HFD-160 Clinical Team Leader's Memo to File

NDA 21-357 (MULTIHANCE) – RESUBMISSION

COVER SHEET

Resubmission Date:	October 10, 2003
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium Contrast Agent for MRI
Route:	Intravenous as rapid bolus or infusion
Indication: [Foot note 1]	For Central Nervous System (including the spine) in Adult

"*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.*"

Dose:	CNS Adult- 0.1 mmol/kg

HFD-160 Team:

Medical:	Robert Yaes, MD; Ph.D.
Statistics:	Sonia Castillo, Ph.D.
Chemistry:	David Place, Ph.D.
Biopharm/Tox:	Yanli Ouyang, Ph.D.
Pharmacology:	Young-Moon Choi, Ph.D.
Microbiology:	Stephen Langille, Ph.D.
Project Manager:	Diane Smith, R.Ph.

Ramesh Raman, MD Clinical Team Leader	Concurrence	George Mills, MD, MBA Division Director

Foot note: 1 = Previously Sought CNS Indications
Initial (NDA Submission): "MultiHance is indicated for intravenous use in adults

Amended (Major amendment): "MultiHance is indicated for intravenous use in MRI to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues."

Foot note: 2 = The underlined section was an amendment received February 27, 2004

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EXECUTIVE SUMMARY

CONCLUSION

In the risk v/s benefit assessments, since Multihance can be considered safe both from pre-clinical and clinical perspectives (pending label changes), the two important aspects that could determine if the drug provided benefits were- a) whether effectiveness of Multihance was demonstrated based on the data/results, and b) whether Multihance provided greater benefit over existing tools.

It is the opinion of this reviewer that the efficacy results at best provided preliminary Phase 2 type of information. The main concerns were lack of sufficient information to justify the sought global regions (for brain and spine); global abnormalities (for all CNS lesions); lack of information to justify the sought adult dose (0.1 mmol/kg) ——— ——— failed performance (non significant results in the pivotal study on the agreed primary level); and biased results on secondary level or in the non-pivotal trials (due to intrinsic flaws such as lack of complete sequences, and mismatch between the sought claim, the type of analyses and the objective of the re-read protocol). Multihance targeted certain lesions only such as brain tumors (in ~ 72 % of the adults ——— brain lesions were tumors in the re-read) and this was achievable with any of the studied doses, (there were no differences between the 0.05 mmol/kg dose or the 0.1 mmol/kg dose in all the 3 studies in primary and secondary analyses) and such achievement stemmed from flawed trials. There were only 4 spinal disorder patients in the pivotal adult study. Therefore, the global CNS Brain and Spine claim is not justified and the results were not sufficiently convincing or clinically meaningful to restrict the claim to a single CNS type of disease, viz., tumor. There are other approved class agents that subserve these functions and other functions. These limited and biased results, further, did not suggest that Multihance could convincingly provide more information than a baseline non-contrast image with any of the studied doses- a requirement and commitment based on blinded re-read protocol agreement on the primary efficacy analysis. With the adult market dose not established, ——— ——— ——— The supportive trials originally conducted in Europe that showed positive results although they were re-read by US trained readers were not conducted in accordance with the medical practices in US Specifically, not all the required baseline images were part of the pre-contrast images and therefore, such studies (the non-pivotal re-read studies 106 and 112) provided results that were significant in favor of Multihance. Several fundamental questions remain unanswered- Does Multihance provide benefit over a baseline image? What dose would one use? Would Multihance work for all CNS disorders (brain and spine and all diseases) in adults and pediatric populations? ——— Such limited data cannot be considered as evidence of confirmatory effectiveness.

Barring the physiochemical and PK differences between Multihance and the four approved class agents (Omniscan, Prohance, Magnevist and Optimark), on broader

aspects, Multihance is comparable with the others in terms of the safety profile and the indications. Therefore, Multihance does not offer unique advantages over existing tools.

On these grounds, approval is not justified.

RECOMMENDATION

Safety

Approval with label changes. The new ——— efficacy studies should additionally monitor safety (particularly ECG and renal functions) to alleviate the lapses in safety in the current database.

Efficacy

Approvable for — Adul ——— indications.

Next Steps

The sponsor should first identify the right dose for both the adult and the pediatric population. The new adult and pediatric studies should enroll patients with all CNS diseases (brain and spine) represented in adequate numbers. The study should be designed to demonstrate congruence between the sought indication and the primary efficacy variables with an appropriate pre-specified analysis that will fetch clinical usefulness. The study should be conducted in accordance with the clinical standards of practice in US to replicate the conditions under which a physician would consider administering a contrast agent such as Multihance. Such a scenario should be prospectively implemented in the blinded reader methodology. The pediatric study/s should collect safety data.

DISCUSSION

General Background

MultiHance, a gadolinium paramagnetic i.v. contrast MRI agent, was first submitted for review as a NDA in April 2001 ——— in two patient populations (Adults for both indications and pediatric for the CNS only).

The data stemmed from trials across the world- US based ~ 1/6, Europe ~ ½, and ~ 1/3 from Japan. The data from the Japanese trials were not submitted for full review.

Two formulations- the .25 M and the .5M proposed market formulation were used across the trials. ~ 10% of the subjects were exposed to the .25M formulation and ~ 89% to the .5M formulation. The pivotal trials for safety and efficacy included both formulations (as identified in the tables E1B and E2B of review cycle 1) in their trials. For purposes of

relevance, only those studies that used the proposed market formulation of .5M were analyzed.

Four other marketed gadolinium agents are approved for use in the US (OptiMARK for adult CNS and adult Liver, Magnevist for adult and pediatric CNS and adult & pediatric whole body, Prohance for adult and pediatric CNS only, Omniscan for adult and pediatric CNS and adult and pediatric whole body) and the physico-chemical properties of MultiHance are comparable to the others with the exception that MultiHance has the highest osmolality and viscosity. The general AE profile of MultiHance appears to be comparable with the other class agents. The proposed dose of MultiHance is also comparable to the others for [redacted] adult indications. The fecal/biliary elimination profile of MultiHance is different than the others (others are not eliminated so) and MultiHance is additionally lipophilic. How these differences may affect safety and efficacy was discussed in the appropriate sections during cycle 1 review.

MultiHance is marketed in 16 different countries for CNS and liver indications.

Approach

Details of the NDA are contained in previous reviews and memos (attached review cycle 1 memo) and the current review of Dr. Yaes and Dr. Castillo. This memo is intended to discuss and highlight the main issues and the limitations of the results that justified the recommendation. Because efficacy determinations were intrinsically arduous and additionally seemed to significantly influence the overall recommendation, the discussions on the effectiveness of MultiHance will be comprehensively presented. As a prelude to the discussions on the results, the relevant regulatory aspects will be discussed first.

Regulatory Milestones

NDA (21,357) Submission Date-	April 27, 2001/PDUFA Feb 28, 2002
Amendment-	Feb 26, 2002/PDUFA May 27, 2002
Administrative NDA Split-	May 23 and 24, 2002
	CNS Indication NDA # = 21,357
	CNS Multipack NDA # = 21,358
Action Letter (21,357 and 21,358) Date-	May 24, 2002 (Dr. Houn)
Cardiorenal Consultation-	January 3, 2003
Blinded CNS Re-read Adult Protocol	January 2003
Letter on CNS Re-read concerns-	March 7 2003 (Dr. Houn)
Letter on Safety (QT)-	March 10, 2003 (Dr. Houn)

Resubmission (Current)

CNS Indication- NDA 21,357-	October 10, 2003
CNS Multipack- NDA 21,358-	October 10, 2003

Subsequent Correspondence

Clin/Stat request for information-	November 19, 2003
TCON with sponsor-	November 25, 2003
Submission (21,357/000/BM/BS)-	December 9, 2003
Clin/Stat TCON (safety clarification- AE)-	January 28, 2004
Submission Clin/Stat-	February 3, 2004
[redacted]	February 2004
TCON with Sponsor (Deaths/SAE & Peds)	Feb 25 04

NDA was first submitted April 27, 2001. Based on collective pre-clinical and clinical deficiencies, the non-approval recommendation meant to conveyed in the action letter was shared with the sponsor 3 days prior to the PDUFA due date of February 28, 2002. A major amendment was received on February 26, 2002, extending the PDUFA due date to May 27, 2002. During this extended period, the sponsor made changes to [redacted]

The safety and efficacy deficiencies that were identified, with the recommendations, are listed in the action letter of May 2002 and in the primary clinical review by Dr. Yaes. An "approvable" action for the CNS indication was taken and new CNS adult studies and pediatric PK studies [redacted] were recommended. Likewise, for safety, new drug interaction studies for drugs using a ~~similar path~~ in the liver as MultiHance, QT studies, and additional data from existing studies not presented during review cycle 1 or re-analyses of presented data were recommended.

For efficacy, this re-submission was a blinded re-read of old data and did not include new studies. No new CNS studies were performed as recommended in the action letter. Instead, the sponsor submitted a proposal for a blinded re-read of the adult CNS studies with anatomic endpoints for a visualization claim. It is to be noted that this re-read approach was one that was neither recommended nor suggested by the Agency. 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 the changes in the endpoint to support the sought anatomic claim. The sponsor was made

aware that the agency's recommendation still was new study/s and agreement on the blinded re-read protocol was on its design and not on its acceptance as an alternate to new studies to support an indication. The agreements primarily involved demonstration of significance in results for each of the primary endpoints and readers on the primary level (pre v/s post) for the pivotal re-read study 105.

There were a total of three adult studies and one pediatric study that was included in the blinded re-read. The two identical adult pivotal studies 9A and 9B conducted in the US were combined under re-read protocol 105 and the third adult study 020 involving patients with brain mets conducted in Europe was included in re-read protocol 106. 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 was for the adult studies

the adult indication seeks for a meaningful broad disease claim- but the re-read was carried out only on tumor patients.

The specifics of the re-read database and its differences from review cycle 1 are presented in Tables 1 and 2 below.

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 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 Data base Compared- Review Cycle 1 v/s Current		
	CYCLE 1	CURRENT
	Adult	
Adult Indication		Visualization
Adult population [1]	All CNS and Mets	No Change
Adult Patients (N)		
105 (43,779-9A & 9B) 106 (B19036/020)	136 (0.1 dose) (276 all doses) 76 (0.1 dose) (150 all doses)	136 (0.1 dose) (276 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

Ref = Review cycle 1 memo; Table 2.1 of Dr. Castillo's review; Sponsor's Vol. 24, pp. 083, 117
1 = Type of patients/diagnosis = 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 Italian blinded readers for pivotal US trial 105 and three US 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.

There were several editorial discrepancies in the re-submission that required clarification from the sponsor on several occasions (see Feb 3, 2004 correspondence). These errors resided in critical sections of the application such as safety, label, etc. The discussed statistics in the text, for e.g., did not correlate with the respective referenced table. Such quality of the submission made the review process arduous.

Key Re-read Protocol Features

Prior to the discussions on the results in terms of its value and limitations, it would be best to understand some key aspects of the studies and the blinded re-read protocol.

The protocol specified primary objective for re-read studies 105 (the two pivotal adult US studies similar in design) and 106 (the adult mets 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, and 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 (table 3.1, Dr. Castillo's review). The pre-contrast image sets included T1, T2, and PD for re-read study 105, and T1 and T2 for re-read studies 106 and 112. The post contrast image was a single sequence of T1. The score that a pre-contrast image received was a composite score given to the entire sequences that comprised that pre-contrast set.

The secondary endpoint/variable was number of lesions.

The primary level of analysis was the comparison between the pre contrast images (a set of different sequences) and the post contrast images and the secondary level of analysis was the comparison between the pre contrast images and the paired images (paired = pre contrast + post contrast). The schema in appendix 1 provides an overview of the blinded re-reader methodology and the analyses

Key Protocol and Trial Design Issues

Although the focus of this review was on the re-read, and since no new studies were conducted, the flaws in the overall study design of the original protocol and those directly related to the re-read protocol is worth noting. These are discussed below.

a Enrollment bias/enrichment- all enrolled patients were with known disease and had received another imaging study as part of inclusion criteria.
b 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 this re-read were tumor patients. Therefore, sought indication for global disease (all CNS diseases) and all regions (brain and spine) is not justified.
c There was no gold standard. Study 105 had an active comparator (Omniscan), study 106 had none, and study 112 had Magnevist as the active comparator. 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 for diagnostic claims. What is obviously missing in the sponsor's arguments is the justification for the discordance between the re-read protocol that was designed to provide anatomic information obtained via the pre v/s paired read and the sought visualization claim (see results below).
d Image Acquisition Methodology- and its impact on the results is discussed below under results. The lack of consistency in the acquisition of image sequences and the lack of complete representation of the required sequences in the pre-contrast set of images were fundamental flaws with respect to the practice of medicine. On these grounds, the sponsor 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) was compared with the post contrast T1 image. But when additional pre-contrast sequences (e.g. T2 and or 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 single pre-contrast sequence (see tables E1I, E1J, E1K, and E1L review cycle 1 memo).

e Based on the previously identified flaws due to the multiple dosing regimen in the adult studies and the lack of a dose response, the re-read was 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. This approach reduced the adult sample sizes (not an issue for the

f The schema for the blinded re-read protocol in provided in the appendix. The composite scoring methodology and its impact on the secondary level of analyses (pre v/s paired) is discussed below under results.

g The change in endpoints to support 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 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 which 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 because of 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	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*
Adult All Lesions	0.1	136	271-381	NS*	0.1	136	299-395	S*
106	0.05	74	142-180	S*	0.05	74	149-171	S*
Adult Mets Only	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 <0.001for all primary variables for single blinded reader and single dose studied)
A = 0.1 mmol/kg dose is the sought market dose for — adult — indications.

Value and Limitations of the Re-read Results

The value and limitations of the results can be discussed based on each of the following broad issues:

1. Non-significant results in the pivotal trial for the primary level (pre v/s post) for the primary endpoints.
2. Inadequate patient population (types of diseases and region studied) and discordance to sought claim.
3. Limitations of primary level (pre v/s post) results for non-pivotal studies due to substandard imaging conditions and improper clinical practices (issue on incomplete sequences).
4. Limitations of secondary level (pre v/s pair) results with respect to the sought visualization claim (and type of analyses).
5. Limitations of secondary level results (pre v/s pair) and blinded reader scoring methodology — anatomic claim and type of scoring).
6. Absence of dose response and lack of justification for the sought adult — dose.

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, on a fundamental level, required evidence of effectiveness that Multihance performed better than the device alone that was agreed upon, was not established. The statistical significance demonstrated for 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 re-read committed to provide as the primary measure, and further, 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.

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

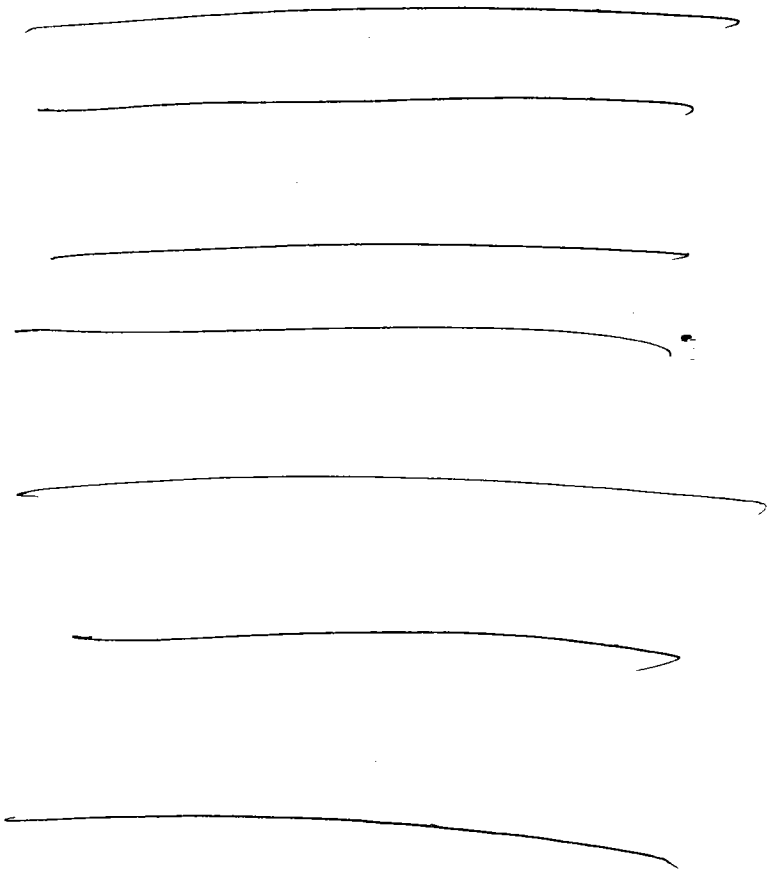
	STUDY 105	STUDY 106
Patient Type	Adult CNS	Adult Mets
US Study Site	Yes	No
Pivotal	Yes	No
CNS Disease Type	70% tumors 30 % others	100% mets
US blinded reader/s	No	Yes
Number of blinded readers	3 European	3 US
Significant Primary Level Results	No	Yes
Significant Secondary Level Results	Yes	Yes
Incomplete 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 (———————)

First, the non-pivotal studies in which statistical significance was demonstrated for the primary analyses did not enroll representative diseased patients. Patients with only tumors (mets or primary tumors) were studied. This does not justify the sought indication for global visualization of lesions (meaning all lesions) in the brain and spine. There were only 4 patients with spine disorder that were studied. Therefore, the sought spine and associated tissue indication is not justified. The sponsor's arguments that the Multihance program enrolled representative patient population for which the drug would be used routinely used are, baseless.

Second, the blinded readers were not provided with the complete set of pre images that should include all the sequences because they were not acquired during imaging. Not all of the required sequences that typically constitute a non-contrast baseline MRI were included in the analyses (as previously). Unlike the pivotal trial (re-read study #105) that included all the three sequences of T1, T2 and PD in the pre-image-sets, the analyses in

the non-pivotal studies (re-read studies 106 ———) included only the T1 and T2 sequences in the pre-image-sets (whether or not to acquire PD images was left to the PI's discretion in the mets study #106).



In this context, the true benefit of a drug over a device is not determinable and therefore, was not demonstrated. This is a fundamental flaw. As much 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 ———. But in this single re-read study #105 that was closer to the conditions of clinical practice in the US, the results were not significant in the primary analysis. In short, the analyses with positive results were achieved in studies performed under sub standard conditions of clinical practice and 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. It is worth noting that in the pivotal re-read study 105 in which the results were significant only at a secondary level and not significant at a primary level

Another potential concern that was identified by Dr. Yaes was related to the differences between the background of the readers and the sites at which the studies were originally conducted. The three blinded-readers for the pivotal US re-read study 105 were physicians from Italy and the three blinded-readers for re-read European study 106 were from US.

Despite such reader qualification differences, the results demonstrated consistency between the readers, thereby placing value on the results. However, concomitantly, such reader qualification differences unfolded another argument in favor of the concerns on the quality of the baseline images discussed below under the sequences. In essence, when complete pre contrast sequences (as it would be in clinical practice in the US) from the pivotal US re-read study 105 were presented to the European blinded readers, there was failure at the primary level and when incomplete pre-contrast images were presented to the US blinded readers in the non-pivotal European re-read study 106, the results were significant. The presence or absence of the required sequences in the pre-contrast image sets drove the results.

Third, the sponsor's arguments that effectiveness was demonstrated for the secondary level of analyses (pre v/s pair) for all studies, and therefore a success, 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 , 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 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 – namely Magnevist, Prohance, Omniscan and 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 pathologically well represented 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
Liver	No	No	No	Yes	
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
Pediatric Brain and Spine subjects (N)	NR**	103	84	N/A	
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
Diagnostic Information/value	?	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

B = Included histopath for Magnevist for brain tumors. 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 for a with a pre-specified statistical plan.
C = No truth standard. Approved class agent/s were 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 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 (see appendix 1) 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 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. The re-submission focused on two clinically relevant aspects in these analyses. They were lesion tracking and changes in those lesions that were 0 or 1 or 2 at baseline. Such analyses were presented for the adult indication
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 number 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.

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)	
0.1 mmol/kg	98 - 111	Yes	No	Majority (51 - 76)	All readers (21 - 27)	Not Significant
Study MH-106						
0.05 mmol/kg	66 - 71	Yes	No	Majority (37 - 40)	All readers (24 - 30)	
0.1 mmol/kg	59 - 66	Yes	No	Majority (27 - 34)	All readers (30 - 31)	Not Significant

* 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 endpoint

These lesion number results were driven by 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) and 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. Stated simply, 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.

[redacted]

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

SAFETY

General Safety Comments

Reference is made to the primary reviews (current review by Dr. Yaes and cycle 1 review by Dr. Li) and to the review cycle 1 memo (appendix 2) for details. According to the agency pre-clinical pharmacology-toxicology team, the sponsor has adequately addressed all the pre-clinical issues and an approval (with minor label changes) has been recommended. Like wise, the agency chemistry discipline is recommending approval. The agency clinical pharmacology discipline is also recommending approval with label changes. 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 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:

1. 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.
2. 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.
3. 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.
4. 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.
5. Death CRF: Case report forms on all patients who died during the clinical trials.
6. Reporting of all patients in the integrated safety summary.

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

1. 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%).

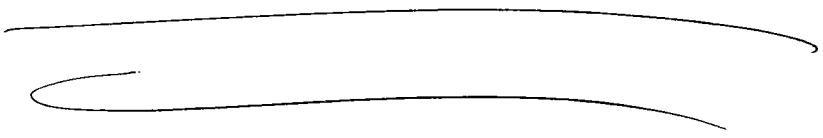
Sponsor's Response

- 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.
- Reanalyses of safety results in patients with liver disease.
- Post marketing reports from European and Asian countries where ——— units were sold.

Discussion

The drug interaction and liver disease results have been discussed in detail in the primary review by Dr. Yaes. 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 (described above in the regulatory section), 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 02, 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 decision was based primarily on the PK properties (rapid clearance) of Multihance, and its dosing regimen (single dose as a diagnostic 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 Recommendation:



b) Close monitoring in patients receiving other drugs known to compete for the ATP-dependent canalicular multispecific anion transporter (cMOAT).

2. 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 during recent review of ——— NDA).
- Literature search for *torsade de pointes* and gadolinium.
- Postmarketing experience

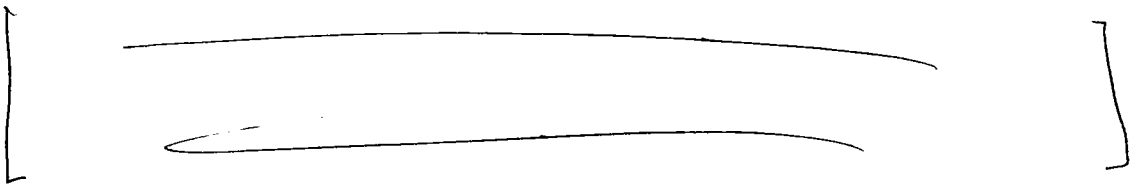
Discussion

The re-submission in essence is 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- 1) the lack of effects of calcium channel blockade in the action potential studies, and 2) 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.

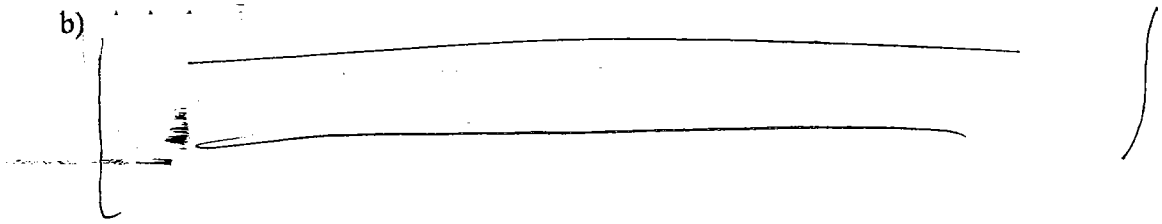
It is to be noted that the Multihance program is the first in its class in which such comprehensive preclinical studies have been conducted. It is re-assuring that the preclinical studies did not identify problems with respect to the potassium channels in the HERG studies (although calcium ion studies 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):

a) Concur with the sponsor's caution on preexisting severe cardiovascular disease under the — section of the label.

b)



3. 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.

4. 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 (Vol. 2, pp. 157-159).
- New analyses of local events by method of drug administration (infusion, bolus and [redacted] Vol. 2, pp. 153-157).
- Preclinical local tolerance studies (intravenous, [redacted]).
- 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 was 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, [redacted] resulted in greater reactions than the intravenous injections. The [redacted] 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.

5. 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) and have been incorporated in Dr. Yaes' review (tables 13-19).

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

Clarifications on the exposure rate, AE rates with the sources of the database were also sought during the review cycle. The summary on exposures, AEs and the sources are presented in Dr. Yaes' review (tables 13-19).

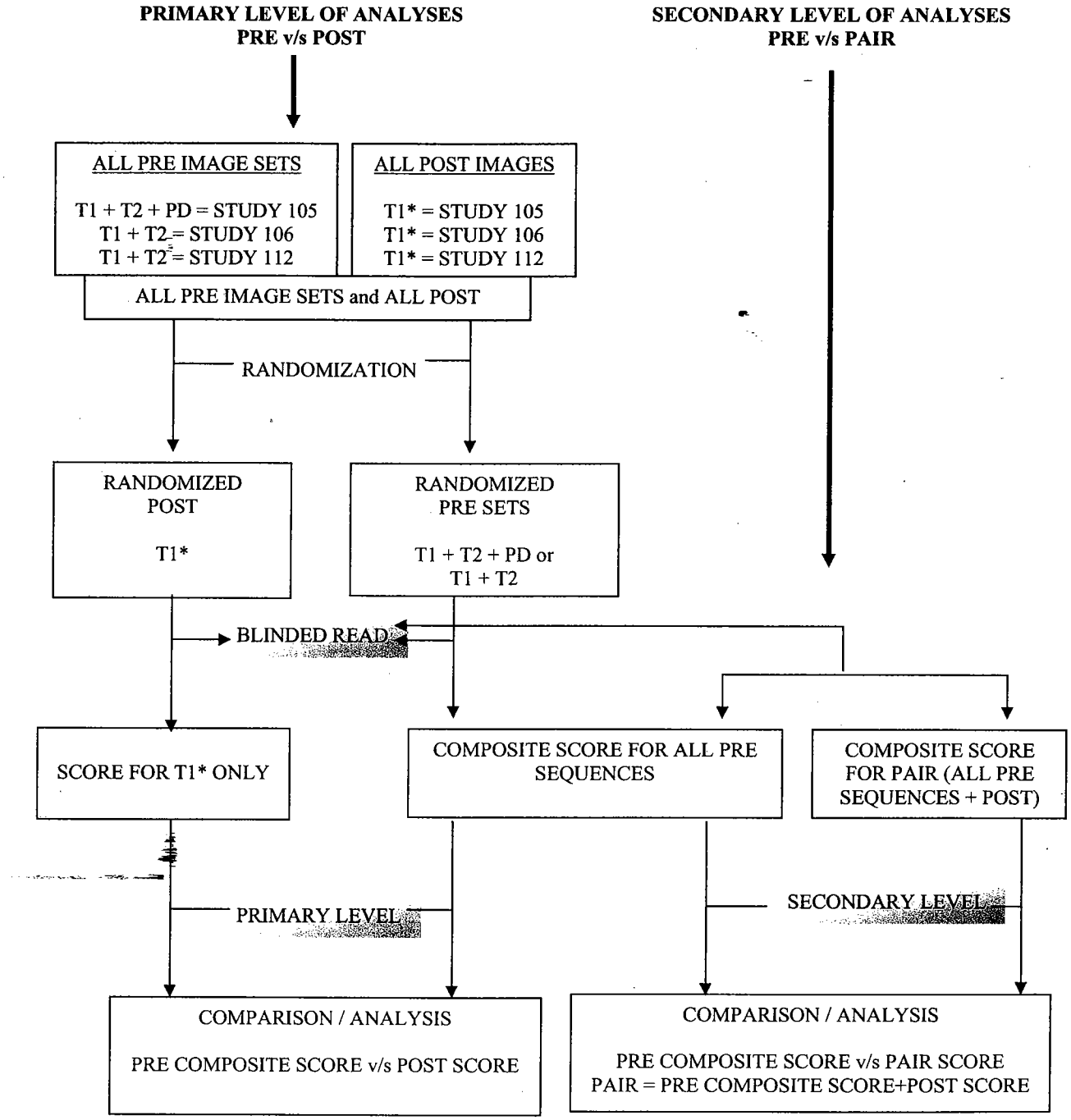
END OF SAFETY REVIEW

SEE APPENDIX BELOW

APPENDIX 1

RE-READ SCHEMA- BLINDED READER METHODOLOGY*

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



SEE APPENDIX 2A & 2B BELOW

APPENDIX 2A

REVIEW CYCLE 1 MEMO

APPENDIX 2B

REVIEW CYCLE 1 ADDENDUM MEMO

Appears This Way
On Original

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

/s/

Ramesh Raman
4/7/04 12:31:47 PM
MEDICAL OFFICER
This memo to file is a response to the re-submission that justifies the recommendation. Details are contained in the primary medical and primary statistical reveiws.

George Mills
4/9/04 11:58:42 AM
MEDICAL OFFICER

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

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

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

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

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

Pediatric study MH-112 is a re-read of study B19036/036

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

HFD-160 Medical Officer's Review

NDA 21-357 (MultiHance)

Letter Date:	April 27, 2001
Sponsor:	Bracco Diagnostics, Princeton, NJ
Drug Name:	MultiHance (Gadobenate dimeglumine)
Class:	Gadolinium MRI Contrast Agent
Route:	Intravenous as rapid bolus or infusion
Indication:	MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain spine or associated tissues.
Formulation:	0.5 mmol/ml
Dose:	CNS Adult- 0.1 mmol/kg (0.2 ml/kg)
How Supplied	5, 10, 15 and 20 ml single dose vials 50 ml and 100 ml rubber stoppered glass bottles (MultiHance Multipack)

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

Table of Contents

Executive Summary

I. Recommendations

A. Recommendations on Approvability

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

2. ———

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

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

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

6. [redacted]

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

II Summary of Clinical Findings

A. Brief Overview of Clinical Findings

B. Efficacy

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

C. Safety

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

D. Dosing

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

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

- The superiority of the 0.1 mmol/kg dose of MultiHance over the 0.05 mmol/kg dose of MultiHance has not been demonstrated in adults.
- [redacted]

E. Special populations

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

Clinical Review

I Introduction and Background

A. Drug

1. Name

A. Generic: gadobenate dimeglumine

B. Trade : MultiHance, MultiHance Multipack

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

2. Class: Gadolinium paramagnetic MRI contrast agent

B. State of Armentariun for Indications

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

- Magnevist
- Prohance
- Omniscan
- Optimark

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

C. Important Milestones

April 27, 2001

NDA 21-357 and NDA 21-358 for MultiHance and MultiHance Multipack was received. Indications for CNS [redacted]

September 13, 2001

Safety Update Received

February 25, 2002

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

February 26,2002

Efficacy amendment received

May 24, 2002

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

August 28,2002

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

September 18, 2002

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

November 15, 2002

Additional comments faxed to sponsor

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

December 3, 2002

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

December 11, 2002 Industry T-con

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

D. Other Relevant Information"

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

E. Important Issues with Related Agents

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

II Clinically relevant Findings from other Disciplines

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

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

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

Results:

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

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

III Pharmacokinetics

A. Pharmacokinetics

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

No effect by age or sex in adults was seen

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

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

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

B. Pharmacodynamics

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

IV Description of Clinical Data and Sources

A. Overall Data

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

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

B. Tables Listing Clinical Trials

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

*Scheduled to receive MultiHance

** Received MultiHance

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

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

C. Postmarketing Experience

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

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

D. Literature Review

N/A

V Clinical Review Methods

A. Description of How Review Was Conducted

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

B. Overview of material Consulted in Review

Material consulted for this review included

Sponsor's 44 volume resubmission

Medical officer review of previous submission

Clinical team leader's memorandum on previous submission

Minutes of industry meeting August 28, 2002

FDA comments to sponsor dated November 15, 2002

Minutes of T-con dated December 11, 2002

Drafts of reviews by other disciplines, particularly statistics and pharmacology

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

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

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

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

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

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

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

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

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

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

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

D. Were trials Conducted in According to Accepted Ethical Standards

There were no new clinical trials reported in the resubmission.

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

E. Evaluation of Financial Disclosure.

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

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

Appears This Way
On Original

VI Integrated review of Efficacy

A. Summary of Conclusions

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

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

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

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

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

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

C. Detailed review of Trials by Indication

1. Indication:

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

Reviewer's Comment: In the original NDA submission the sponsor sought indications —— CNS . —— In the re-submission, —— the single indication for CNS imaging is sought

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

1. The two key adult trials (43779-9A and 43779-9B) were not sufficient to establish the proposed dose to visualize lesions. Because of an unknown dose-response relationship to liver and cardiac adverse events, it is important to establish the lowest effective dose. Additionally the application lacks sufficient information to establish the anatomic detection in an appropriate clinical setting.

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

Reviewer's Comment:

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

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

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

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

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

Reviewer's comment:

Therefore in the analysis of the reread, only scans obtained after the first dose but before the second dose were considered. No such scans were, of course obtained more than 15 minutes after dosing

Table 4 The Three Dosing Regimens For Pivotal Trials 43779-9A and 43779-9B p. 023 v. 25			
MultiHance, N = 276			
Regimen	First Dose	Second dose	PATIENTS (A+B)
1	0.05 mmol/kg	0.1 mmol/kg	140 (71+ 69)
2	0.1 mmol/kg	0.1 mmol/kg	136 (65 +71)
Omniscan, N = 134			
3	0.1 mmol/kg	0.2 mmol/kg	134 (69 + 65)
Total			410 (205 + 205)

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

Caucasian 81%

Black 9%

Hispanic 7%

Asian 2%

Other 1%

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

Table 5 Diagnosis by Treatment arm (specified by first dose) p.23 v.25			
Diagnosis	MultiHance		Omniscan
	0.05 mmol/kg	0.1 mmol/kg	0.1mmol/kg
Normal parenchyma	5	10	7
1° CNS tumor	14	14	16
Metastases	17	13	15
Benign tumor	38	36	36
Infection	5	4	2
Vascular	6	3	10
Inflammation	6	4	11
Infarct	14	15	19
MS	12	18	14
Post op changes	16	14	10
Spinal lesion	4	4	3
other	1	2	5
Differential Dx	8	11	7
Unknown	10	5	4

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

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

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

- Border delineation
- Visualization of internal morphology
- Contrast enhancement

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

remain the same since all pre dose scans are still part of the set. Thus the score for the paired read can go up or remain the same but will not go down. For the whole population of lesions, the score for the paired read is virtually guaranteed to be higher than the pre-dose read. On the other hand on a pre dose vs. post dose read, the score can go down if the post is worse than the pre and since the score can go either up or down for each lesion the result may be positive or negative. These visualization endpoints although they have been used previously do not determine whether the post dose scan is clinically useful or not. Changes between the pre and post scans may be as important in making a diagnosis as properties of the individual scans. An important criterion in making a diagnosis is whether a lesion enhances or not (malignant lesions tend to enhance) This can only be determined by comparing the pre T1 to the enhanced T1. If a lesion doesn't enhance this fact may be important in making a diagnosis even if the lesion is not well visualized on the post T1. Thus a comparison between pre dose and paired reads, while appropriate for a ——— endpoint would not be appropriate for the three ***visualization*** *endpoints used in this study.*

Results:

MH-105

Primary outcome variables: By lesion analysis, pre-dose vs. post –dose, Lesion Border Delineation, Visualization of Internal Morphology, Contrast Enhancement

Pre vs. Post all lesion analysis

Table 6 Scores for Lesion Border Delineation Mean ±SD by individual lesion (table 3-4 p149 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N**	297	363	350
Predose score (mean ± SD)	1.7±1.05	1.7±1.05	1.6±1.08
Postdose score (mean ± SD)	1.7±1.33	1.8±1.40	1.8±1.34
p	0.393	0.286	0.010
Reader 2			
N**	355	381	373
Predose score (mean ± SD)	1.6±1.01	1.7±0.99	1.6±106
Postdose score (mean ± SD)	1.6±1.42	1.6±1.44	1.8±1.48
p	0.742	0.729	0.171
Reader 3			
N**	245	271	282
Predose score (mean ± SD)	1.9±1.06	1.8±1.19	1.8±1.13
Postdose score (mean ± SD)	1.6±1.53	1.8±1.59	1.7±1.50
p	(0.009)*	0.936	0.713

*p values in parenthesis mean that pre-dose had a higher score than post-dose

* *Total number of lesions seen by reader on all scan sets

Table 7 Scores for Visualization of Internal Morphology Mean ±SD by lesion analysis (table 3-5 p150 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	297	363	350
Predose score (mean ± SD)	1.8±110	1.8±103	1.6±106
Postdose score (mean ± SD)	1.8±135	1.8±137	1.8±131
p	1.00	0.697	0.029
Reader 2			
N*	355	381	373
Predose score (mean ± SD)	1.7±108	1.8±106	1.6±109
Postdose score (mean ± SD)	1.7±102	1.7±150	1.9±156
p	0.897	0.642	0.034
Reader 3			
N*	245	271	282
Predose score (mean ± SD)	2.0±1.07	1.9±1.21	1.9±1.15
Postdose score (mean ± SD)	1.6±1.56	1.9±1.64	1.8±1.53
p	(0.002)	0.979	0.679

* Total number of lesions seen by reader on all scan sets

Table 8 Scores for Contrast Enhancement Mean ±SD by lesion analysis (table 3-6 p151 v24) MH-105			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	297	363	350
Predose score (mean ± SD)	2.1±1.19	2.1±1.19	1.9±1.25
Postdose score (mean ± SD)	2.0±1.44	2.0±1.48	2.1±1.42
p	(0.636)	(0.449)	0.229
Reader 2			
N*	355	381	373
Predose score (mean ± SD)	1.7±1.08	1.8±1.09	1.7±1.14
Postdose score (mean ± SD)	1.7±1.51	1.7±1.51	1.9±1.56
p	0.712	(0.374)	0.257
Reader 3			
N*	245	271	282
Predose score (mean ± SD)	2.4±1.17	2.2±1.33	2.2±1.29
Postdose score (mean ± SD)	1.7±1.60	2.0±1.65	2.0±1.62
p	(<0.001)	(0.113)	(0.131)

* Total number of lesions seen by reader on all scan sets

Reviewer's Comment: It is interesting to note that on contrast enhancement, pre dose gets a higher score than post dose in the majority of cases

- For the primary outcome variables, a statistically significant difference in favor of the post dose scans does not occur for any of the three parameters for any of the three blinded readers for the pivotal trial. Efficacy has not been demonstrated

- No statistically significant difference between the scores for the two MultiHance doses is seen for any of the three visualization outcome variables, for any of the three clinical trials

MH-106

Study MH-106 Supportive study (Re-read of study B19036/020)

B19036/020 was a European randomized double blind study testing two dosing regimens, each consisting of three sequential doses of MultiHance given at 15 minute intervals. The regimens were

1. 0.05 + 0.05 +0.1 mmol/kg
2. 0.1 + 0.1+ 0.1 mmol/kg

149 patients (74 regimen 1 and 75 regimen 2) were available for re-read

Reread Results: Primary outcome variables pre-dose read vs. post dose read

There was no active comparator in this study

The blinded read was performed in the same way as for MH-105

Table 9 Scores for Lesion Border Delineation: Mean ±SD (By Lesion analysis) MH-106 (table 3-36 p200v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.0±0.85	0.7±0.81	N/A
Postdose score (mean ± SD)	2.3±1.13	2.4±1.09	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.2±1.18	1.0±1.10	N/A
Postdose score (mean ± SD)	2.5±1.18	2.6±1.19	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.3±1.14	1.0±1.10	N/A
Postdose score (mean ± SD)	2.5±1.32	2.9±1.14	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

Table 10 Scores for Visualization of Internal Morphology: Mean ±SD (By Lesion analysis) MH-106 (table 3-37 p200 v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.1±0.98	0.8±0.98	N/A
Postdose score (mean ± SD)	2.5±1.11	2.5±1.10	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.3±1.20	1.2±1.21	N/A
Postdose score (mean ± SD)	1.7±1.51	2.6±1.13	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.6±1.39	1.2±1.21	N/A
Postdose score (mean ± SD)	2.9±1.29	3.2±1.04	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

Table 11 Scores for Contrast Enhancement Mean ±SD(By Lesion analysis) MH-106 (table 3-38 p201 v24)			
	MultiHance		Omniscan
	0.05mmol/kg	0.1mmol/kg	0.1mmol/kg
Reader 1			
N*	142	250	N/A
Predose score (mean ± SD)	1.0±0.93	0.7±0.84	N/A
Postdose score (mean ± SD)	2.5±1.12	2.6±1.06	N/A
p	<0.001	<0.001	N/A
Reader 2			
N*	180	274	N/A
Predose score (mean ± SD)	1.4±1.31	1.2±1.24	N/A
Postdose score (mean ± SD)	2.6±1.10	2.7±1.13	N/A
p	<0.001	<0.001	N/A
Reader 3			
N*	171	259	N/A
Predose score (mean ± SD)	1.4±1.20	1.1±1.24	N/A
Postdose score (mean ± SD)	2.7±1.27	3.05±1.65	N/A
p	<0.001	<0.001	N/A

* Total number of lesions seen by reader on all scan sets

- In this study the difference between post dose scores and pre dose scores is statistically significant for both doses, for all three readers for al three visualization endpoints. This result is contradictory to the result of the pivotal trials
- In this study, there was no statistically significant difference between the two doses for any of the three readers for any of the three visualization endpoints. This result is in agreement with the result of the pivotal trials

MH-112 is a reread of pediatric study B19036/036

D. Conclusions

1. Efficacy has not been demonstrated for the primary outcome variables for the re-read of the pivotal trials.
2. A difference in efficacy has not been demonstrated between the 0.05 mmol/kg dose and the 0.1 mmol/kg dose in any clinical trials in adults
3.

4. Demonstration of efficacy in the supportive European trial alone is not sufficient to support approval

VII Integrated review of Safety

A. Brief Statement of Conclusions

1.The sponsor has not performed the drug interaction study requested by the agency in the action letter of May 24, 2002

2.The sponsor has not performed the placebo controlled cardiovascular study requested by the agency in the action letter of May 24, 2002

3.In the integrated safety database from the US and Europe the overall incidence of adverse events is higher in the treatment group than in the Placebo group. This difference is statistically significant (p =0.0003). This higher incidence is also seen in some subgroup analyses (e.g. Table LLL p156 v2)

4.The sponsor's analysis of patients taking Glyburide does not directly address the question of drug-drug competition for the CMOAT/MRP2 transporter system. A drug interaction study is required to resolve this issue.

B. Description of Patient Exposure

The sponsor's reanalysis of safety data is based on a review of data from 2892 adult subjects and 110 pediatric subjects in the Europe-US-China database, and 1218 adult subjects in the Japanese database. The sponsor analyzed THE Japanese database of 1218 subjects separately.

1. Patient exposure, deaths and serious adverse events

Table 13 Population Exposed to MultiHance (p 6-11, table I p23, table T p54, table U p55 v 42)				
	Adult Subjects		Peds	Total
	US, Europe, China	Japan		
Completed trials	71	11	2	84
Ongoing trials	9	0	0	9
Exposed to MultiHance	2892	1218	110	4220
Adverse events	519 (18%)	49 (4%)	14 (13%)	582 (14%)
Deaths	2 (0.06%)	3 (0.2%)	0	5 (0.15%)
SAEs (including deaths)	14 (0.5%)	6 (0.5%)	2	22 (0.5%)
Discontinuations for AEs	10 (0.3%)	0	0	10 90.2%)

C. Deaths and serious Adverse Events

All deaths and serious adverse events were reported in the previous submission. There were no new deaths or serious adverse events reported in the resubmission The individual patients who died or experienced serious adverse events were discussed in the medical officer's review of the previous submission

2. Deaths and Serious Adverse events in adults re-submission and previous submissions

Table 14 Adults (US, Europe China) (Table P p42, Table I p23 v42)			
	Previous		Re-submission (10/10/03
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	1808	2637	2892
Deaths	1	2	2
SAEs	10	14	14
Discontinuations for AEs	8	10	10

There were no <u>new</u> deaths, SAEs or discontinuations re3ported in this re-submission. All deaths, SAEs and discontinuations have been discussed in the medical review of the previous submission

3.Deaths and Serious Adverse events in the pediatric population re-submission and previous submissions

Table 15 Deaths and Serious Adverse events in the pediatric population (table u p55 v42)			
	Previous		Re-submission (10/10/03
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	110	110	110
Deaths	0	0	0
SAEs	2	2	2
Discontinuations	0	0	0

There were no new deaths SAEs or discontinuations reported in the re-submission for the pediatric population

4. Deaths and Serious Adverse events in the Japanese studies re-submission and previous submissions.

Table 16 Deaths and Serious Adverse events in the Japanese studies (table v p56 v42)			
	Previous Submissions		This Submission (10/10/03)
	Submission (4/20/00)	Safety Update (9/13/01)	
Exposed to MultiHance	1213	1213	1218
Deaths	3	3	3
SAEs	6	6	6

There were no new deaths SAEs or discontinuations reported in the re-submission for the Japanese population

D. Sponsor's Response to Specific Deficiencies Mentioned in the Action Letter

Safety data contained in this re-submission consisted of re-analyses of data from subgroups of patients contained in the previous submission

1. The sponsor identified 42 subjects taking the diabetes drug Glyburide, which, is excreted by the CMOAT/MRP2 system. AE data on these 42 subjects were analyzed and compared to data from the 2531 subjects who did not take Glyburide (table B p22)

2. Re-analysis of QTc prolongation was based on the 47 subjects (p86) in the cardiovascular study 43-770-12 and on the 25 pediatric subjects who had EKG data from the pediatric pharmacokinetic study 43-779-10 (p121)
3. Data on urinalysis variables is presented in table VV (p133 v2) and WW (p135 v2) The number of subjects for whom data is available varies with both time of measurement and the parameter being measured.

Reviewer's comment: With the number of Patients so variable it is difficult to interpret the data presented by the sponsor. There is no explanation for this variability in this submission

AE data is available from 852 renally impaired (679 mild, 128 moderate and 45 severe)

Urinalysis data is available from 31 renally impaired subjects (11 placebo, 20 MultiHance) from study 43-779-4

85/2637 patients from the US and European studies have been identified with local adverse events.

E. Methods and specific Findings of Safety Review

1) Only a small number of patients taking Glyburide were identified in the database. The adverse event rate was actually higher in patients not taking Glyburide than in patients not taking Glyburide, whereas a drug interaction with MultiHance would be expected to lead to a higher AE incidence in the Glyburide group. Even if MultiHance did interfere with the excretion of Glyburide it is not clear that lower serum glucose or AEs associated with hypoglycemia would occur. The antineoplastic drugs which could also compete for the CMOAT/MRP2 transporter and which probably have a narrower therapeutic index than Glyburide were not studied, because too few patients taking these drugs were identified in the safety database. However MultiHance is eliminated primarily by the kidney with an elimination half -life of 1-2 hours. MultiHance will be given as a single dose. If it is competing with other drugs for the CMOAT/MRP2 transporter, it will only do so for a short period of time. Even for renally impaired patients, the half-life is short compared to that of most drugs metabolized by the liver. In dialysis patients MultiHance will be eliminated. To obtain a definitive answer to this question a pre clinical drug interaction study, as previously requested by the agency, is required.

The agency expressed a concern with potential liver toxicity when the sponsor was seeking [redacted] a CNS indication. [redacted] only a minority of patients imaged for the CNS indication would be expected to have hepatic impairment. As stated in the action letter of May 24, 2002 concern was raised because of clinical data showed increase in liver enzymes and bilirubin in patients with pre-existing liver disease and an increased incidence of pruritis in patients with pre-existing cirrhosis. Since only a relatively small number of patients imaged for the CNS indication would be expected to have pre-existing liver disease, this concern could be handled by a warning, and should not be an approvability issue. The sponsor should be asked to identify all patients with liver impairment in the CNS studies and present relevant laboratory values and AEs.

2) The sponsor has not performed the clinical cardiovascular study requested. The sponsor has reanalyzed old EKG data from study 43-770-12 using a questionable individualized correction method. The most commonly used correction methods used are Bazet's and Fredericia's. Correction formulas based on linear regression have been proposed (QTc preliminary concept paper, 11/15/02) The sponsor uses a *non-linear* regression method of individualized correction to reanalyze QT data from study 43-779-12. Data from the entire database was not reanalyzed.

A. Clinical Safety Database

Table 17 83 Clinical Studies in Clinical Safety Database (MO review first cycle table 8 p27)					
Study	location	Imaged Organ	Patients completed	comments	Number of studies
43,779-9A, 43,779-9,B placebo controlled studies	USA	CNS	276	Pivotal	2
B19036/020	Europe	CNS	150		1
B19036/036	Europe	CNS	85	pediatric	1
Other European	Europe	CNS	144		14
Japanese	Japan	CNS	379		3
US Liver Studies	USA	Liver	317		4
European Liver Studies	Europe	Liver	935		22
Japanese Liver Studies	Japan	Liver	485		5
Other US (pediatric and renal dialysis)	US	Liver	56		3
Other European (PK, Cardiac, MRA, Breast)	Europe		784		21
Other Japan	Japan		352		3

Reviewers Comment:

Subjects who received MultiHance

In the US-Europe- China studies, there were 2785 adult patients, and 107 adult normal volunteers for a total of 2892 adult subjects

In the Japanese studies there were 1196 adult patients, 22 adult volunteers for a total of 1218 Japanese adult subjects

In the pediatric studies, there were 85 patients and 25 normal volunteers

Table 18 Subjects Dosed with MultiHance (tables VVV p191 v2, table WWW p192 v, table PPP p176 v2, table LLLp166 v2)			
	Adult	Pediatric	Total
US and Europe	2653	110	2763
Japan	1218	-	1218
China	132	-	132
US Europe, China	2785	110	2895
US Europe, China and Japan		110	4113

Table 19. Adverse Events by Subgroup Adult Patients Dosed With MultiHance (US, Europe and China) (table VVV p191 v2, table LLLp166 v2)			
	Number of patients	Number with AEs	Percent with AEs
All	2785	493	18%
Male	1585	262	17%
Female	1200	231	19%
Age < 65	2005	382	19%
Age > 65	780	111	14%
White	2498	444	18%
Black	79	24	30%
Hispanic	29	4	14%
Asian	162	19	11%
Other	11	2	18%
Missing?	6	0	0%
Europe	2006	253	13%
US	647	230	36%
China	132	10	7.6%
Adverse Events by Age in Pediatric Subjects Dosed With MultiHance Table WWW p192			
Total	110	14	13%
Age < 2	15	2	13%
2 < age < 12	69	8	12%
>12	26	4	15%
Adverse Events in Japanese Subjects Dosed with MultiHance (analyzed separately by sponsor and not included in above totals (table PPP p176 v2)			
Japan	1218	49	4%

B. Safety deficiencies identified in the action letter of May 24, 2002

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

a) MultiHance is excreted by the liver through the ATP dependent canalicular multispecific anion transporter (cMOAT). This may result in competition for cMOAT with other drugs eliminated by the same mechanism. The effect of MultiHance on the pharmacokinetics of such drugs may be clinically significant for drugs with a narrow therapeutic index

"Appropriate drug interaction studies are needed. Please submit protocols for FDA comments prior to initiation of these studies"

b) The stated mechanism of action [redacted] is hepatocellular uptake. The preclinical observation of hepatic vacuolization and necrosis raises concern about the hepatocellular safety of MultiHance

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

1) "Conduct placebo controlled studies in patients using higher than indicated doses of MultiHance (at least 4x) to determine QT effects. We recommend that you submit your proposed protocol. It will be consulted to the Division of Cardio-Renal Drug Products to assess the acceptability in evaluating QT effects

3) The application lacks sufficient data in adults and pediatric patients to determine the effect of MultiHance on the renal system

4) The application lacks sufficient data on local adverse events

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