a small subset of patients that actually received the proposed for market dose and imaging regimen. Additionally, the studies did not include prospectively stated imaging criteria that were used to make ——————— assessments. The imaging sequences that were used were not consistent across studies. Also, there is a lack of clarity in what imaging sequences and criteria were used across readers within a study. Likewise, the approach to confirm ——— lacked consistent methods to link the lesions to histopathology. Thus, the net effect is that these studies are considered to be preliminary, good phase 2 studies.

In order to address these deficiencies, the following are needed.

CNS: At least one large, robust study in adults with CNS disease is needed. This study must enroll patients in an appropriate clinical setting that have a well defined, need more MR contrast. For example, stroke patients with evidence of hemorrhage on CT who require a follow-up MR stroke evolution; multiple sclerosis patients who require MR to evaluate the lesion features; 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 include the following: homogeneity, ring patterns, margins, and technical information to confirm ischemia, edema, or tissue.

Before this confirmatory study begins, additional data are needed to establish the proposed for market dose and imaging sequences to be used. Because of the toxicity concerns and the results that suggest that a repeat dose of 0.05 plus 0.05 mmol/kg may be more effective than 0.1 plus 0.1 mmol/kg, a small dose regimen confirmation study is needed before the definitive study is conducted

Additionally, because this product may have a different safety profile from the other gadolinum agents all outstanding safety concerns must be addressed before approval.

ACTION: Non-approvable

A. Letter inclusions

1. CMC comments as per reviewer

2. Pharmacology-toxicology studies as requested by the reviewer plus additional comments on the local irritation study, neurologic findings, free gadolinium

3. PK studies needed in pediatric patients

4. New clinical studies in patients should be preceded by additional dose regimen and imaging sequence evaluations

5. Special non-imaging safety study with EEG monitoring in patients with large numbers of brain lesions

6. Continuous ECG monitoring in all patients.

B. Review note items for when the application is otherwise approvable:

Labeling should include the following items.

1. [redacted]

2. Testicular vacuolization and abnormal spermatogenesis in animals

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/s/

Patricia Love
5/24/02 03:08:21 PM
MEDICAL OFFICER

Office of Drug Safety

MEMO

To: Sally Loewke, M.D.
Acting Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

From: Linda M. Wisniewski, RN
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Diane E. Smith, RPh
Project Manager, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

Date: January 08, 2004

Re: ODS Consult 01-0140-1, Multihance and Multihance Multipack
(Gadobenate Dimeglumine Injection) 529 mg/mL, NDAs 21-357 and 21-358

This memorandum is in response to a December 22, 2003 request from your Division for a final review of the proprietary names Multihance and Multihance Multipack. The container label and package insert labeling were provided for review and comment (see #2 below).

1. ~~Look-alike~~ and sound-alike similarities

The proposed proprietary name, Multihance, was found acceptable by DMETS. However, DMETS did not recommend the use of the name Multihance Multipack which represents the pharmacy bulk package configuration (see ODS Consult 01-0140, dated January 07, 2002). Since the initial review, DMETS has identified the proprietary name Matulane, as having the potential to look like Multihance.

Matulane may look similar to Multihance when scripted. Matulane is indicated in combination with other antineoplastics for treatment of stages III and IV Hodgkin's Disease. Both names begin with the letter 'm' and when scripted the ending letters (hance vs. lane) look similar. However, the middle letters (ult vs. atu) may help to differentiate the names, especially due to the number and placement of upstrokes in each name. Although, both drugs are administered on a per kilogram basis [Matulane 1 to 6 mg/kg/day or 100mg/m^2 vs. Multihance 0.1mmol/kg or 0.2 mL/kg], the dosing units are different (mg/kg/day or mg/m^2 vs. mmol/kg or mL/kg). There are additional distinguishing product characteristics that will decrease the potential for confusion as well: route of administration (oral vs. intravenous injection), dosage form