CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-357

21-358

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Information:

1) Active Ingredient(s)	gadobenate dimeglumine
2) Strength	529 mg/mL
3) Trade Name	MultiHance®
4) Dosage Form, Route of Administration	Injection, solution Intravenous
5) Applicant Firm Name	Bracco Diagnostics Inc.
6) NDA Number(s)	21-357, 21-358
7) Approval date	Pending
8) Exclusivity- Data first could be approved and length of exclusivity period	5 years after approval date
9) Applicable Patent Number	4,916,246 (See attached chart)

* After NDA approval, Bracco Diagnostics Inc. will file for a Waxman/Hatch patent term extension as a result of the delay in obtaining product approval from the FDA.

Pursuant to 21 C.F.R. Section 314.50 we are hereby providing required patent information:

Patent Number	Expiration Date	Type of Patent	Name of Patent Owner	Name of US Agent
4,916,246	April 10, 2007	Drug, Drug Product	Bracco International, B.V.	M. Caragh Noone Senior Patent Counsel Bracco Research USA Inc. 305 College Road East Princeton, NJ 08540

The undersigned declares that U.S. Patent No. 4,916,246 covers the formulation, composition, and/or method of use of MultiHance. This product is the subject of this application for which approval is being sought.

M Benson

Melanie Benson
Director US Regulatory Affairs

April 23, 2001
Date

EXCLUSIVITY SUMMARY FOR NDA # _21-357__ SUPPL #_____

Trade Name MultiHance__ Generic Name gadobenate dimeglumine_

Applicant Name Bracco Diagnostics, Inc. HFD#160

Approval Date If Known November 23, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_**X**__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_**X**__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____ _____

Signature /S/ Date November 23, 2004

Title: Project Manager

Signature of Office/ Division Director

Date

Form OGD-011347 Revised 05/10/2004

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

/s/

Diane Smith
11/23/04 12:29:29 PM

EXCLUSIVITY SUMMARY for NDA # 21-357/ 210358 SUPPL #____
Trade Name MultiHance Generic Name gadobenate dimeglumin
Applicant Name Bracco Diagnostics, Inc. HFD-160
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. **An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.**

   a) **Is it an original NDA?** YES/_X__/ NO /___/

   b) **Is it an effectiveness supplement?** YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) **Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO."**

      YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

   d) **Did the applicant request exclusivity?**

      YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No – Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no"

if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#_____

NDA#_____

NDA#_____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#_____

NDA#_____

NDA#_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. **Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.**

   YES /___/ NO /___/

   IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. **A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.**

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 Study#

Investigation #2 Study#

Investigation #3 Study#

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	**YES /___/**	**NO /___/**
Investigation #2	**YES /___/**	**NO /___/**
Investigation #3	**YES /___/**	**NO /___/**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	**YES /___/**	**NO /___/**
Investigation #2	**YES /___/**	**NO /___/**
Investigation #3	**YES /___/**	**NO /___/**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # Study #

Investigation # Study #

Investigation # Study #

4. **To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.**

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /___/ NO /___/ Explain:

Investigation #2

IND # YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain:

/S/

Signature of Prepare. Date: February 18, 2004
Title: Project Manager/Diane C. Smith

Signature of Office or Division Director Date:

cc:
Archival NDA
HFD-160 /Division File
HFD- 160 /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi
Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 21-357/21-358 SUPPL #_____
Trade Name: Multihance Generic Name: gadobenate dimeglumine
Applicant Name: Bracco Diagnostics, Inc. HFD # 160
Approval Date If Known:

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /x / NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / x/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA 20-937

Division File NDA 20-937

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES / x/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO / x/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /x/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /x/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature: /S/ *Date: January 8, 2002*
Title: Project Manager James Moore

Signature of Office/Division Director
Signature: *Date:*

cc: *Original NDA 2 -*
Division File 2 -
HFD-93 Mary Ann Holovac

Item 16: Debarment Statement

Bracco Diagnostics Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.

M Benson

Melanie Benson
Director of US Regulatory Affairs

February 11, 2004

Date

Item 16: Debarment Statement

Bracco Diagnostics Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.

M Benson

Melanie Benson
Director of US Regulatory Affairs

April 23, 2001

Date

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-357 & 21-358 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: August 2, 2004 Action Date: November 23, 2004

HFD 160 Trade and generic names/dosage form: MultiHance® and MultiHance®Multipack™ (gadobenate dimeglumine) injection

Applicant: Bracco Diagnostics Inc. Therapeutic Class: 1S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Intravenous use in magnetic resonance imaging of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues.

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

X No: Please check all that apply: X Partial Waiver X Deferred ____ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo. 0	yr.____	Tanner Stage____
Max____	kg____	mo. 24	yr.____	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- X Adult studies ready for approval
- ☐ Formulation needed
- X Other: Studies may be required for the ages 0 to 2 in the future depending on feasibility.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred: See below

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- **X Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- **X Adult studies ready for approval**
- ☐ **Formulation needed**

Other: PK 2 to 5; Safety and Efficacy 2 to 16

Date studies are due (mm/dd/yy): December 1, 2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo. < 6 yr.____ Tanner Stage____
Max____ kg____ mo.____ yr. 17 Tanner Stage____

Comments: Information is from Study B19036/036 (Clinical study)

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Diane C. Smith, R.Ph.
Regulatory Project Manager

cc: NDA 21-357 & 21-358
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Diane Smith
11/23/04 12:38:31 PM

ITEM 19: FINANCIAL DISCLOSURE

In compliance with 21 CFR 54, Bracco Diagnostics Inc. is submitting the required Financial Disclosure Information and Form FDA 3454 for its clinical investigators of the covered studies in support of NDA 21-357.

All covered studies and those having a large patient population were completed prior to February 02, 1999, the effective date of the Final Rule of Financial Disclosure, with the exception of study B19036-036. Study B19036-36 was completed in February 1999.

The studies considered are as follows:

Study # (US Studies)	**End Date**
43,779-1	March 97
43,779-9A	January 98
43,779-9B	September 98
43,779-15	December 95
Study # (EU Studies)	
B19036-010	July 95
B19036-016	July 95
B19036-020	September 97
B19036-036	February 99

Please refer to Form FDA 3454 (3/99) and the attached listing of investigators.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if applicable)) submitted in support of this application, I certify to one of the statement below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

— 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator has a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	please see attached list	

— (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

— (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Melanie Benson	Director, US Regulatory Affairs
FIRM / ORGANIZATION Bracco Diagnostics Inc. Princeton, NJ 08543	
SIGNATURE MBenson	DATE April 23, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

ADM-1

16 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

_____

ADMINISTRATIVE REVIEW OF NDA ACTION PACKAGE
OFFICE OF DRUG EVALUATION III

NDA: 21,357, 21-358
Drug: Multihance and Multihance Multipack (gadomenate dimeglumine injection)
Classification: 1 S
Sponsor: Bracco
Project Manager/CSO: Diane Smith, R.Ph.

Reviewer: Bronwyn Collier, ADRA ODE III
Review Date: November 23, 2004

Review Cycle 1
Date Submitted: April 27, 2001
Date Received: April 27, 2001
Goal Date: February 27, 2002
Extended Goal Date: May 27, 2002
Action: Approvable May 24, 2002

Review Cycle 2
Date Submitted: October 10, 2003
Date Received: October 14, 2003
Goal Date: April 14, 2004
Action: Approvable April 14, 2004

Review Cycle 3
Date Submitted: July 30, 2004
Date Received: August 2, 2004
Goal Date: February 2, 2005
Proposed Action: Approval

	STATUS	COMMENTS
ACTION LETTER	draft	
EXCLUSIVITY CHECKLIST	draft	
DEBARMENT STATEMENT	verified 1st review cycle	
PEDIATRIC PAGE	draft	
TRADE NAME REVIEW	completed	Disagreement between DMETS and DDMAC conclusions addressed in Division Director's review.
DSI AUDITS	completed 1st review cycle	
FACILITY INSPECTIONS	Acceptable	2/24/04

REVIEWS	STATUS	COMMENTS
DIV. SUMMARY REVIEW	draft	
CLINICAL	draft	
SAFETY UPDATE	completed	included in clinical review
FINANCIAL DISCLOSURE	completed 1st review cycle	
STATISTICAL	draft	
BIOPHARM	completed 1st review cycle	
CMC	completed	
EA	completed	included in CMC review
MICRO (validation of sterilization)	completed 1st review cycle	
STABILITY (stats)	completed	included in CMC review
PHARM/TOX	completed 1st review cycle	
CAC (stats)	N/A	
CAC/ECAC REPORT	N/A	

Labeling: Agreements reached with sponsor.
Postmarketing Commitments: Agreement reached with sponsor regarding pediatric commitments required under PREA.
Advisory Committee Meeting: N/A

Comments: Draft documents must be finalized prior to taking an action. Pediatric page and exclusivity summary checklist must be completed.

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

/s/

Bronwyn Collier
11/23/04 11:04:29 AM
CSO

DIVISION DIRECTOR'S MEMORANDUM

NDA:	21-357 (Single dose) 21-358 (Pharmacy Bulk Pack)
DRUG:	MultiHance® (Gadobenate dimeglumine) and MultiHance® Multipack™ Injection
ROUTE:	Intravenous
MODALITY:	Magnetic Resonance Imaging (MRI)
INDICATION:	Contrast enhancement in adult CNS disease
SPONSOR:	Bracco Diagnostics, Inc.
RECEIVED:	August 2, 2004
PDUFA:	February 14, 2005
COMPLETED:	November 23, 2004

RELATED DRUGS:

1. Magnevist (approved - 1989)
2. ProHance (approved - 1992)
3. Omniscan (approved - 1993)
4. Optimark (approved - 1999)

RELATED REVIEWS:	Clinical:	Robert Yaes, MD, Ramesh Raman, MD
	Statistics:	Sonia Castillo, Ph.D., Mike Welch, Ph.D.
	Chemistry:	David Place, Ph.D. (2/25/04)
	Pharmacology-toxicology:	Yanli Ouyang, Ph.D. (4/07/04) Adebayo Laniyonu, Ph.D. (4/07/04)
	Clinical Pharmacology:	Young-Moon Choi, Ph.D.
	Microbiology:	Stephen Langille, PhD, 01/04/02
Project Manager:		Diane Smith

RELATED DIVISION DIRECTOR MEMOS: 2/10/02, 5/20/02 (addendum), 4/16/04

RECOMMENDED REGULATORY ACTIONS:

1. Approval for the 0.1 mmol/kg dose of MultiHance for evaluation of the Central Nervous System (~~including the~~ spine) in adults for the following 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, and associated tissues."

2. Approval for the negotiated label, as recommended by the various division disciplines and as agreed to by the sponsor

3. Approval for the negotiated Phase 4 commitments to perform a safety and efficacy study for evaluation of the CNS in the pediatric population ages 2 - 16 years and to perform a pharmacokinetic study in the pediatric population ages 2 – 5 years as agreed to by the sponsor.

4. Approval of the requested waiver for the evaluation of subjects less than 2 years of age.

Background

MultiHance (Gadobenate dimeglumine) Injection is an investigational, paramagnetic gadolinium based MRI contrast agent that is administered for CNS imaging by a rapid bolus intravenous injection or by intravenous infusion at a dose of 0.1 mmol/kg. MultiHance is renally excreted and it is minimally metabolized in the liver. Of the gadolinium agents, MultiHance has the greatest viscosity and it is the most hyperosmolar. MultiHance's imaging efficacy is based on its increase signal intensity on T1 weighted MRI images and on its leakage through the damaged blood-brain barrier associated with specific types of lesions in the brain.

MultiHance is being studied for intravenous use in MRI of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues.

The original two NDAs [21-357 (Single dose), 21-358 (Pharmacy Bulk Pack)] were submitted in April 2001 and an Approvable action letter was sent to the sponsor in May 2002 for the intravenous use of MultiHance in MRI contrast enhancement of the CNS to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. In the Approvable letter, there were multiple deficiencies noted for safety and clinical efficacy. Several safety issues stated in the Approvable letter were the lack of sufficient data to fully assess the risk of MultiHance on the liver, the lack of sufficient data to fully characterize the safety of MultiHance on the cardiovascular system, and the lack of sufficient data in adults and pediatric patients to determine the effect of MultiHance on the renal system. An additional safety deficiency was the lack of sufficient detail on local adverse events. In this regard, MultiHance's osmolality and viscosity are higher than that of the currently approved gadolinium agents. These chemical parameters have been associated with serious adverse events. The clinical efficacy section of the Approvable letter noted the key studies that were submitted to establish the indications and doses were designed as dose escalation studies. These studies contained several design flaws which resulted in a small number of patients who actually received the proposed dose and the imaging regimens proposed in the labeling. Also noted, the image acquisition and blinded reader methodology were insufficiently documented to support validity of the clinical trials' data and to determine appropriate acquisition methods. In addition, the composite information score lacked sufficient clarity to document it relevance to the proposed indication. Also noted was a lack of a dose response between the studied 0.05 and the 0.1 mmol/kg doses. To address these multiple safety and efficacy issues, the Action letter stated at least one additional large, robust clinical trial in adults with CNS disease was needed.

In August 2002, the Agency met with the sponsor to review the sponsor's action plan and to address the safety and efficacy issues noted in the May 2002 Approvable action letter. In response to the efficacy issues raised in the action letter, the sponsor proposed a re-read of the original imaging dataset. The division noted that a blinded re-read of the original imaging dataset alone may not resolve the issues discussed in the first cycle action letter and the division restated the request for a new clinical trial. In September 2002 the sponsor submitted a proposal to address the efficacy issues with a re-read of the original imaging dataset, without a new clinical trial as requested in the Action letter. Further discussions with the division in November and December 2002 established the design of the re-read of the imaging dataset based on a revised anatomic visualization claim for an adult CNS indication utilizing three visualization endpoints: lesion border delineation, visualization of internal morphology, and lesion contrast enhancement. For an adult CNS indication, utilizing the three originally submitted CNS studies in adult subjects, the primary efficacy endpoint was established to demonstrate that the post-contrast MRI was better than the baseline, pre-contrast MRI for the assessment of the three visualization endpoints. The secondary efficacy endpoint

was that the paired MR images (pre-contrast and post-contrast) were better than the pre-contrast MRI for the assessment of the three visualization endpoints.

In October 2003, the sponsor submitted a complete Response to the Approvable action letter of May 2002. In April 2004, an Approvable action letter was sent to the sponsor for the intravenous use of MultiHance in MRI of the CNS in adults [redacted] to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. In the Approvable letter there were deficiencies noted for clinical adult efficacy related to the primary efficacy analyses, the target population, the dose selection, and the image evaluation, as well as deficiencies related to pediatric safety and efficacy related to study design, evaluated population, and lack of sufficient safety data. For the primary efficacy analyses of pre-contrast versus post-contrast interpretations, depending on the reader or the dose, either that was no statistical difference between pre- and post-contrast mean scores for the co-primary endpoints: lesion border delineation, visualization of internal morphology, and lesion contrast enhancement, or mean scores were statistically inferior after the administration of MultiHance. Statistical significance was demonstrated for the secondary efficacy analyses (pre-contrast versus paired reads) for both adult studies, but these analyses were not prospectively established as a primary measure of success. Review of the enrolled population for re-read study MH 105 noted insufficient numbers of patients with varied neurological diseases, for which a contrast MRI would typically be used in clinical practice, and the MH 105 study included only four patients with spinal disorders. In reference to dose selection, the re-read results for the two adult re-read studies did not demonstrate statistically significant differences between the 0.05 mmol/kg and 0.1 mmol/kg administered doses, which failed to support the proposed dose of 0.1 mmol/kg dose over the lower 0.05 mmol/kg dose. In reference to image evaluation, the Action letter acknowledged that in clinical practice, comparisons of the pre-contrast MR images are typically interpreted with the post-contrast MR images to provide useful [redacted] information to help in the clinical management of patients. However, the letter noted the re-read adult studies were designed to establish a visualization claim using visualization endpoints via the comparison of a pre-contrast MRI image to the post-contrast MRI image. The re-read design was necessitated by the absence of a truth standard in the original clinical trials. In view of these clinical adult efficacy issues, the Action letter stated the need for at least one new adequate and well-controlled study in adults with a variety of CNS disease involving the brain and spine to support a visualization claim [redacted] the study design would require the incorporation of a truth standard. [redacted] In reference to pediatric safety, the application lacked sufficient safety data to determine the effect of MultiHance on the renal and cardiovascular systems. Also noted was the pharmacokinetic study of healthy pediatric patients enrolled only one subject under age 5 years. The letter stated to resolve these deficiencies [redacted], the sponsor must provide clinical data from at least one adequate and well-controlled trial, which studies at least two doses and enrolls a sufficient number of patients with a spectrum of diseases that would be present in the targeted population. [redacted] the study design would require the incorporation of a truth standard.

The Agency met with the sponsor on July 9, 2004 and sent a letter to the sponsor on July 23, 2004, regarding the Approvable action letter of April 2004 and the outstanding matters: appropriateness of the patient population studied, the analytical methodology and data collected, and the need for a new study. The Agency's letter stated the target population and the spectrum of disease for adult CNS imagines is adequately represented in the combined re-read studies, MH 105 and 106. The letter also noted agreement with the sponsor, that when lesions do not enhance with contrast, the lack of lesion enhancement may be of clinical value and should not be considered necessarily as a drug failure. In addition, the letter stated the primary efficacy analyses for MH 106, using pre- vs. T1 post-drug image comparison, as well as the pre- vs. paired

reads do demonstrate efficacy for the indication of anatomic/structural delineation for patients in whom there is a suspicion of CNS metastatic malignancy. The letter also noted the Agency found the reread study MH 105 was supportive for efficacy in the pre- vs. paired results. In the letter, the Agency requested the sponsor conduct a sub-analysis of tumor-only patients (both primary and metastatic) from MH 105 using the pre- vs. post and pre- vs. paired analyses for the same three anatomic endpoints and to submit a sub-analysis of MH 105 in the non-tumor brain and spine patients using the pre- vs. paired results for the three anatomic endpoints. Provided that these sub-analyses showed efficacy for the three endpoints, the Agency informed the sponsor they could submit labeling to be negotiated for a general CNS anatomic/ ——— delineation indication.

On August 2, 2004, the sponsor submitted a response to the April 2004 Approvable letter, consistent with Agency's letter of July 23, 2004, seeking the following revised indication for the 0.1 mmol/kg dose of MultiHance for evaluation of the Central Nervous System (including the spine) in adults,

> "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, and associated tissues."

In the August 2, 2004 submission, the sponsor provided re-analyses of the re-read MH 105 study, consistent with the Agency's letter of July 23, 2004 and submitted an update of the safety database. ——— ——— the sponsor requested a waiver for the < 2 years old population, and requested a deferral for a PK study in subjects 2-5 years of age.

Statistical Review

The statistical review of the submitted reanalysis of study MH-105 was performed by Sonia Castillo, Ph.D. Dr. Castillo has also re-presented the statistical analysis results of study MH-106 (prior analysis of MH-106 reported in March 9, 2004 statistical review) in her draft statistical report. I have read Dr. Castillo's draft statistical review report and concur with her reported analysis findings, comments, and conclusions.

In the Agency's July 23, 2004 letter, the Agency requested the sponsor conduct a sub-analysis of tumor-only patients (both primary and metastatic) from the re-read study MH 105 using the pre- vs. post and pre- vs. paired analyses for the three anatomic endpoints and to submit a sub-analysis of MH 105 in the non-tumor brain and spine patients using the pre- vs. paired results for the three anatomic endpoints. Provided that these sub-analyses showed efficacy for the three endpoints, the Agency informed the sponsor they could submit labeling to be negotiated for a general CNS anatomic/ ——— delineation indication.

In Dr. Castillo's review, the assessment of the dose performance for MultiHance, at the 0.1 mmol/kg dose, demonstrates reproducible performance across all blinded readers, for all co-primary efficacy endpoints in tumor and non-tumor patients. As compared to the 0.1 mmol/kg dose, the MultiHance dose of 0.05 mmol/kg demonstrates variability in performance amongst the blinded readers. Therefore, based on these reported performance findings for the blinded readers, the 0.1 mmol/kg dose is the effective dose as compared to the 0.05 mmol/kg dose.

Based upon the findings, conclusions and recommendations in Dr. Castillo's review that are quoted and summarized below, the sponsor has met the stated conditions to submit labeling to be negotiated for the 0.1 mmol/kg dose of MultiHance for a general CNS anatomic/ ——— delineation indication.

Dr. Castillo's Conclusions and Recommendations

"Study MH-105 in adults shows statistically significant results for the three co-primary efficacy endpoints in tumor and non-tumor patients. These results plus the statistically significant results for study MH-106 (see the March 9, 2004 statistical review) provide evidence of efficacy for the 0.1 mmol/kg dose of Multihance for use in MR imaging of the CNS in adult patients."

"This reviewer has no additional issues with the way the data have been analyzed by the Sponsor and concludes that no further analysis is necessary."

Overview Summary

Tumor vs. Non-tumor Sub-setting

The requested reanalysis of re-read study MH-105 required sub-setting subjects as tumor subjects or non-tumor subjects and Dr. Castillo's Table 3.1 below documents the final number of tumor subjects and non-tumor subjects assigned for each Multihance dose.

Table 3.1
Study MH-105: Number of Subjects Classified as Either Tumor or Non-tumor and How Many Had Image Efficacy Data

	Number Classified as Tumor Subjects (Number of Subjects with Image Data)	Number Classified as Non-tumor Subjects (Number of Subjects with Image Data)
Multihance 0.05 mmol/kg	70 (65)	70 (59)
Multihance 0.1 mmol/kg	69 (65)	67 (61)

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

Dr. Castillo reported analysis findings for the predose vs. postdose image sets and predose vs. paired (predose + postdose) image sets for the three co-primary efficacy endpoints in both tumor and non-tumor subjects for study MH 105. Dr. Castillo's reported analysis findings are summarized as follows:

MH 105 Re-analysis

Tumor patients subset: predose to postdose image sets

0.10 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate a significant improvement in the postdose image set compared to the predose image set (all $p<0.005$)

0.05 mmol/kg dose

Blinded reader 1 only: all three co-primary efficacy variables demonstrate a significant improvement in the postdose image set compared to the predose image set (all $p<0.007$)

Blinded reader 2: lesion border delineation and lesion internal morphology demonstrate a significant improvement in the postdose image set compared to the predose image ($p<0.05$).

Comparison between the two doses

Blinded reader 3: the 0.10 mmol/kg dose is significantly better than the 0.05 mmol/kg dose for all three co-primary efficacy variables

Blinded readers 1 & 2: no comparisons demonstrate significant differences between the two doses for each of the three co-primary efficacy variables (all $p>0.10$).

Tumor patients subset: predose to predose + postdose (paired) image sets

0.10 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate a significant improvement in all efficacy variables (all $p<0.05$)

0.05 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate a significant improvement in all efficacy variables (all $p<0.05$) except for lesion contrast enhancement for blinded reader 3 ($p=0.24$)

Comparison between the two doses

Blinded reader 3, the 0.1 mmol/kg dose for all three co-primary efficacy variables is better than the 0.05 mmol/kg dose (all $p<0.001$)

Blinded readers 1 & 2: no comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all $p>0.15$)

Non-tumor patients subset: predose to postdose image sets

0.10 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate significant differences (all $p<0.05$) for all efficacy variables, in favor of the predose image set

0.05 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate significant differences (all $p\leq0.05$) for all efficacy variables, in favor of the predose image set

Comparison between the two doses

For each blinded reader: No comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.20$).

Non-tumor patients subset: predose to predose + postdose (paired) image sets

0.10 mmol/kg dose

All blinded readers: all three co-primary efficacy variables demonstrate a significant improvement in the paired image set compared to the predose image set (all $p<0.02$)

0.05 mmol/kg dose

Blinded reader 1 and blinded reader 2: all three co-primary efficacy variables demonstrate a significant improvement in the paired image set compared to the predose image set (all $p<0.001$).

Comparison between the two doses

No comparisons between the two doses for each of the three co-primary efficacy variables for each blinded reader demonstrate significant differences (all $p>0.05$).

Study MH-106

Postdose image set compared to the predose image set

0.10 mmol/kg dose

All blinded readers: for the three co-primary efficacy variables significant improvement

0.05 mmol/kg dose

All blinded readers: for the three co-primary efficacy variables significant improvement

Comparison between the two doses

No comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.10$)

Paired (predose + postdose) image set compared to the predose image set

0.10 mmol/kg dose:

All blinded readers: for the three co-primary efficacy variables significant improvement (all $p<0.001$)

0.05 mmol/kg dose:

All blinded readers: for the three co-primary efficacy variables significant improvement (all $p<0.001$)

Comparison between the two doses

Blinded readers 1 and 2: no comparisons between the two doses for each of the three co-primary efficacy variables demonstrate significant differences (all $p>0.13$).

Blinded reader 3: the 0.1 mmol/kg dose for all three co-primary variables is better than the 0.05 mmol/kg dose (all $p<0.03$)

Dr. Castillo provided the following table for inclusion to the clinical trials section of the label.

This table, from Dr. Castillo's report, demonstrate statistical significance on the lesion level for all endpoints, by all readers, with the 0.1 mmol/kg dose. (Study A = MH 105, Study B = MH 106)

TABLE X: Lesion Level Results of MRI Central Nervous System Studies with 0.1 mmol/kg MULTIHANCE

	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Endpoints	N=395	N=384	N=299	N=245	N=275	N=254
Border Delineation: Difference of Means (a)	0.8*	0.6*	0.8*	1.8*	1.5*	1.9*
Worse (b)	44 (11%)	61 (16%)	57 (19%)	13 (5%)	24 (9%)	15 (6%)
Same	146 (37%)	168 (44%)	89 (30%)	11 (5%)	19 (7%)	18 (7%)
Better	205 (52%)	155 (40%)	153 (51%)	221 (90%)	232 (84%)	221 (87%)
Internal Morphology: Difference of Means	0.8*	0.6*	0.7*	1.7*	1.4*	2.1*
Worse	37 (10%)	63 (17%)	62 (21%)	13 (5%)	26 (10%)	14 (5%)
Same	147 (37%)	151 (39%)	84 (28%)	16 (7%)	22 (8%)	22 (9%)
Better	211 (53%)	170 (44%)	153 (51%)	216 (88%)	227 (82%)	218 (86%)
Contrast Enhancement: Difference of Means	0.7*	0.5*	0.8*	1.9*	1.5*	1.9*
Worse	75 (19%)	74 (19%)	50 (17%)	13 (5%)	32 (12%)	17 (7%)
Same	148 (37%)	152 (40%)	109 (36%)	11 (5%)	21 (7%)	14 (5%)
Better	172 (44%)	158 (41%)	140 (47%)	221 (90%)	222 (81%)	223 (88%)

(a) Difference of means = (paired[c] mean) - (pre mean)
(b) Worse = paired score is less than the pre score
Same = paired score is the same as the pre score
Better = paired score is greater than the pre score
(c) Paired = side-by-side pre and post MULTIHANCE
* Statistically significant for the mean (paired t test)

Source: Sponsor End-of-Text tables - Tables 3.1 – 3.3, pp. 013 – 021, Tables 6.1 – 6.3, pp. 034 – 036, Table 15, p. 067, and Table 17, pp. 071 – 073 from Vol. 27 and Tables 3.1 – 3.3, pp. 013 – 021, Tables 6.1 – 6.3, pp. 034 – 036, Table 15, p. 066, and Table 17, pp. 070 – 072 from Vol. 34.

Clinical Review

The clinical review of the August 2, 2004 submission was performed by Robert Yaes, M.D. and Dr. Ramesh Raman. I have read and reviewed Dr. Yaes' and Dr. Raman's reports and I concur with their clinical reviews.

Clinical Safety Review

At the conclusion of the second review cycle (Approvable action letter, 4/14/04), the clinical safety review for MultiHance was recommended for Approval with label changes related to the cardiovascular system, the liver, and the skin. The Approvable action letter, requested the sponsor submit an update of all safety information regarding MultiHance. The sponsor has submitted a safety update containing safety data from newly exposed subjects from January 1, 2003 through June 30, 2004 and for the post marketing experience.

Dr. Robert Yaes reviewed the submitted safety update and reanalyzed the cumulative safety data through June 30, 2004 and reported his findings in his clinical review. I have reviewed Dr. Yaes' safety review and I concur with his review findings and conclusions.

Dr. Yaes states the following conclusions in his clinical safety review,

> "The incidence of adverse events, serious adverse events and deaths, found in the safety update, is comparable to the incidence with other MRI contrast agents and with the incidence seen in the previous review cycle."
>
> "This new safety data raises no new safety issues."

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

Dr. Yaes summarized the safety database population statistics in the following table from his Clinical review.

1. Subject exposure, deaths and serious adverse events

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

Dr. Yaes' report provided the following summary comments on the updated post marketing experience for MultiHance,

"Post Marketing Data

To date . . . . single dose units of MultiHance have been sold in countries where MultiHance is approved. 473 patients (0.05%) have reported adverse events, 114 patients (0.01%) have reported serious adverse events and there have been 4 reported patient deaths (0.0004%). The most commonly reported adverse events were nausea vomiting and urticaria. These results are similar to those reported in the previous safety update of October 10 2003 at which time 468,775 patients had been exposed. 265 patients experienced adverse events (0.05%), 52 patients (0.01%) experienced serious adverse events and there was 1 patient death (0.0002%)

Other Relevant Information

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

Injection Site Adverse Event

Of the gadolinium agents, MultiHance has the greatest viscosity and it is the most hyperosmolar. These characteristics are of concern for skin and adjacent soft tissue toxicities with injection site extravasation. Only one report of such an adverse event is present in the safety database. The post marketing experience reports a spontaneous serious adverse event report of a 79 year old female experienced extravasation when a wrist vein ruptured. Two days after the event the arm was swollen and a blister was seen on the wrist. The swelling decreased and the wound healed without sequelae.

Clinical Efficacy Review

No new clinical trials to support the efficacy of MultiHance have been submitted.

Dr. Yaes and Dr. Raman in their clinical reviews of the submitted reanalysis of MH 105 have recommended Approval for the 0.1 mmol/kg dose of MultiHance for evaluation of the Central Nervous System (including the spine) in adults for the following 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, and associated tissues."

I have read Dr. Yaes and Dr. Raman's clinical reviews and I concur with their reported findings, comments, and conclusions.

The three clinical trials submitted with the original NDAs in 2001 to support the CNS indication for use of MultiHance in adults are listed in the table below.

MultiHance Clinical Trials – Adult CNS Indication				
Original Study Titles Re-Titles	Location of clinical sites	Enrolled Population	Subjects Reported	
			Intent To Treat Database	Safety Database
43,779-9A, 43,779-9,B Re-read: MH-105 Label: Study A	USA	CNS (Tumor & Non-tumor)	277	276
B19036/020 Reread: MH-106 Label: Study B	Europe	CNS (Brain Metastases)	154	150

Studies 43,779-9A and 43,779-9B are identically designed clinical trials. These two clinical trials are double-blind, randomized, parallel-group, multi-center studies with three arms:

1. MultiHance - sequential dosing - 0.05 and 0.1 mmol/kg
2. MultiHance - sequential dosing - 0.1 and 0.1 mmol/kg
3. Omniscan - sequential dosing - 0.1 and 0.2 mmol/kg

Eligibility criteria requirement: at least one lesion identified on a pre-enrollment imaging study

Study B19036/020 - This clinical trial is a double-blind, parallel group study of 150 adult subjects with known metastatic CNS disease. Subjects were randomized to receive one of two dose sequences:

1. 0.05 + 0.05 + 0.1

or

2. 0.1 + 0.1 mmol/kg

Dosing interval: 10 minutes.

Imaging: 5 minutes post dosing.

Reference is made to the first and second cycle clinical review memos and the associated Division Director memos to provide further information on these protocols, their study design, the associated clinical efficacy databases for each review cycle, and the assessment of those clinical efficacy databases.

Independent Review and Visualization Assessment Comment

The visualization indication for MultiHance is based on the premise that use of an MRI contrast agent will produce an improved "contrast enhanced image" as compared to the baseline "non-contrast" enhanced

image.

In the re-read protocols, MH-105 and MH-106, subjects were enrolled with a variety of CNS abnormalities to emulate the expected patient population for the use of MultiHance. As such, in the re-read protocols, MH-105 and MH-106, subjects were enrolled with metastatic brain tumors and primary brain tumors. In general, these primary and metastatic brain tumors are characterized by disruptions of the blood-brain-barrier and demonstrate increased contrast enhancement with the use of an MRI contrast agent. In addition, subjects were enrolled in the re-read protocol MH-105 with non-tumor CNS abnormalities, which, in general do not have disruptions of the blood-brain-barrier, and as such, do not demonstrate increased contrast enhancement with the use of an MRI contrast agent. For metastatic and primary brain tumors as well as non-tumor CNS lesions, the imaging patterns seen on the contrast MRI and on the non-contrast MRI produce variable findings for internal morphology and border delineation, which may be characteristic for various tumors or non-tumor lesions. Hence, in clinical practice, MRI non-contrast and MRI contrast studies are read together (paired), rather than separately and paired interpretation is accepted as necessary and an improvement for overall MRI interpretation.

For the visualization indication for MultiHance, the designed comparative image interpretation for the demonstration of improved imaging performance was the comparison of the non-contrast (pre-) MRI to the (post) contrast MRI (pre- vs. post). The independent read scoring for the re-read protocols, MH-105 and MH-106, incorporated three endpoints: lesion border delineation, visualization of internal morphology, and lesion contrast enhancement. These endpoints are significantly dependent on contrast enhancement. The design (pre- vs. post) of the MRI comparison for MultiHance with the contrast enhancement endpoint, supported the visualization performance of MRI contrast for metastatic and primary brain tumors, which commonly are associated with a disruption of the blood-brain-barrier and associated contrast enhancement. This is consistent with the statistically significant performance of MultiHance in the pre- vs. post assessment for the MH-106 trial, which enrolled subjects with metastatic brain tumors.

However, MH-105 enrolled subjects with metastatic brain tumors, primary brain tumors, and non-tumor CNS lesions failed to show statistical significance in the pre- vs. post assessment. Sub-analyses of MH-105 demonstrated statistical significance in the pre- vs. post assessment for the subset of subjects with primary and metastatic tumors, consistent with the demonstrated visualization performance of MultiHance in MH-106. The sub-analysis of Pre- vs. post MRI for the subjects with non-tumor lesions in MH-105 demonstrated a statistically significant performance in favor of the pre-contrast MRI, consistent with the lack of disruption to the blood-brain-barrier and the lack of increased contrast enhancement with the post contrast study.

Analyses of the performance of MultiHance for metastatic and primary brain tumors and non-tumor CNS lesions, based on clinically based model of pre- vs. paired (pre + post contrast MRI), demonstrate statistically significant improvement in imaging performance for the paired MRI as compared to the pre-(baseline) MRI. These findings are compatible with improved visualization of target lesions with paired MRI vs. post-contrast MRI alone.

These overall findings are compatible with an intrinsic weakness in the visualization performance assessment model associated with a contrast enhancement endpoint and the use of the pre- vs. post comparison model in a heterogeneous population (metastatic CNS tumors, primary CNS tumors, and non-tumor CNS lesions). Metastatic and primary brain tumors are associated with a disruption of the blood-brain-barrier and, as such, will show increased visualization based on the significant contrast enhancement on the post-contrast MRI. Non-tumor CNS lesions will not be associated with disruption of the blood-brain-barrier and will display decrease visualization due to minimal to no significant contrast enhancement. However, for all lesions (metastatic CNS tumors, primary CNS tumors, and non-tumor CNS lesions) correlation of pre and post

contrast studies (paired reading) will provide additional imaging information which may improve visualization of target lesions as compared to the pre-contrast MRI alone.

Thus, it is recommended that in the development of future clinical trial designs for MRI contrast agents, careful consideration should be given to assess performance in a manner consistent with clinical practice MRI interpretation (paired read: pre-contrast read with post-contrast). As such, for visualization performance of an MRI contrast agent in a heterogeneous population (e.g., metastatic CNS tumors, primary CNS tumors, and non-tumor CNS lesions), the MRI contrast study visualization performance considerations should include a comparison of the pre-contrast MRI vs. paired (pre-contrast and post-contrast) MRI.

Pre-clinical Reviews

I have reviewed the pre-clinical reports completed in previous review cycles. I concur with their findings, and the recommendations for approval with proposed label revisions.

Chemistry:	David Place, Ph.D. (2/25/04)
Pharmacology-toxicology:	Yanli Ouyang, Ph.D. (4/07/04)
	Adebayo Laniyonu, Ph.D. (4/07/04)
Microbiology:	Stephen Langille, PhD, 01/04/02
Clinical Pharmacology:	Young-Moon Choi, Ph.D.

Pediatric Safety and Efficacy

An Approvable action letter for the intravenous use of MultiHance in magnetic resonance imaging (MRI) of the central nervous system (CNS) for the following indication was sent to the sponsor on April 14, 2004.

> "MULTIHANCE is indicated for intravenous use in magnetic resonance imaging (MRI) of the CNS in adults [redacted] to visualize lesions with abnormal blood-brain-barrier or abnormal vascularity of the brain, spine, and associated tissues."

The letter stated the following requirements to resolve review issues:

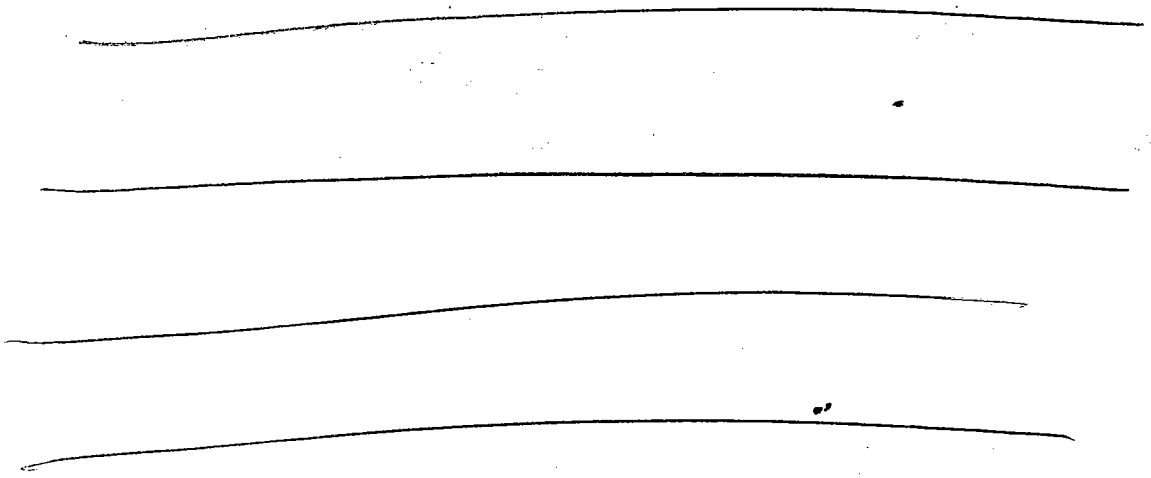
> [redacted] Also noted, the application lacks sufficient safety data in pediatric patients to determine the effect of MultiHance on renal and cardiovascular systems. Therefore, the requested trial must have increased safety monitoring to include complete urinalysis, blood/serum renal function tests, and complete EKGs with hemodynamic monitoring.
>
> [redacted]
>
> "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, and associated tissues."

The sponsor has performed two limited pediatric studies: a pediatric pharmacokinetic study and a pediatric safety/efficacy study. There are a total of 110 patients in the pediatric safety database, as compared; there are 2982 patients in the sponsor's adult safety database.

Pediatric Pharmacokinetic/Safety Study: 43,779-10

Enrollment: 25

Age range: 2-16 years with only 1 subject less than 5 years of age



Deferral of Pediatric Studies

Negotiated and agreed Phase 4 commitments

1. Deferred pediatric safety and efficacy study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16.
    a. Protocol Submission: Within 6 months of the date of the approval of MultiHance for known or suspected CNS disease for adults
    b. Study Completion: Within 30 months after the agreement of the Protocol

    Final Report Submission: 12/1/07

2. Deferred pediatric pharmacokinetic study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 5 years.
    a. Protocol Submission: Within 6 months of the date of the approval of MultiHance for known or suspected CNS disease for adults
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: 12/1/07

Waiver of Pediatric Studies

The sponsor has requested a waiver to study MultiHance in the < 2 years of age population. The enrollment and evaluation of an adequate number of subjects in the < 2 years of age group for a clinical trial with MultiHance is considered highly unlikely. A waiver to study subjects < 2 years is recommended at this time, while reserving the Agency's option to reconsider in the future.

Proposed Labeling

The final proposed label has been reviewed, edited and approved by all disciplines. The sponsor has agreed to the proposed final label. I have reviewed and concur with the final proposed label.

The following are brief summary comments on several changes to the sponsor's proposed label:

Clinical Trials

The clinical trials section was amended to incorporate the re-analyses that support the visualization claim and to include the scientific justifications.

Clinical Safety

The clinical safety sections and the adverse events listings were reformatted for consistency with the draft guidance for industry, "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics."

Pediatrics

The sponsor is not seeking a pediatric indication for MultiHance. The existing pediatric data is limited, and the sponsor has agreed to two pediatric studies to supply data for the use of MultiHance in the pediatric population. All efficacy and safety information pertaining to the pediatric population has been removed from the proposed final label.

Specific Safety Issues Identified for Labeling During the Safety Review

Examples: QT, CVS arrhythmias, Hepatic (cMOAT - drug and inherent metabolic disorders), precaution related to decreased renal function in the elderly (major elimination route of MultiHance is renal)

These issues were addressed and formatted in the necessary label sections

Pregnancy Category

The ——— Pregnancy ——— for MultiHance. The sponsor had not appropriately attributed study data demonstrating teratogenic effects in rabbits such as microphthalmia/small eye and/or focal retinal fold in 3 fetuses from 3 separate litters. The study data implied a pregnancy category C and following review and discussion, the sponsor agreed to a pregnancy category C for MultiHance, as exists for other approved gadolinium compounds.

Trade Name Review

Review of the proprietary names MultiHance and MultiHance Multipack has been completed by DMETS. Within the DMETS review, it was noted that DDMAC did not agree with the trade name MultiHance. However, DMETS found the name MultiHance acceptable. DMETS did not recommend the use of the name MultiHance Multipack., which represents the pharmacy bulk package configuration.

The division has considered the review recommendation from DMETS and noted that similar products (ProHance, Isoview) have approvals for Multipacks. Therefore, the division has refuted the DMETS recommendation and accepted the proprietary name MultiHance Multipack.

The division has carefully considered DDMAC's concerns related to the proprietary name, MultiHance. The drug is approved for a limited area of the body, CNS, and will evaluate multiple structures, brain, spinal cord and associated tissues. Therefore, the division has no objection to the structure of the name MultiHance.

Thus, following the divisions review, the division has accepted the proprietary names MultiHance and MultiHance Multipack.

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/s/

George Mills
11/23/04 02:34:08 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 22, 2004

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

Subject: Pharm Tox labeling comments 112204

Total no. of pages including cover: 3

Comments: Please respond as soon as possible. Thank you,

Document to be mailed: • YES ☑ NO

COMMENTS TO THE SPONSOR
NDA 21-357 and 21-358 MultiHance
November 22, 2004

We have changed the wording in the labeling for the Pregnancy category. Please provide your feedback by 3pm today. If call Diane Smith, Project Manager, if you have any questions.

Pregnancy category C

MULTIHANCE has been shown to be teratogenic in rabbits when intravenously administered at 2 mmol/kg/day (6 times the human dose based on body surface area) during organogenesis (day 6 to 18 inducing microphthalmia/small eye and/or focal retinal fold in 3 fetuses from 3 separate litters. In addition, MULTIHANCE intravenously administered at 3 mmol/kg/day (10 times the human dose based on body surface area) has been shown to increase intrauterine deaths in rabbits.

There was no evidence that MULTIHANCE induced teratogenic effects in rats at doses up to 2mmol/kg/day (3 times the human dose based on body surface are) however, rat dams exhibited no systemic toxicity at this dose. There were no adverse effects on the birth, survival, growth, development, and fertility of the F1 generation at doses up to 2 mmol/kg in a rat peri- and post-natal (Segment III) study.

There are no adequate and well-controlled studies in pregnant women. MULTIHANCE should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

COMMENTS TO THE SPONSOR
NDA 21-357/21-358 MultiHance
November 22, 2004

These comments were generated after reviewing your submission dated July 30, 2004. Please provide a written agreement by COB November 22, 2004. We have changed the wording in the commitments (e.g., from ——— to "evaluation"). If you have any questions please contact Diane C. Smith, Regulatory Project Manager, at (301) 827-7510.

Phase 4 commitment(s):

1. Deferred pediatric safety and efficacy study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16.

    a. Protocol Submission: Within 6 months of the date of this letter
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: December 1, 2007

2. Deferred pediatric pharmacokinetic study under PREA for the evaluation of known or suspected CNS disease in pediatric patients age 2 to 5.

    a. Protocol Submission: Within 6 months of the date of this letter
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: December 1, 2007

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/s/

Diane Smith
11/22/04 02:45:58 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 18, 2004

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

Subject: Phase 4 commitment November 18, 2004

Total no. of pages including cover: 2

Comments:

Document to be mailed: • YES ☑ NO

COMMENTS TO THE SPONSOR
NDA 21-357/21-358 MultiHance
November 18, 2004

These comments were generated after reviewing your submission dated July 30, 2004. Please provide a written agreement by COB November 19, 2004. Please provide the appropriate number of months for submission and completion of the protocol and the final report dates in commitment #1. If you have any questions please contact Diane C. Smith, Regulatory Project Manager, at (301) 827-7510.

Phase 4 commitment(s):

1. Deferred pediatric safety and efficacy study under PREA for the ——— of known or suspected CNS disease in pediatric patients ages 2 to 16.

    a. Protocol Submission: Within XX months of the date of this letter
    b. Study Completion: Within XX months after the agreement of the protocol

    Final Report Submission: XX/XX/XXXX (MM/DD/YEAR)

2. Deferred pediatric pharmacokinetic study under PREA for the ——— of known or suspected CNS disease in pediatric patients age 2 to 5.

    a. Protocol Submission: Within 6 months of the date of this letter
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: ———

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/s/

Diane Smith
11/18/04 04:40:01 PM
CSO

THE IMAGE OF INNOVATION

November 12, 2004

Diane C. Smith, R Ph, Regulatory Health Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160)
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Document Control Room 8B-45
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-357 and NDA 21-358
MultiHance® (gadobenate dimeglumine)
Response to Facsimile dated November 10, 2004

Dear Ms Smith:

Reference is made to our new drug applications (NDA 21-357 and NDA 21-358) for MultiHance® (gadobenate dimeglumine) injection and to your facsimile dated November 10, 2004 wherein you requested responses to three comments and on proposed labeling text.

Please find enclosed our responses and comments. A table has been provided noting each change requested and an explanation as to why Bracco has proposed the change.

Should you have any questions or require additional information, please feel free to contact me at 609-514-2254.

Sincerely,

Melanie Benson
Director, US Regulatory Affairs

Bracco Diagnostics Inc.
107 College Road East - Princeton, New Jersey 08540 USA - Telephone: (609) 514-2200 / (800) 631-5245 - Facsimile: (609) 514-2424 www.bdi.bracco.com

ADM-2

17 Page(s) Withheld

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

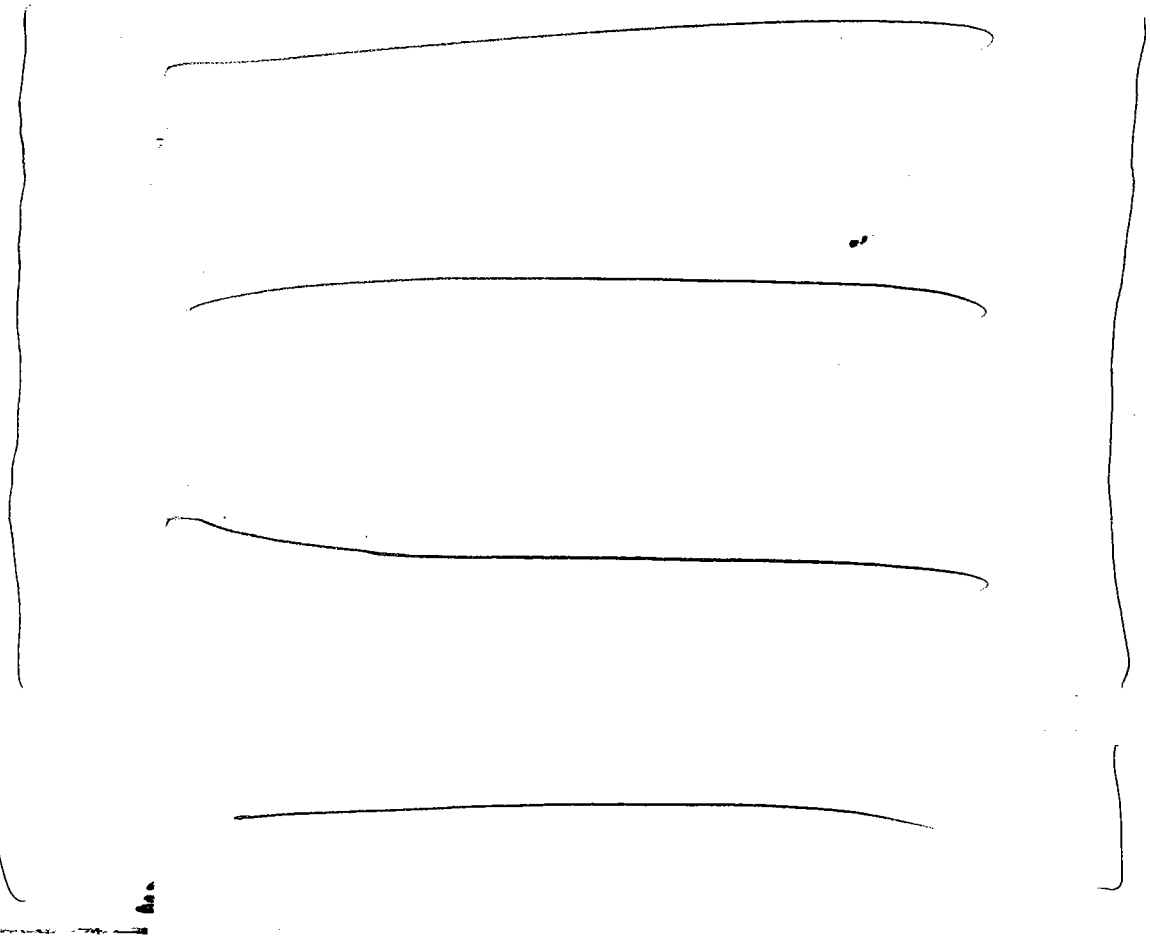
_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Comments on NDA 21357, Multihance, gadobenate dimeglumine
From Abby Jacobs 11/19/04

I recognize that the original Pharm/tox NDA review was written some time ago and that Dr. Laniyonu, the current Pharm/tox supervisor, was not a signatory to that review. I have reviewed the pharm/tox reviews and the proposed labeling and have the following comments:

I. Pregnancy section



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/s/

Abby Jacobs
11/19/04 02:41:41 PM
PHARMACOLOGIST

Melanie Benson
Regulatory Operations

BRACCO

Fax

To: Diane Smith

From: Melanie Benson

Fax: 609-514-2539

Fax: 301-480-6036

Pages: 3 including cover

Phone: 301-827-1603

Date: November 12, 2004

Re: MultiHance NDAs 21-357 and 21-358

• Comments:

Dear Ms Smith,

Please find following our acceptance of the proposed changes for the Pregnancy Category C labeling and also the Phase IV commitment wording.

Should you have any questions, please contact me at 609-514-2254.

Best regards,

Melanie Benson

COMMENTS TO THE SPONSOR
NDA 21-357/21-358 MultiHance
November 22, 2004

These comments were generated after reviewing your submission dated July 30, 2004. Please provide a written agreement by COB November 22, 2004. We have changed the wording in the commitments (e.g., from ' ——— to "evaluation"). If you have any questions please contact Diane C. Smith, Regulatory Project Manager, at (301) 827-7510.

Phase 4 commitment(s):

1. Deferred pediatric safety and efficacy study under PREA for the evaluation of known or suspected CNS disease in pediatric patients ages 2 to 16.

    a. Protocol Submission: Within 6 months of the date of this letter
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: December 1, 2007

2. Deferred pediatric pharmacokinetic study under PREA for the evaluation of known or suspected CNS disease in pediatric patients age 2 to 5.

    a. Protocol Submission: Within 6 months of the date of this letter
    b. Study Completion: Within 30 months after the agreement of the protocol

    Final Report Submission: December 1, 2007

Bracco Diagnostics Inc accepts the noted changes.

11/22/04 MJ Benson
MJ Benson

COMMENTS TO THE SPONSOR
NDA 21-357 and 21-358 MultiHance
November 22, 2004

We have changed the wording in the labeling for the Pregnancy category. Please provide your feedback by 3pm today. If call Diane Smith, Project Manager, if you have any questions.

Pregnancy category C

MULTIHANCE has been shown to be teratogenic in rabbits when intravenously administered at 2 mmol/kg/day (6 times the human dose based on body surface area) during organogenesis (day 6 to 18 ——— inducing microphthalmia/small eye and/or focal retinal fold in 3 fetuses from 3 separate litters. In addition, MULTIHANCE intravenously administered at 3 mmol/kg/day (10 times the human dose based on body surface area) has been shown to increase intrauterine deaths in rabbits. ———

——— There was no evidence that MULTIHANCE induced teratogenic effects in rats at doses up to 2mmol/kg/day (3 times the human dose based on body surface are) however, rat dams exhibited no systemic toxicity at this dose. There were no adverse effects on the birth, survival, growth, development, and fertility of the F1 generation at doses up to 2 mmol/kg in a rat peri- and post-natal (Segment III) study.

There are no adequate and well-controlled studies in pregnant women. MULTIHANCE should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Bracco Diagnostics accepts purposed changes.

11/22/04 MJ Benson

MJ Benson

ADM-3

27 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

_____

Office of Drug Safety

MEMO

To: George Q. Mills, M.D.
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

From: Linda Y. Kim-Jung, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

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

Date: October 21, 2004

Re: ODS Consult 01-0140-2, Multihance and Multihance Multipack (Gadobenate Dimeglumine Injection) 529 mg/mL, NDAs 21-357 and 21-358

This memorandum is in response to a September 30, 2004, request from your Division for a final review of the proprietary names Multihance and Multihance Multipack. The container label, carton and insert labeling were provided for review and comment. The proposed proprietary name, Multihance, was found acceptable by DMETS. However, DMETS did not recommend the use of the name, Multihance Multipack, which represents the pharmacy bulk package configuration (see ODS Consult 01-0140 dated January 7, 2002 and ODS Consult 01-0140-1 dated January 8, 2004).

Since the last review, DMETS identified the proprietary names, Multilex and Multilex T & M, as having potential sound-alike and look-alike confusion with Multihance. However, upon further review, it was determined that Multilex and Mulitilex T& M lacked convincing sound-alike and look-alike similarities with Multihance in addition to having numerous differentiating product characteristics such as the product strength [multivitamin composed of various ingredients and strength vs. 529 mg/mL which is dosed by patient's body weight (0.2 mL/kg)], indication for use (dietary supplement vs. a contrast agent for MRI of central nervous system and liver), route of administration (oral vs. intravenous) and dosage formulation (tablet vs. injection), and frequency of administration (one tablet daily vs. a single rapid intravenous infusion or bolus injection). Moreover, the setting of use (inpatient or outpatient setting vs. radiology department/clinic) may also decrease the potential for confusion. Overall, the lack of convincing sound-alike and look-alike similarities and different product characteristics will minimize the potential for confusion between Multilex and Multilex T & M and Multihance.

In the review of the container labels, carton and insert labeling of Multihance and Multihance Multipack, DMETS has attempted to focus on safety issues relating to possible medication errors. However, it is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used on the marketplace (i.e. color, placement of name, etc.). DMETS has identified the following areas of possible improvement, which might minimize potential user error.

ADM-4

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

_____

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

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

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/s/

Linda Kim-Jung
11/19/04 07:49:01 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/19/04 08:03:23 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/19/04 08:21:50 AM
DRUG SAFETY OFFICE REVIEWER

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS HFD-160

Teleconference

NDA: 21-357/21-358

DRUG: **MultiHance®**

SPONSOR: Bracco Diagnostics, Inc.

DATE: August 20, 2004

FDA ATTENDEES:
Sonia Castillo, Ph.D., Biometrics Reviewer, HFD-710
Michael Welch, Ph.D., Biometrics Team Leader, HFD-710
Robert Yaes, M.D., Clinical Reviewer, HFD-160
Diane C. Smith, R.Ph., Regulatory Health Project Manager, HFD-160

SPONSOR ATTENDEES:
Usha Halemane, Sr VP Director, Head Corporate Biostatistics
Alberto Spinazzi, VP Group Medical Affairs
Melanie Benson, Director Regulatory Affairs
J. Kris Piper, VP-Global Preclinical and Clinical Regulatory Affairs
Andrew Betournay, Head Group Regulatory Affairs

BACKGROUND/AGENDA:

The Statistical team had a short t-con with the sponsor to discuss the sponsor's July 30, 2004 submission.

DISCUSSION:

The Statistical team began the discussion by stating that there were four questions that required clarification from the sponsor.

Agency question #1:

On page 007 of the July 30, 2004, submission, it is stated that "Based on final diagnosis and relevant clinical information, patients were grouped into patients with neoplastic disease and patients with no disease or non-neoplastic disease." Please clarify if there is a flag in the October 10, 2003 submission data set for tumor/non-tumor patients. If not, please describe the algorithm used on the October 10, 2003 submission data set to classify tumor and non-tumor patients.

Discussion:

The sponsor clarified that the database contained 13 diagnostic categories; some were a final diagnosis and some were conditions.

The Agency reminded the sponsor that there had been previous agreement on the data sets, and wanted to ensure that the data sets were the same as those from the October 10, 2003 submission.

The Agency requested that the sponsor provide in writing the classification algorithm, flag the patients with tumors versus non-tumor patients, clarify how a final diagnosis of tumor versus non-tumor was determined, and provide the SAS code.

The sponsor also noted that there were nine patients defined as critical cases. Of these nine cases, five were tumor and four were non-tumor patients.

The Agency requested that the sponsor submit all information used by clinicians to determine tumor status for those patients who did not have a final diagnosis or who were classified as post-op changes in the database.

The sponsor stated that they would flag the tumor patients and merge these data with the blinded read data from the October 10, 2003.

The sponsor also agreed to provide the information that the clinicians were supplied for classifying a patient's tumor status and how a decision on tumor status was made.

Agency question #2:

Please provide the number of tumor and non-tumor patients in each treatment group.

Agency question #3:

Please provide the predose versus postdose comparison for non-tumor patients.

Discussion:

The sponsor noted that this information was not required in the Agency's July 23, 2004, General Advice Letter.

The Agency noted that the request was for completeness in the evaluation of efficacy and would, most likely, not adversely affect the expected results for the non-tumor group.

The Agency also asked that the sponsor clarify why there was no lesion score data from the blinded read for some of the patients.

The sponsor agreed to find and review the information on lesion scoring and how each reader was trained.

Agency question #4:

Please provide a SAS transport file of the data sets used in the analyses.

ACTION ITEMS:

The sponsor will provide the information requested by the Agency within 2 weeks.

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/s/

Diane Smith
10/7/04 12:27:46 PM
CSO