Val M. Runge, M.D.
University of Kentucky
A.B. Chandler Medical Center
800 Rose Street
A122 Kentucky Clinic
Lexington, Kentucky 40506

Dear Dr. Runge:

Between August 8-14, 2001, Ms. Kathleen D. Culver representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #43,779-1) of the investigational drug, gadobenate dimeglumine injection (MultiHance®), performed for Bracco Diagnostics Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

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

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

Sincerely yours,

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

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

If Headquarters classification is a different classification, explain why:
Deficiencies noted:
____inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
____inadequate records
____failure to report ADRS
____other

cc:
HFA-224
HFD-160 Doc.Rm. NDAs#21-357 & #21-358
HFD-160 Review Div.Dir.
HFD-160 MO Li
HFD-160 PM Moore
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP/CIB File #10446
HFD-46 GCP/CIB Reviewer Ju
HFD-46 CSO Prager
HFR-CE450 DIB Heppe
HFR-CE450 Bimo Monitor Eastham
HFR-CE4550 Field Investigator Culver
r/d: hwj/09/05/01
reviewed:JRM:9/6/01
f/t:jau:9/6/01
o:\ju\Runge2001.doc

Note to Rev. Div. M.O.

30 subjects were enrolled and 29 subjects completed the study. All 30 subjects signed informed consent. Shadow files of hospital medical records had been created for each subject. The original medical records for subjects 1032, 1321, and 1328 were compared with the shadow files and found no discrepancies or significant omissions. The shadow files were subsequently used for auditing the remaining subjects. An audit of the CRFs versus the source documents in the shadow file (or original hospital record) was conducted for subjects 1302, 1305, 1310, 1317, 1321, 1327, and 1328. No significant deficiencies were observed. The data may be used in support of the drug application.

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2001

To: Melanie Benson	**From:** James Moore
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: Multihance NDA 21-357

Total no. of pages including cover: 4

Comments: Attached is the data request from the biostatistician.

Document to be mailed: ☐ YES ☑ NO

July 19, 2001

Regarding your pending NDA # 21,357 (MultiHance), Bracco Diagnostics, the following requests/comments from the biostatistician should be addressed. The followings are some suggestions and general recommendations to expedite the data evaluation procedure.

REQUEST FOR TRANSFER OF DATA:

Please provide the data for pivotal studies (study 43,779-9A &43,779-9B) only.

1. Data Submission by Study Number:
   Efficacy and safety data sets should be submitted by study. The Study number should be carried as a common variable to facilitate pooling of the data across studies.

   A listing from PROC CONTENTS from each data library should be provided which lists all the data sets, clearly labeled for each study and variable type. ***For each study, please, provide only three or four data sets (if possible).***
   For example:
   Study # 1, Demographic Data
   Study # 1, Efficacy Data
   Study # 1, Safety Data

   Study # 2, Demographic Data
   Study # 2, Efficacy Data
   Study # 2, Safety Data

2. Uniformity of Data and Data Layout:
   All data should be named, coded and described in the same manner for all studies throughout the NDA.

   All files should include patient number, investigator number and treatment group as common variables. The data layout should have one record per patient, with all visit information available in a single record.

   The patient numbers in all the data sets should be unique, so that it is possible to merge the data sets if necessary.

3. Description of Data:
   Please provide a data dictionary which lists and describes the variables.
   Example: TRT = Treatment, INVID = Investigator id#.

   Please provide a description of the values of the variables. Example: TRT (A=Test Drug, B=Placebo); SEX (1=male, 2=female). (A useful data layout is to have the actual value already embedded in the data sets instead of codes and numbers; i.e.: SEX: Male, Female; TRT: Test Drug, Placebo.)

4. Data Formats:
   All format libraries and variable labels should be provided, along with step-by-step outline of attaching the format catalogs to SAS data sets.

5. SAS Programs:
   Please provide the programs used to generate the results, and a description of their intended use, for each of the studies separately (no need for programs that create tables or pages.)

For each study please provide:

Demographic Data:
Example:

Patient Id
Investigator Id
Treatment Group
Age
Race
Gender
Baseline Clinical Evaluability
Any Concomitant Drug Use & Drug Type
Number of Days in Study
Number of Days on Therapy
.
.
.

(All available related demographic variables)

Efficacy Data:

Example:
Patient Id
Investigator Id
Treatment Group
Visit Number
Days from start of treatment
Signs & Symptoms
Clinical Responses
.
.
.

(All the variables needed for the efficacy analyses)

Safety Data:
Example:
Patient Id
Investigator Id
Treatment Group
Visit Number
Days from Start of Treatment to Adverse Event
Adverse Event
List of Adverse Events
Death
Date of Death

Questions for the sponsor regarding Studies 43,779-9A & 43,779-9B (the CNS studies):

Why are the datasets for the two studies merged together?
There is no variable for "AGE".
There is no variable for "WEIGHT".
What is the code for the "TREATMENT" variable and the related values?
What is the variable that was used and analyzed as the "primary endpoint variable"?
Most of the variable labels (or variable description) and their values, in the PROC CONTENT, are not understandable.
The "WORD" documents provided by the sponsor on the CD are not readable.

After you have received this fax, please telephone CAPT James Moore to arrange a brief t-con to discuss the questions contained in this fax and some questions regarding format of the data.

If you have questions, please call CAPT James Moore at (301) 827-7510.

James Moore, R.Ph., M.A.
Project Manager, HFD-160

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

/s/

James Moore
7/23/01 02:01:03 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-357

Bracco Diagnostics, Inc.
Attention: Melanie Benson
Director, U S Regulatory Affairs
P.O. Box 5225
Princeton, New Jersey 08543-5225

Dear Ms. Benson:

We have received your new drug application (NDA 21-357) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Multihance® (gadobendate dimeglumine) Injection
Review Priority Classification:	Standard (S)
Date of Application:	April 27, 2001
Date of Receipt:	April 27, 2001
Our Reference Number:	NDA 21-357

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 27, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 27, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call CAPT James Moore, Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Kyong Cho, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Kyong Cho
5/29/01 02:06:33 PM

Filing Meeting for MultiHance NDAs 21-357/21-358 May 24, 2001,
Parklawn Building, Room, 18B-37

FDA Attendees:

Patricia Love, M.D., M.B.A., Division Director, HFD-160
Sally Loewke, M.D., Deputy Division Director, HFD-160
Roger Li, M.D., Clinical Reviewer, HFD-160
Alfred Eric Jones, M.D., Clinical Team Leader, HFD-160
Nakissa Sadrieh, Ph.D., Pharmacology/Toxicology Team Leader, HFD-160
Eldon Leutzinger, Ph.D., Chemistry Team Leader, HFD-820
Michael Welch, Ph.D., Team Leader Biometrics, HFD-715
Robert K. Leedham, Jr., R.Ph., M.S., Associate Director for Regulatory Policy, HFD-160
James Moore, R.Ph., M.A., Project Manager, HFD-160

Introduction

This was the filing meeting for Multihance (NDAs 21-357/21-358). Each discipline was asked whether the application should be filed. Here are the responses from each discipline.

Chemistry

Chemistry recommended filing of the application.

Pharmacology/Toxicology

Pharmacology/Toxicology recommended filing of the application.

Clinical Pharmacology

Clinical Pharmacology recommended filing of the application.

Clinical

Clinical recommended filing of the application.

Biometrics

Biometrics recommended filing of the application.

Discussion

The medical officer raised several questions regarding the proposed dose and the design of the studies but said these questions would be addressed in the review of the application.

The application was filed on May 24, 2001.

The minutes were prepared by CAPT James Moore, Project Manager.

James Moore, R.Ph., M.A.
Project Manager, HFD-160

Minutes of the Pre-NDA Meeting between Bracco and the Division of Medical Imaging and Radiopharmaceutical Drug Products, June 17, 1999, Parklawn Building, Conference Room B, 1:00pm

Topic: MultiHance (I 43,779)

Bracco Attendees:

Melanie Benson, Senior Manager Regulatory Operations, Bracco

Norman Lafrance, Medical and Regulatory Affairs, Bracco
Alberto Sinazzi, Medical and Regulatory Affairs, Bracco, Milan
Andrew Betournay, Group Regulatory Affairs, Milan

FDA Attendees:

Patricia Y. Love, M.D., M.B.A., Division Director, HFD-160
Sally Loewke, M.D., Team Leader, Clinical, HFD-160
Ramesh Raman, M.D., Clinical Reviewer, HFD-160
Ruthanna Davi, M.S., Biometrics Reviewer, HFD-715
David Place, Ph.D., Chemistry Reviewer, HFD-820
Tushar Kokate, Ph.D., Pharmacology/Toxicology Reviewer, HFD-160
Nakissa Sadrieh, Ph.D., Team Leader, Pharmacology/Toxicology, HFD-160
Alfredo Sancho, Ph.D., Clinical Pharmacologist, HFD-870
James Moore, Project Manager, HFD-160

The meeting began with introduction of attendees. After introductions, each FDA discipline began discussion of the meeting package provided.

Chemistry

The chemistry reviewer commented that it is unusual during synthesis not to isolate the drug substance. If an application is presented in which the drug substance is not isolated, then it becomes a review issue and the application may not be approved or deemed not fileable from the CMC perspective. The only exception to this is some of the biotechnology products, which for various reasons cannot be isolated. The summary provided by the sponsor is incomplete/sketchy and does not provide data on the isolation, separation, or purity of the drug substance. The relaxivity, IR specifications of a product, and its physical chemistry should be well defined. The specifications for MultiHance were not well defined according to the reviewer.

It is recommended that the sponsor synthesize and characterize the drug substance in the traditional way, which makes characterization of the product much less burdensome. Isolating the drug substance will change the impurity profile of the drug product.

Pharmacology/Toxicology

Dose multiples used in most of the animal studies (0.3 to 2 times the intended clinical dose of 0.2 mmol/kg based on body surface area) are not high enough to adequately evaluate potential toxicity. Also, there is a very low safety margin between the intended clinical dose (0.2 mmol/kg) and the lethal dose (LD_{50}) in animals (e.g., 2.4 for mice and 5.5 for rats). These concerns may be reflected in the label.

FDA recommended that the sponsor comment on the intended use of MultiHance in the pediatric population based on the pre-clinical data. FDA's published pediatric rule recommends studying the potential for toxicity of drugs in immature animals.

Bracco attributed the adverse effects of MultiHance on the liver and the cardiovascular system (CVS) to hyperosmolarity. FDA recommended that this issue be addressed in detail. FDA also asked how histological changes (histocytosis of peri-portal spaces and vacuolization) in liver can be due to hyperosmolarity. Experiments using hyperosmotic mannitol solution as a positive control are recommended to assess adverse effects on the liver and the CVS.

FDA asked the sponsor to submit any data the sponsor had evaluating MultiHance's effect on the ECG at various doses, especially its effect on the QT interval.

FDA recommended that the sponsor perform studies evaluating the local tolerance of MultiHance after perivascular administration.

According to FDA, reproductive toxicity study doses (0.3-2 mmol/kg) used were too low to ~~assess~~ the potential for reproductive toxicity. FDA asked if there was a specific reason for using low dose levels. FDA recommended studying dose levels that produce some maternal toxicity to examine the potential for reproductive toxicity.

From the meeting package (page 30), excretion data in the monkey, when a dose is injected, approximately 70% of the dose (1 mmol/kg) is accounted for in the excretion data. The remaining 30% of the dose is not. FDA asked the sponsor what happens to the remaining 30% of the dose.

FDA asked the sponsor to provide data in detail for all single dose toxicity studies and a full copy of all references in the non-clinical pharmacology/toxicology section of the meeting document.

MultiHance Pre-NDA Meeting Minutes-Continued

FDA recommended modification of the summary table to include main results, number of animals per group, gender, and NOAELs for all studies and dose multiples based on body surface area and maximal human dose.

FDA recommended that all protocols for future animal studies be sent to the Agency prior to initiation of the study. FDA also stated that a review of the protocols would assure that studies fully address all the safety concerns.

Clinical Pharmacology

On page 31 of the pre-meeting package, there is no clear description of body clearance. FDA asked, what percent of the cleared drug is cleared renally and what percent is cleared hepatically? There were only eleven patients included in the study of hepatic clearance. In the pharmacokinetic study cited, the subjects numbered 57 and all were male. Consideration should be given to inclusion of females in future studies to ascertain pharmacokinetic parameters in these patients. If no females are included in the NDA submission, then the sponsor must justify the exclusion of females.

Clinical

As part of its presentation regarding clinical trials with this product, Bracco made the following statements:

(1) There were a total of 410 patients included in the CNS trial.
(2) Three indications were the subject of this investigation.
(3) There were three studies for the CNS indication, [redacted] and a study of the brain and spine in pediatric patients. The pediatric study was a PK study in normal pediatric patients.
(4) The dose for the CNS study was 0.1mmol/kg, [redacted] for the brain and spine 0.1mmol/kg in the pediatric population.
(5) Omniscan was used as the comparator in these trials.
(6) Multihance has greater relaxivity than other gadolinium agents do.
(7) There is active hepatic uptake, [redacted]

[redacted]

FDA would like to see the data on biliary disease in pediatric patients.

FDA asked, does Gd remain attached to the complex in the liver? How does it affect the bones? The sponsor responded that they would research this.

A pediatric plan must accompany the marketing application when it is submitted.

FDA emphasized the need for safety data. There was no evaluation of EKGs included in the package. EKG safety data should be presented by dose.

FDA recommended a perivascular study and kidney study because of the observed hepatic and renal toxicity in animals.

FDA expressed its concern that the drug affects biliary transport and this would be a concern for pediatric patients 2 years and below and in patients with inborn errors of metabolism.

There was no safety data included in this package, no protocols, time points for measuring parameters and no sample tables. FDA recommended reporting of normal ranges, time points, scatter plots, shift tables for changes in hematocrit, hemoglobin, and other measured plasma values.

FDA inquired about the methods used by blinded readers to examine and evaluate images and cautioned the sponsor to insure that blinded readers remain independent so that bias is not introduced into the evaluation of the images.

Safety data that should be included in the submission include the following:

(1) Baseline safety data with laboratory values including urinary, hematologic, and hepatic values, normal ranges, parameters tested, all changes from baseline, scatter plots with easy reference to patients.

(2) Safety data by dose: 0.1mmol, < 0.1mmol, >0.1mmol.

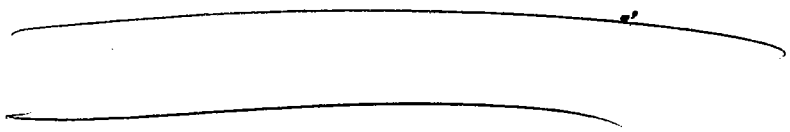
(3) Demographic data to include all races, [e.g., not whites and others].

(4)

(5)

Biostatistics

For studies 43-779-9A, 43779-9B, ——— the sponsor plans to summarize the primary endpoint ——————— by displaying the number and percent of subjects with an increase in this parameter. The sponsor plans to present this information by dose group and reviewer. FDA requested that this information also be presented in 3x3 frequency tables (pre-image: limited, adequate, excellent versus paired image: limited, adequate, excellent). This presentation would indicate the number and percent of patients that shifted from category X to category Y.



The sponsor explained the format planned for submitting the electronic data. Efforts are being made to create one data set including all variables used in the primary and secondary efficacy analyses. FDA stated that such a data set would be quite helpful for review purposes and thanked the sponsor for their willingness to create this type of file.

Electronic Submission and Telephone Conferences

The sponsor proposes to submit much of the NDA in the electronic format and expressed a desire to discuss with the division the format for this type of a submission. The sponsor also suggested that telephone conferences be set up to discuss specific points in depth that were highlighted by different discipline at the meeting.

These minutes were prepared by James Moore, Project Manager, HFD-160.

/S/

James Moore, R.Ph., M.A.
Project Manager

drafted by:jm 8/99
edited by rd/ns/
revised jm/9/24/9910/18/99 11:04 AM/4/5/00

cc: Original IND 43,779/Division File IND 43,779
HFD-160\love\loewke\raman\davi\place\kokate\sadrieh\sancho\moore

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-357 & 21-358**	Efficacy Supplement Type	Supplement Number	
Drug: **MultiHance (Gadobenate Dimeglumine)**		Applicant: **Bracco Diagnostics, Inc.**	
RPM: **Diane C. Smith, R. Ph.**		HFD- **160**	Phone # (301) 827-7510
Application Type: **(X)** 505(b)(1) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	**Standard**
• Chem class (NDAs only)	**1**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**February 2, 2005**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4097
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) N/A
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) N/A
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified **N/A** 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A**
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (ADRA) 11/23/04

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE 5/24/02 and 4/14/04**
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Trade name review per DMETS, see review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	X see Chemistry & DMETS reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X 6/17/99
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	OD/ DD/MTL
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	(X) 2/22/02; 4/7/04; and 11/123/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	*See Clinical Review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	(X) 2/25/02; 3/3/04 and 11/22/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	(X) 2/22/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	(X) 2/25/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	(X) 1/25/02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	(X) 1/5/02
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable 2/24/04 ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	(X) 5/14/02; 4/6/04 & 4/7/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Diane Smith
11/23/04 03:19:15 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDAs 21-357 & 21-358	Efficacy Supplement Type -	Supplement Number
Drug: MultiHance (Gadobenate Dimeglumine)		**Applicant: Bracco Diagnostics, Inc.**
RPM: Diane C. Smith, R.Ph.	**HFD- 160**	**Phone #** (301) 827-7510
Application Type: (X) 505(b)(1)	Reference Listed Drug (NDA #, Drug name):	

❖ **Application Classifications:**	
• Review priority	**Standard**
• Chem class (NDAs only)	**1S**
• Other (e.g., orphan, OTC)	
❖ **User Fee Goal Dates**	**April 14, 2004**
❖ **Special programs (indicate all that apply)**	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ **User Fee Information**	
• User Fee	**(X)** Paid
• User Fee waiver **N/A**	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception **N/A**	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ **Application Integrity Policy (AIP)**	
• Applicant is on the AIP	( ) Yes **(X)** No
• This application is on the AIP	( ) Yes **(X)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ **Debarment certification**: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ **Patent**	
• Information: Verify that form FDA-3542a was submitted.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	**N/A**
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	**NA**

Exclusivity (approvals only)	
• Exclusivity summary	**N/A**
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ ( ) No
❖ **Administrative Reviews** (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ **Actions**	
• Proposed action	( ) AP ( ) TA **(X)** AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE 5/24/02**
• Status of advertising (approvals only)	**N/A**
❖ **Public communications**	
• Press Office notified of action (approval only)	**(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**N/A**
❖ **Labeling** (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**(X) Chemistry, Pharm/Tox. And Clinical Pharmacology**
• Most recent applicant-proposed labeling	**(X)**
• Original applicant-proposed labeling	**(X)**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Trade name review per DMETS, see review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ **Labels** (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	**(X)**
• Reviews	**(X)** see Chemistry & DMETS reviews
❖ **Post-marketing commitments**	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**N/A**
❖ **Outgoing correspondence** (i.e., letters, E-mails, faxes)	**(X)**
❖ **Memoranda and Telecons**	**(X)**
❖ **Minutes of Meetings**	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**(X)** 6/17/99
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**
❖ **Advisory Committee Meeting**	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ **Federal Register Notices, DESI documents, NAS/NRC reports** (if applicable)	**N/A**

Summary Application Review	
❖ **Summary Reviews** (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**OD/ 4/8/04; DD/MTL/ 4/9/04**
Clinical Information	
❖ **Clinical review(s)** *(indicate date for each review)*	**(X) 4/9/04**
❖ **Microbiology (efficacy) review(s)** *(indicate date for each review)*	**N/A**
❖ **Safety Update review(s)** *(indicate date or location if incorporated in another review)*	***See Clinical Review**
❖ **Risk Management Plan review(s)** *(indicate date/location if incorporated in another rev)*	**N/A**
❖ **Pediatric Page**(separate page for each indication addressing status of all age groups)	**(X)**
❖ **Demographic Worksheet** *(NME approvals only)*	**N/A**
❖ **Statistical review(s)** *(indicate date for each review)*	**(X) 3/3/04 & 3/9/04**
❖ **Biopharmaceutical review(s)** *(indicate date for each review)*	**(X) 2/22/02**
❖ **Controlled Substance Staff review(s) and recommendation for scheduling** *(indicate date for each review)*	**N/A**
❖ **Clinical Inspection Review Summary (DSI)**	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ **CMC review(s)** *(indicate date for each review)*	**(X) 2/25/04**
Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**(X) 1/25/02**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ **Microbiology** (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**(X) 1/5/02**
❖ **Facilities inspection** (provide EER report)	Date completed: **(X)** Acceptable **2/24/04** ( ) Withhold recommendation
❖ **Methods validation**	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ **Pharm/tox review(s),** including referenced IND reviews *(indicate date for each review)*	**(X) 4/6/04 & 4/7/04**
❖ **Nonclinical inspection review summary**	**N/A**
❖ **Statistical review(s) of carcinogenicity studies** *(indicate date for each review)*	**N/A**
❖ **CAC/ECAC report**	**N/A**

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-357 & 21-358**	Efficacy Supplement Type	Supplement Number	
Drug: **MultiHance (Gadobenate Dimeglumine)**		Applicant: **Bracco Diagnostics, Inc.**	
RPM: **Diane C. Smith, R. Ph.**		HFD- **160**	Phone # (301) 827-7510
Application Type: **(X)** 505(b)(1) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	**Standard**
• Chem class (NDAs only)	**1**
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**February 2, 2005**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number 4097
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) N/A
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) N/A
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified **N/A** 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A**
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (ADRA) 11/23/04

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**AE 5/24/02 and 4/14/04**
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	Trade name review per DMETS, see review
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	**N/A**
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	X see Chemistry & DMETS reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X 6/17/99
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary and Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	OD/ DD/MTL
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	(X) 2/22/02; 4/7/04; and 11/123/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	*See Clinical Review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	(X) 2/25/02; 3/3/04 and 11/22/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	(X) 2/22/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	(X) 2/25/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	(X) 1/25/02
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	(X) 1/5/02
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable 2/24/04 **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	(X) 5/14/02; 4/6/04 & 4/7/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Diane Smith
11/23/04 03:19:15 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDAs: 21-357 & 21-358		
DRUG: MultiHance (Gadobenate Dimeglumine) Injection	**APPLICANT: Bracco Diagnostics, Inc.**	
RPM: Thuy Nguyen	**HFD-160**	**Phone # :** (301) 827-7510
Application Type: (X) 505(b)(1)		

❖ **Application Classifications:**	
• Review priority	**Standard**
• Chem class (NDAs only)	**1S**
❖ **User Fee Goal Dates**	**May 27, 2002 (05/24/02)**
❖ **Special programs (indicate all that apply):**	**(X)** None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ **User Fee Information**	
• User Fee	**(X)** Paid
• User Fee waiver: **N\A**	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception: **N\A**	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ **Application Integrity Policy (AIP)**	
• Applicant is on the AIP	( ) Yes (**X**) No
• This application is on the AIP	( ) Yes (**X**) No
❖ **Debarment certification:** verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	**(X)** Verified
❖ **Patent**	
• Information: Verify that patent information was submitted	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted:	**N\A**
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	**N\A**
❖ **Exclusivity Summary** (approvals only)	**N\A**
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	04\30\02

Actions	
• Proposed action	( ) AP ( ) TA (X) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N\A
• Status of advertising (approvals only)	N\A
❖ **Public communications**	
• Press Office notified of action (approval only)	N\A
• Indicate what types (if any) of information dissemination are anticipated	N\A
❖ **Labeling** (package insert, patient package insert (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N\A
• Sponsor's original proposed labeling	(X)
• Sponsor's most recent proposed labeling	N\A
• Labeling reviews (Office of Drug Safety trade name review, nomenclature reviews)	(X)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N\A
❖ **Labels** (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission) labels	N\A
• Sponsor's proposed labels	(X)
Post-marketing commitments	
• Agency request for post-marketing commitments	N\A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N\A
❖ **Outgoing correspondence** (i.e., letters, E-mails, faxes)	(X)
❖ **Memoranda and Telecons**	(X)
❖ **Minutes of Meetings**	
• Pre-NDA meeting: 06/17/99	(X)
❖ **Advisory Committee Meeting**	
• Date of Meeting	N\A
• 48-hour alert	N\A
❖ **Federal Register Notices, DESI documents, NAS, NRC** (if any are applicable)	N\A
Clinical and Summary Information	
❖ **Summary Reviews** (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	* PENDING
❖ **Clinical review(s)** *(indicate date for each review)*	(X) 05/23/02
❖ **Microbiology (efficacy) review(s)** *(indicate date for each review)*	(X) 01/04/02
Safety Update review(s) *(indicate date or location if incorporated in another review)*	* See Clinical Review
❖ **Pediatric Page** (separate page for each indication addressing status of all age groups)	N\A

❖ **Statistical review(s)** *(indicate date for each review)*	**(X) 02/25/02 & 04/30/02**
❖ **Biopharmaceutical review(s)** *(indicate date for each review)*	**(X) 02/22/02**
❖ **Controlled Substance Staff review(s)** and recommendation for scheduling *(indicate date for each review)*	**N\A**
❖ **Clinical Inspection Review Summary (DSI)**	
• Clinical studies	**(X)**
CMC Information	
❖ **CMC review(s)** *(indicate date for each review)*	**(X) 01/25/02**
❖ **Environmental Assessment**	
• Categorical Exclusion *(indicate review date)*	**(X) 01/25/02**
• Review & FONSI *(indicate date of review)*	**N\A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N\A**
❖ **Micro** (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ **Facilities inspection** (provide EER report)	**Date completed:** 02/20/02 **(X)** Acceptable
❖ **Methods validation**	**(X)** Not Yet Requested
Nonclinical Pharm/Tox Information	
❖ **Pharm/tox review(s)**, including referenced IND reviews *(indicate date for each review)*	**(X) 04/29/02**
❖ **Nonclinical inspection review summary**	**N\A**
❖ **Statistical review(s)** of carcinogenicity studies *(indicate date for each review)*	**N\A**
❖ **CAC/ECAC report**	**N\A**