CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208143Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #**208143** SUPPL # HFD # **160**

Trade Name **READI-CAT 2 / READI-CAT 2 Smoothie**

Generic Name **barium sulfate oral suspension 2% (w/v)**

Applicant Name **Bracco Diagnostics Inc.**

Approval Date, If Known **January 15, 2016**

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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

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

505(b)(2) NDA

b) 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 ☒ 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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written 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 ☒

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 ☐

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

NDA# 208036 (01/11/16) E-Z-HD (barium sulfate) powder for oral suspension

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 NDAs 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 ☒

The application is a 505(b)(2) NDA relying solely upon published literature studies [by cross reference to NDA 208036 E-Z-HD (barium sulfate)] to support the safety and effectiveness of READI-CAT 2. The submitted published literature studies were not conducted or sponsored by the applicant.

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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

==========

Name of person completing form: **Frank Lutterodt**
Title: **Senior Regulatory Project Manager**
Date: **01/14/2016**

Name of Office/Division Director signing form: **Charles Ganley, M.D.**
Title: **Director ODE IV**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

FRANK A LUTTERODT
01/26/2016

CHARLES J GANLEY
01/26/2016

1.3.3 Debarment Certification

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.

In compliance with 21 CFR 54, Bracco Diagnostics Inc. acknowledges the request for the required Financial Disclosure Information and Form FDA 3454 for its clinical investigators of the covered studies in support of this supplemental NDA 208143.

This application contains no covered clinical studies and is supported by information from peer reviewed literature, textbooks and guidelines. Therefore, FDA Form 3454 has not been included in this application.

M Benson

Melanie Benson
Director, US Regulatory Operations

12/16/14
Date

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

/s/

LIBERO L MARZELLA
09/17/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **208143** BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: **Readi-CAT/Readi CAT2 Smoothie** Established/Proper Name: **Barium Sulfate 2% w/v** Dosage Form: **Suspension**		Applicant: **Bracco Diagnostics Inc.** Agent for Applicant (if applicable):
RPM: **Frank Lutterodt**		Division: **Division of Medical Imaging Products**

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 12/14/15

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action • User Fee Goal Date is **January 18, 2016**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) ssessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☒ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **January 15, 2016**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**March 27, 2015** **March 25, 2015**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None DMEPA: ☐ None **07/10/2015** DMPP/PLT (DRISK): ☐ None OPDP: ☐ None **1/5/2015** SEALD: ☐ None **12/23/2015** CSS: ☐ None Product Quality ☐ None **11/18/2015** Other: ☐ None **DPMH 9/02/2015**
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	**Feb 17, 2015** ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 10/21/2015 If PeRC review not necessary, explain: _____	**October 21, 2015**
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*	
Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10/23/14
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None **1/15/2016**
Division Director Summary Review *(indicate date for each review)*	☐ None **1/13/2016**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **1/15/2016**
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	11/17/15
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not *(indicate date of review/memo)*	see Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None **01/06/15**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **08/12/15**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None **07/23/15**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None **11/18/15**
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None **Drug Product-11/24/15** **Drug Substance-10/19/15** **Microbiology-11/3/15**
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None **BioPharmaceutics 11/07/15**
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**10/21/15**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable-**10/20/15** Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

PeRC Meeting Minutes
October 21, 2015

PeRC Members Attending:
Hari Cheryl Sachs
Linda Lewis (Acting Chair)
Gettie Audain
Lily Mulugeta
Thomas Smith
Shrikant Pagay
Daiva Shetty
Wiley Chambers
Meshaun Payne
George Greeley
Freda Cooner
Gregory Reaman
Peter Starke (Methylphenidate, Delzicol , RPC 1063, Etrolizumab and Natroba reviews only)
Dionna Green
Belinda Hayes
Kevin Krudys
Maura O'Leary (Methylphenidate, Delzicol and RPC 1063 reviews only)
Julia Pinto (Did not review Methylphenidate, Delzicol and and RPC 1063)
Dianne Murphy
Andrew Mulberg (Did not review Methylphenidate, Delzicol and and RPC 1063)

Reference ID: 3844801

Agenda

9:00	NDA 207960	Methylphenidate ER Chewable Tables iPSP (Partial Waiver/Deferral/Plan)	DPP	Hiren Patel	Attention Deficit Hyperactivity Disorder (ADHD)
9:20	NDA 204412	Delzicol (mesalamine) Deferral Extension	DGIEP	Kelly Richards	Treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older Maintenance of remission of ulcerative colitis in adults
9:30	IND 115243	RPC 1063 Non-Agreed iPSP (Partial Waiver/Deferral)	DGIEP	Kelly Richards	Ulcerative Colitis
9:50	IND 119725	Etrolizumab iPSP (Partial Waiver/Deferral)	DGIEP	Kelly Richards	Crohn's Disease
10:10	IND 066657	Natroba (spinosad) topical suspension, 0.9% iPSP (Partial Waiver/Deferral)	DDDP	Dawn Williams	Treatment of scabies in patients 4 years of age and older
10:30	IND 113306	BI 655066 iPSP (Partial Waiver/Deferral)	DDDP	Cristina Attinello	Plaque Psoriasis
10:50	NDA 208036	E-Z –HD (barium sulfate suspension) Assessment	DMIP	Frank Lutterodt	Indicated for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.
11:00	NDA 208143	Readi-Cat2 (barium sulfate suspension) Assessment	DMIP	Frank Lutterodt	For use in Computed Tomagraphy of the abdomen to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.
11:20	NDA 22527	Gilenya (fingolimod) Capsules Deferral Extension	DNP	Nahleen Lopez	Treatment of Multiple Sclerosis
	BLA 125504/001 /002	Cosentyx (secukinumab) Full Waiver (With Agreed iPSP)	DPARP	Michelle Jordan Garner	S01 – Treatment of psoriatic arthritis; S02 – Treatment of ankylosing spondylitis
	IND 123482	Keytruda (pembrolizumab) Agree iPSP	DOP2	Sharon Sickafuse	Treatment of colorectal cancer
	IND 110799	Clobetasol Propionate Cream Agreed iPSP (Partial Waiver/Deferral)	DDDP	Belainesh Robnett/ J. Paul Phillips	Psoriasis
	IND 116537	Fluticasone Propionate Gel Agreed iPSP (Partial Waiver)	DDDP	Matthew White	Treatment of atopic dermatitis in patients 3 months of age and older
	IND 105379	Dupilumab Agreed iPSP Deferral/Assessment	DPARP	Colette Jackson	Asthma
	IND 73176	Abaloparatide Agreed iPSP (Full Waiver)	DBRUP	Samantha Bell	Treatment of postmenopausal osteoporosis
	IND 112292	EVZIO (naloxone) Auto-Injector Agreed iPSP (Assessment)	DAAAP	Diana Walker	Reversal of opioid-induced central nervous system (CNS) depression.

Reference ID: 3844801

- *PeRC Recommendations:*
  - The PeRC agreed with the sponsors plan to waive studies in patients 0 to less than 6 years of age as the condition does not occur in this pediatric population.
  - The PeRC agreed with the sponsor's plan to defer studies in pediatric patients 6 to less than 18 years of age. Adult phase 3 data will be required to allow for PK/PD modeling in order to determine the appropriate dose and dosing regimen for this pediatric age group.
  - The PeRC recommends that the sponsor provide the date in which the protocol will be submitted to the Agency.

E-Z –HD (barium sulfate suspension) Assessment

- Proposed Indication: Indicated for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum to locate and outline normal structures, or to distinguish between normal and abnormal anatomy. While pediatric use for this specific procedure is low, overall, barium products for radiographic contrast are widely used in pediatrics
- The division clarified that this is a new NDA of a marketed unapproved product and that the sponsor requested a full waiver in their submitted iPSP. The division determined there is no reason to waive this product in pediatric patients as it has been widely used for many years in both adults and pediatric patients. The division proposed labeling to cover all age groups based on the sponsor submitting literature, safety data and a use survey to support labeling of this product.
- The pediatric assessment for this product will provide the basis for many other barium products.
- *PeRC Recommendations*:
  - The PeRC agreed with the comments on the plan made by the division.
  - The PeRC agreed with the Division's comments to label the product for use in all age groups based on literature and safety data and not to waive pediatric patients.
  - The PeRC recommends that the Division revise the PeRC template based on the Division's recommendation that literature and safety data be used.

Readi-Cat2 (barium sulfate suspension) Assessment

- Proposed Indication: For use in Computed Tomagraphy of the abdomen to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.
- The division clarified this NDA is being cross-referenced with the other barium sulfate product. This is a newly submitted NDA for a marketed unapproved drug. The sponsor requested a full assessment for all pediatric age groups based on published literature to support labeling in all pediatric age groups.
- *PeRC Recommendations*:
  - The PeRC agreed with the sponsor's plan as stated within the iPSP
  - The PeRC recommends that the Division update the PeRC template to indicate this will be an Assessment.

Gilenya (fingolimod) Capsules Deferral Extension

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

/s/

MESHAUN L PAYNE
11/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208036
NDA 208143

MEETING MINUTES

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd. Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 18, 2015, received December 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EZ-HD (barium Sulfate) powder for oral suspension 98% (w/w), and Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v).

We also refer to the telecon between representatives of your firm and the FDA on July 30, 2015. The purpose of the meeting was to discuss your current plan for filing the "initial" Pediatric Study Plan (iPSP) for barium sulfate products and to address the Request(s) for Information (RFI) to NDA 208036 and NDA 208143, dated May 27, 2014.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Product
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Guidance
Meeting Date and Time:	Thursday, July 30, 2015: 12:00PM to 1:00PM
Meeting Location:	Teleconference
Application Number:	NDA 208-0360 and 208-143
Product Name:	Barium Sulfate (E-Z-HD) and (Readi-Cat 2/ Readi-Cat 2 Smoothies)
Indications:	For use in radiographic examinations of the esophagus, stomach and duodenum to locate and outline normal structures, or distinguish between normal and abnormal anatomy. For use in Computed Tomography of the abdomen to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.
Applicant Name:	Bracco Diagnostics Inc.

FDA ATTENDEES

Libero Marzella, M.D., Director, Division of Medical Imaging Products, (DMIP)
Alex Gorovets, M.D., Deputy Director, Division of Medical Imaging Products
Linda Lewis, M.D., Lead Medical Officer, Division of Pediatric and Maternal Health (DPMH)
Alyson Karesh, M.D., Medical Officer, DPMH
Denise Pica-Branco, Ph.D., Senior Regulatory Project Manager, DPMH
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Alberto Spinazzi, MD, Head, Global Medical and Regulatory Affairs
Maria Luigia Storto, MD, Executive Director, Medical Planning and Management
Andrew Betournay, Head, Global Regulatory Affairs
John Spaltro, PhD, Senior Director, Global Regulatory Affairs
Melanie Benson, BA, RAC, Director, US Regulatory Operations
Usha Halemane, Executive Director, Medical Biometrics and Medical Writing
Adrianne Setton, PhD, Head Corporate Product Information, Regulatory Affairs

1.0 BACKGROUND

Following receipt of an FDA information request (IR) Letter dated May 27, 2015 for both Barium Sulfate NDAs, Bracco requested a Type A meeting with FDA to discuss and confirm their Pediatric

Study Plan for the Barium Sulfate products. The following constitutes FDA's preliminary responses to questions in the June 26, 2015 meeting package.

2. DISCUSSION

After introductions, the meeting was focused on the two clarification items Bracco requested in their July 29, 2015 email.

Clarification Item 1:

1. Bracco will provide PSP for EZHD (waiver) to NDA 208036 and PSP for RC2/RC2S (Full Assessment) to NDA 208143 as requested by FDA, by end of August 2015. These PSP filings to NDAs 208036/208143 will fulfill requirements to submit a pediatric plan as required under PREA for these NDAs. Does FDA Concur?

FDA's response: Yes, we agree with Bracco's proposal.

2. As requested by FDA, Bracco will submit survey data (supporting the iPSP for all products) to the flagship NDA 208036 by 11 Oct. The survey data is not necessarily required for approval of NDAs 208036/208143, but is being submitted to NDA 208036, as previously agreed, to file all clinical information to the flagship NDA. Submission of survey data to NDA 208036 will not trigger a separate user fee, and submittal by 11 Oct to NDA 208036 will not result in a delay approval of these NDAs. Does the FDA Concur?

FDA's response: As agreed, the survey data should be submitted to the EZHD NDA. The survey data is essential for FDA as there is very little in the literature for barium use in pediatrics. FDA understands that barium pediatric use is declining and Bracco is relying on the opinions of medical experts as to what (which products) is/are being used in that population. FDA will review the survey results/information as part of the EZHD NDA and this will be used for the development of labeling for the upcoming barium NDAs/sNDAs. The survey results need to be submitted timely, so FDA has the opportunity to review (EZHD PDUFA date is October 11, 2015).

Bracco proposed and it was agreed that the survey results would be submitted to the EZHD NDA after Labor Day (week of September 8th). Depending on the amount of information, timing, etc, FDA stated the PDUFA clock may need to be extended (considered a major amendment). Bracco acknowledged this.

Clarification item 2:

1. Bracco will submit an iPSP for all barium products to PIND 115090, as soon as possible. The timing of the iPSP submission (anticipated in October 2015) will be partially based on availability of results obtained from the survey to be conducted. Based on the FDA response to Question 2 indicating that " the iPSP must be filed at least 210 days before submission of a marketing application… that failure to include an Agreed iPSP with the next marketing application may be grounds for Refusal to File Action", we understand that

schedule for submission of all remaining NDAs/sNDAs should be delayed accordingly and a revised submission schedule is required. Does the FDA concur?

FDA's response: FDA stated that because of all the work already done to date on this project, discretion will be used and Bracco should not alter the timelines of the submission plan. Bracco will not be held to the 210 day timeframe. FDA inquired how many submissions are planned for the remainder of 2015; Bracco responded 2 sNDAs and 1 NDA are planned for this year.

Labeling for the products should not be submitted at one time, but separately at the time of submission of the relevant NDA/sNDA.

FDA requested that for future submissions, Bracco should reference and replicate the pertinent information from the pediatric development submission. Background information should be provided and Bracco should add whatever else is needed to provide complete information for that product. If the indication is different, then there will be parts of the PSP which will need to be different. If Bracco is or is not pursuing a pediatric indication, it should state why.

The discussion regarding the pediatric development plan terminated at this point.

Bracco took the opportunity to inform FDA that there are companies introducing barium sulfate products similar to ReadiCat, on the market post the September 19, 2011 Unapproved Drugs Compliance Policy. FDA asked that Bracco send the information, indicating Bracco's concerns to DMIP and they would forward the information to the Office of Compliance.

ATTACHMENTS AND HANDOUTS

- Bracco's July 29,2015 Clarification Items for Teleconference
- FDA's July 27, 2015 Preliminary Responses

From: Benson Melanie
To: Lutterodt, Frank A
Subject: RE: Barium Sulfate Comments and dial in information
Date: Wednesday, July 29, 2015 12:45:30 PM

Dear Mr Lutterodt,

Thank you and the team for providing Bracco with preliminary responses to the questions contained in our Meeting Information Package.
During tomorrow's tcon, Bracco would like clarification on the following:

Clarification item 1:

1- Bracco will provide PSP for EZHD (waiver) to NDA 208036 and PSP for RC2/RC2S (Full Assessment) to NDA 208143 as requested by FDA, by end of August 2015. These PSP filings to NDAs 208036/208143 will fulfill requirements to submit a pediatric plan as required under PREA for these NDAs. Does FDA Concur?

2- As requested by FDA, Bracco will submit survey data (supporting the iPSP for all products) to the flagship NDA 208036 by 11 Oct. The survey data is not necessarily required for approval of NDAs 208036/208143, but is being submitted to NDA 208036, as previously agreed, to file all clinical information to the flagship NDA. Submission of survey data to NDA 208036 will not trigger as separate use fee, and submittal by 11 Oct to NDA 208036 will not result in a delay approval of these NDAs. Does the FDA Concur?

Clarification item 2:

1- Bracco will submit an iPSP for all barium products to PIND 115090, as soon as possible. The timing of the iPSP submission (anticipated in October 2015) will be partially based on availability of results obtained from the survey to be conducted. Based on the FDA response to Question 2 indicating that " *the iPSP must be filed at least 210 days before submission of a marketing application… that failure to include an Agreed iPSP with the next marketing application may be grounds for Refusal to File Action*", we understand that schedule for submission of all remaining NDAs/sNDAs should be delayed accordingly and a revised submission schedule is required. Does the FDA concur?

Because we will have one participant from Milan, please use the teleconference information provided below:

Domestic: 888 582 3528
Passcode: 767 0653#

Please contact me with any additional questions.
Best regards,
Melanie Benson
Bracco Diagnostics Inc

From: Lutterodt, Frank A [mailto:Frank.Lutterodt@fda.hhs.gov]
Sent: Monday, July 27, 2015 3:56 PM

To: Benson Melanie
Subject: Barium Sulfate Comments

Per our discussion, attached here is FDA comments.

Thank you,

Frank

Frank Lutterodt, M.S., MSDRA ¦ Regulatory Health Project Manager ¦ Division of Medical Imaging Products
Office of Drug Evaluation IV ¦ Center for Drug Evaluation and Research ¦ Food and Drug Administration
10903 New Hampshire Avenue, Room 5483 ¦ Silver Spring, MD 20993
Phone: (301) 796.4251 • Fax: (301) 796.9849 ¦ Frank.Lutterodt@fda.hhs.gov

---

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208036
NDA 208143

MEETING PRELIMINARY COMMENTS

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 18, 2015, received December 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EZ-HD (barium sulfate) powder for oral suspension 98% (w/w), and Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v).

We also refer to your June 26, 2015, correspondence requesting a meeting to discuss your current plan for filing the "initial" Pediatric Study Plan (iPSP) for barium sulfate products and to address the Request(s) for Information (RFI) to NDA 208036 and NDA 208143, dated May 27, 2014.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Product
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: Guidance
Meeting Date and Time: Thursday, July 30, 2015: 12:00PM to 1:00PM
Meeting Location: Teleconference
Application Number: NDA 208-036 & 208-143
Product Name: Barium Sulfate (E-Z-HD) & (Readi-Cat 2/ Readi-Cat 2 Smoothies)
Indications: For use in radiographic examinations of the esophagus, stomach and duodenum to locate and outline normal structures, or distinguish between normal and abnormal anatomy.
For use in Computed Tomography of the abdomen to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.

Applicant Name: Bracco Diagnostics Inc.

FDA ATTENDEES (tentative)
Libero Marzella, M.D., PhD, Director, Division of Medical Imaging Products (DMIP)
Alex Gorovets, MD, Deputy Director, DMIP
Nushin Todd, MD, PhD, Clinical Team Leader, DMIP
Brenda Ye, MD, Medical Officer, DMIP
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES
Alberto Spinazzi, MD, Head, Global Medical and Regulatory Affairs
Maria Luigia Storto, MD, Executive Director, Medical Planning and Management
Andrew Betournay, Head, Global Regulatory Affairs
John Spaltro, PhD, Senior Director, Global Regulatory Affairs
Melanie Benson, BA, RAC, Director, US Regulatory Operations
Adrianne Setton, PhD, Associate Director, Regulatory Affairs

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for Monday, July 30,, 2015, 12:00 PM to 1:00 PM, between Bracco Diagnostics Inc., and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Following receipt of an FDA Information Request (IR) letter dated May 27, 2015, for both Barium Sulfate NDAs, Bracco requested a Type A meeting with FDA to discuss and confirm their Pediatric Study Plan for the Barium Sulfate products. The following constitutes FDA's preliminary responses to questions in the June 26, 2015, meeting package.

2.0 DISCUSSION

Question 1:

Bracco will continue pursuing NDA/sNDA submissions of barium sulfate products according to the previously agreed schedule with FDA. Bracco will also complete a survey among current users and medical experts of barium sulfate products in pediatric patients to confirm how these products are used and to obtain information as required (age subgroups, methods of use, dosing, indication for use, special precautions) to finalize the iPSP and other product-specific pediatric assessment(s) as required for submission in the NDAs/sNDAs for these products. Therefore, Bracco proposes to file the iPSP for barium sulfate products at the time of the NDA submission for Varibar Pudding since Varibar products are currently anticipated to include labeling for pediatric use and Varibar NDA would be the next barium sulfate NDA filing to occur after completion of the above mentioned survey with medical experts. Filing of the iPSP at the time of Varibar Pudding NDA submission in 4Q2015 will also address the RFIs to Bracco dated 27 May, 2015.

Does the FDA concur with the Bracco proposal?

FDA Response to *Question 1*

Since it has been agreed upon that all relevant clinical information be submitted to the flagship NDA for all barium products, we highly recommend that you submit results of the survey and your Pediatric Study Plan (PSP) to NDA 208036, the flagship NDA, by the NDA's PDUFA action goal date of October 11, 2015. This PDUFA date falls within 4th Quarter of 2015, your proposed timeline. Submitting your pediatric study plan to a different NDA would potentially trigger a separate use fee.

For the two barium NDAs that have been filed, you still need to submit pediatric plan as required under the Pediatric Research Equity Act (PREA) for each product. For E-Z-HD, we acknowledge that the use of the product is low in pediatric patients. Therefore, in your pediatric plan, you may request waivers for pediatric assessments based on the fact that studies would be impossible or highly impracticable. You must justify this reason for a request for waiver with any available information.

For the Readi-Cat NDA, we acknowledge that you have provided published literature and survey information to support the approval of the product for all pediatric age groups. Therefore, your pediatric plan should explain that you are pursuing a full pediatric assessment for the product (i.e., approval of the product for all pediatric age groups) and that you will not be requesting waivers or deferrals for pediatric assessments under PREA for this product. However, we remind you that whether the product will be approved for all pediatric age groups is currently under review. If the product is not approved for all pediatric age groups, then deferred studies under PREA may be required.

For additional information on the submission of a pediatric plan for your applications, we refer you to the guidance for industry: How to comply with the Pediatric Research Equity Act,
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf

Question 2:

Bracco plans to include labeling for pediatric use of those barium sulfate products for which there is a medical need in pediatric patients and to request of full waiver for those products for which there is no medical need in pediatric patients. A preliminary list of barium sulfate products with potential medical need in pediatric patients is provided in section 13.9 of the current background package. The list could be updated after feedback received from experts.

Does the FDA concur with Bracco plan?

FDA Response to *Question 2*

Do not submit labeling for other barium sulfate products for review under the current NDAs. However, we agree that you should submit data (e.g., use data, data on medical need, and availability of other products, etc.,) that support plans to request waivers or deferrals for pediatric assessments under PREA. These data should be submitted as an initial pediatric study plan (iPSP) under the IND for each product. We remind you that an iPSP must be submitted at least 210 days before submission of a marketing application for a product. We also remind you that failure to include an Agreed iPSP with your marketing application may be grounds for a Refuse to File Action.

For additional information on the submission of an initial pediatric study plan, we refer you to the guidance for industry: Pediatric Study Plans: content of and Process for Submitting Initial pediatric Study Plans and Amended Pediatric Study Plans, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf

---

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

/s/

FRANK A LUTTERODT
07/27/2015
On behalf of Dr. Marzella

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

/s/

LIBERO L MARZELLA
08/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208036
NDA 208143

MEETING PRELIMINARY COMMENTS

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 18, 2015, received December 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EZ-HD (barium sulfate) powder for oral suspension 98% (w/w), and Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v).

We also refer to your June 26, 2015, correspondence requesting a meeting to discuss your current plan for filing the "initial" Pediatric Study Plan (iPSP) for barium sulfate products and to address the Request(s) for Information (RFI) to NDA 208036 and NDA 208143, dated May 27, 2014.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Product
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type A
Meeting Category:	Guidance
Meeting Date and Time:	Thursday, July 30, 2015: 12:00PM to 1:00PM
Meeting Location:	Teleconference
Application Number:	NDA 208-036 & 208-143
Product Name:	Barium Sulfate (E-Z-HD) & (Readi-Cat 2/ Readi-Cat 2 Smoothies)
Indications:	For use in radiographic examinations of the esophagus, stomach and duodenum to locate and outline normal structures, or distinguish between normal and abnormal anatomy. For use in Computed Tomography of the abdomen to locate and outline normal structures, or to distinguish between normal and abnormal anatomy.
Applicant Name:	Bracco Diagnostics Inc.

FDA ATTENDEES (tentative)
Libero Marzella, M.D., PhD, Director, Division of Medical Imaging Products (DMIP)
Alex Gorovets, MD, Deputy Director, DMIP
Nushin Todd, MD, PhD, Clinical Team Leader, DMIP
Brenda Ye, MD, Medical Officer, DMIP
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES
Alberto Spinazzi, MD, Head, Global Medical and Regulatory Affairs
Maria Luigia Storto, MD, Executive Director, Medical Planning and Management
Andrew Betournay, Head, Global Regulatory Affairs
John Spaltro, PhD, Senior Director, Global Regulatory Affairs
Melanie Benson, BA, RAC, Director, US Regulatory Operations
Adrianne Setton, PhD, Associate Director, Regulatory Affairs

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for Monday, July 30,, 2015, 12:00 PM to 1:00 PM, between Bracco Diagnostics Inc., and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Following receipt of an FDA Information Request (IR) letter dated May 27, 2015, for both Barium Sulfate NDAs, Bracco requested a Type A meeting with FDA to discuss and confirm their Pediatric Study Plan for the Barium Sulfate products. The following constitutes FDA's preliminary responses to questions in the June 26, 2015, meeting package.

2.0 DISCUSSION

Question 1:

Bracco will continue pursuing NDA/sNDA submissions of barium sulfate products according to the previously agreed schedule with FDA. Bracco will also complete a survey among current users and medical experts of barium sulfate products in pediatric patients to confirm how these products are used and to obtain information as required (age subgroups, methods of use, dosing, indication for use, special precautions) to finalize the iPSP and other product-specific pediatric assessment(s) as required for submission in the NDAs/sNDAs for these products. Therefore, Bracco proposes to file the iPSP for barium sulfate products at the time of the NDA submission for Varibar Pudding since Varibar products are currently anticipated to include labeling for pediatric use and Varibar NDA would be the next barium sulfate NDA filing to occur after completion of the above mentioned survey with medical experts. Filing of the iPSP at the time of Varibar Pudding NDA submission in 4Q2015 will also address the RFIs to Bracco dated 27 May, 2015.

Does the FDA concur with the Bracco proposal?

FDA Response to *Question 1*

Since it has been agreed upon that all relevant clinical information be submitted to the flagship NDA for all barium products, we highly recommend that you submit results of the survey and your Pediatric Study Plan (PSP) to NDA 208036, the flagship NDA, by the NDA's PDUFA action goal date of October 11, 2015. This PDUFA date falls within 4th Quarter of 2015, your proposed timeline. Submitting your pediatric study plan to a different NDA would potentially trigger a separate use fee.

For the two barium NDAs that have been filed, you still need to submit pediatric plan as required under the Pediatric Research Equity Act (PREA) for each product. For E-Z-HD, we acknowledge that the use of the product is low in pediatric patients. Therefore, in your pediatric plan, you may request waivers for pediatric assessments based on the fact that studies would be impossible or highly impracticable. You must justify this reason for a request for waiver with any available information.

For the Readi-Cat NDA, we acknowledge that you have provided published literature and survey information to support the approval of the product for all pediatric age groups. Therefore, your pediatric plan should explain that you are pursuing a full pediatric assessment for the product (i.e., approval of the product for all pediatric age groups) and that you will not be requesting waivers or deferrals for pediatric assessments under PREA for this product. However, we remind you that whether the product will be approved for all pediatric age groups is currently under review. If the product is not approved for all pediatric age groups, then deferred studies under PREA may be required.

For additional information on the submission of a pediatric plan for your applications, we refer you to the guidance for industry: How to comply with the Pediatric Research Equity Act,
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf

Question 2:

Bracco plans to include labeling for pediatric use of those barium sulfate products for which there is a medical need in pediatric patients and to request of full waiver for those products for which there is no medical need in pediatric patients. A preliminary list of barium sulfate products with potential medical need in pediatric patients is provided in section 13.9 of the current background package. The list could be updated after feedback received from experts.

Does the FDA concur with Bracco plan?

FDA Response to *Question 2*

Do not submit labeling for other barium sulfate products for review under the current NDAs. However, we agree that you should submit data (e.g., use data, data on medical need, and availability of other products, etc.,) that support plans to request waivers or deferrals for pediatric assessments under PREA. These data should be submitted as an initial pediatric study plan (iPSP) under the IND for each product. We remind you that an iPSP must be submitted at least 210 days before submission of a marketing application for a product. We also remind you that failure to include an Agreed iPSP with your marketing application may be grounds for a Refuse to File Action.

For additional information on the submission of an initial pediatric study plan, we refer you to the guidance for industry: Pediatric Study Plans: content of and Process for Submitting Initial pediatric Study Plans and Amended Pediatric Study Plans, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf

---

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

/s/

FRANK A LUTTERODT
07/27/2015
On behalf of Dr. Marzella

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208143

INFORMATION REQUEST

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd.
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v).

We have the following CMC information requests:

1. Drug Product Comparability:
   To establish comparability of your proposed commercial products to the historical barium sulfate products, provide quality data on the historical barium sulfate products which were manufactured, but not approved, for use in medical imaging since the 1960's. Since the objective is to compare quality attributes, describe significant differences (e.g. manufacturing processes, formulation, particle size, etc).

   For Readi-Cat 2 and Readi-Cat 2 Smoothie products include, in table format where possible, provide:

   a. A timeline description of all the barium sulfate 2% suspension formulations manufactured and sold by EZ-EM - beginning with the initial introduction on the market and ending with the current time (i.e. 2015 formulation).
   b. Quantitative formulations where available. Alternatively, qualitative formulations.
   c. Specifications for each formulation.
   d. Number of units sold, broken down by formulations and time. Specify how units correlate to dose (i.e. one unit per dose, two units per dose, etc.).
   e. Identify any formulations which were used in referenced literature studies. Provide all quality information available for those products - for example, the

formulation which was on the market at the time of that study in the region of the world where the study was conducted.

2. Drug Product Stability:

   a. As per ICH, provide primary stability data for commercial validation lots of all four flavors of Readi-Cat 2 Smoothie products. No data were provided in Section 3.2.P.8.3. The links provided (e.g RC2S-Stability-18M25C) open to stability data tables for Readi-Cat 2 lots, not Readi-Cat 2 Smoothie lots as indicated by the link name. In the absence of stability data, a shelf life cannot be granted.

   b. For the ongoing stability program and the post-approval stability program, provide a stability protocol, including storage conditions, time points and tests conducted, for the proposed shelf life of Readi-Cat 2 and Readi-Cat 2 smoothie products.

3. Drug Product Flavorings: Regarding the flavorings listed in Section 3.2.P.4 for the Readi-Cat 2 and Readi-Cat 2 Smoothie products –

   a. For each flavoring listed in the formulation, provide a list of all ingredients and the Code of Federal Regulations (CFR) section with which each ingredient complies. Include all ingredients in the artificial flavor and natural flavor formulations. If you do not have access to this information due to proprietary reasons, request that the supplier provide this information directly to us.

   b. Provide a statement confirming that all flavorings comply with the Code of Federal Regulations (CFR). Note that the statement provided in Readi-Cat 2 Section 3.2.p.4.1 Table D under the heading "Additives Regulatory Status" that states *"FDA, but is not limited to, the inclusion of those ingredients are listed as Generally Recognized as Safe (GRAS) under condition of intended use in food as published by FEMA"* is not clear and does not confirm that all ingredients comply with CFR. Also note that specifying the flavoring as "Food Grade" in Readi-Cat 2 Smoothie Section 3.2.P.1 Table A does not confirm that all ingredients comply with CFR.

   c. Add CFR compliance to each flavor specification (natural and artificial coffee cappuccino flavor, natural and artificial Bavarian chocolate flavor, artificial vanilla flavor powder, artificial vanilla flavor liquid, naturally fortified banana flavor powder, natural and artificial blueberry flavor, natural and artificial orange flavor).

4. Drug Product batch data:

   a. Provide release batch data for a commercial validation lot of Readi-Cat 2 Smoothie banana flavor, manufactured, analyzed and packaged as per the NDA. Data for the other three flavors vanilla, berry and mochaccino validation lots were submitted to Section 3.2.P.5.4, but banana is missing.

b. Clarify the following discrepancy: Potassium sorbate assay results in the batch results tables: "Table B: Results of Analytical Testing for Readi-Cat 2 Validation Batches" and "Table B: - Results of Analytical Testing for 3 Finished Product Lots of Readi-Cat 2 Smoothie" reports two different w/w% values for each lot. The acceptance criteria are listed on the basis of weight (w/w%) and volume (w/v%). Resubmit the tables with corrected data.

5. Drug Product specifications: revise the description column in Tables A for Readi-Cat 2 and Readi-Cat2 Smoothies to read "Identification Barium Sulfate (FTIR), Sodium Benzoate (HPLC), Potassium Sorbate (HPLC)" and "Assay – Barium Sulfate (HPLC cation/conducting)" to provide details regarding the test performed.

6. Drug substance. Provide release data, including all attributes in the drug substance specifications, for the lots of 1 micron drug substance (#00101368, 00101646, 00100826 and 00101054) used to manufacture the drug product lots of Readi Cat 2 and Readi Cat 2 Smoothies. The submitted Certificates of Analysis for the drug substance lots are inadequate as they are missing many attributes (such as solubility, moisture, acid soluble substances, soluble barium salts, heavy metals, pH, particle size, mesh screen and colorimetry).

7. Analytical Method LC-058 ASSAY AND IDENTIFICATION OF POTASSIUM SORBATE AND SODIUM BENZOATE FOR BARIUM SULFATE PRODUCTS: This standard operating procedure is unclear regarding the detection wavelength at which the spectra are collected. It states "UV detector wavelength 0.1 minutes 226nm , about 3.5 minutes 250 nm (to detect potassium sorbate peak)" We interpret this to mean a single scan is collected at 226nm for the time period of 0.1 minutes until 3.5 minutes, at which time the detection wavelength is changed to 250nm to complete the scan, in order to detect the potassium sorbate peak. However, the submitted spectra in both the Standard Operating Procedure LC-058 and the Method Validation Reports (AV12-051 and AV12-057) report two separate chromatogram scans: one collected at 226nm and another at 250nm. This suggests that the procedure is to conduct a complete 8 minute scan on one sample at 226nm and then to conduct another complete 8 minute scan on another sample at 250nm. Describe in more detail how spectra are collected. Revise the procedure to clarify the regulatory analytical method for Readi-Cat 2 and Readi-Cat 2 Smoothie products.

Please respond by close of business Wednesday, July 22, 2015.

If you have any questions, please contact Frank Lutterodt, Regulatory Project Manager at (301)796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

LIBERO L MARZELLA
07/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA208036
NDA208143

MEETING REQUEST GRANTED

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains RD.
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

- Barium Sulfate (Readi-Cat2, Readi-Cat 2 Smoothie) and
- Barium Sulfate (EZ-HD)

We also refer to your June 26, 2015, correspondence requesting a Type A meeting to discuss plan for submitting Pediatric Study Plan for the Barium Sulfate products. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A teleconference.

The teleconference is scheduled as follows:

Date: July 30, 2015
Time: 12 Noon to 1:00 PM
Phone Arrangements: Call-in number will be provided prior to the teleconference

CDER Participants:
Libero Marzella, M.D., Ph.D., Director, DMIP
Alexander Gorovets, Deputy Director, DMIP
Nushin Todd, M.D., Clinical Team Leader/Associate Director for Labeling
Brenda Ye, M.D., Medical Officer, DMIP
Denise Pica-Branco Ph.D., Senior Regulatory Health Project Manager DPMH
Alyson Karesh, M.D., Medical Officer, DPMH
Tamara Johnson, M.D., Lead Medical Officer, DPMH
Frank Lutterodt, M.S., Regulatory Project Manager, DMIP

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

We acknowledge receipt of the meeting package included with the meeting request. Submit six desk copies to me as soon as possible.

Frank Lutterodt
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5483
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

FRANK A LUTTERODT
07/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208143

INFORMATION REQUEST

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd.
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 18, 2015, received December 18, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v).

We have the following information request:

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), an Initial Pediatric Study Plan (iPSP) must be submitted within 60 days of an End of Phase (EOP2) meeting. In the absence of an EOP2 meeting, an iPSP should be submitted no later than 210 days before submission of an NDA, BLA, or supplement. The iPSP must contain an outline of planned pediatric studie(s) (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); a request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format.

We note that you have not complied with the requirement to submit an iPSP. You must therefore submit an iPSP within 30 days of the date of this letter.

For additional guidance on the timing, content, and submission of an iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

If you have any questions, please contact Frank Lutterodt, Regulatory Project Manager, at (301)796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

LIBERO L MARZELLA
05/27/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208143

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bracco Diagnostics Inc.
259 Prospect Plains Rd.
Building H
Monroe Township, NJ 08831

ATTENTION: Melanie Benson
Director, US Regulatory Operations

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated and received December 18, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Barium Sulfate Oral Suspension, 2% (w/v).

We also refer to your correspondence dated and received January 8, 2015, requesting review of your proposed proprietary names, Readi-Cat 2 and Readi-Cat 2 Smoothie.

We have completed our review of the proposed proprietary names, Readi-Cat 2 and Readi-Cat 2 Smoothie and have concluded that they are conditionally acceptable.

If <u>any</u> of the proposed product characteristics as stated in your January 8, 2015, submission are altered prior to approval of the marketing application, the proprietary names should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Vasantha Ayalasomayajula, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-5035. For any other information regarding this application, contact Alberta Warren Davis, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

TODD D BRIDGES
03/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208-143

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd.
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 11, 2014, received December 11, 2014, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Readi-Cat 2 (Barium sulfate suspension, 2% w/v).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) , this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard.**

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 6, 2015.

During our filing review of your application, we identified the following potential review issues:

Microbiology

1. We refer to document M-010 in Module 3.2.P.5.2. This document was provided in French and the English translation should be submitted.
2. Provide a summary of the product development studies that determined the appropriate preservative content for the formulations. Submit the USP<51> method summary and results

from at least 3 batches of drug product. These summary results should confirm the preservative effectiveness from at least one batch at the minimum preservative contents from the product specification.

3. Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

LIBERO L MARZELLA
02/20/2015

From: Benson Melanie
To: Ayalasomayajula, Vasantha
Subject: RE: Information Request: Bracco Proprietary Name Requests
Date: Wednesday, January 28, 2015 8:46:09 AM

Dear Ms Ayalasomayajula,

I contacted my colleagues regarding your request below and they could offer no additional information to that which may be found in sections 3 (Derivation of Proprietary Name) and 4 (Intended Meaning of Proprietary Name Modifiers) of the respective Request for Proprietary Name Review documents. I have summarized below a more succinct response to your request.

For **E-Z-HD** (barium sulfate) powder for suspension, 98% (w/w), Bracco is requesting to maintain the use of this name as it is well recognized (has been in use since market introduction in 1980), there are no current data to indicate medication errors or name confusion with other named drugs (please see E. Applicant's Assessments of Proprietary Name, Packaging, and/or Labeling of the Request for Proprietary Name Review document for additional information) and the proprietary name combines the name of the original marketing company (E-Z-EM) and the high density (HD) weight of barium contained in the product, both in its powdered (98%) and reconstituted (up to 234%) forms.

For **Readi-Cat 2 and Readi-Cat 2 Smoothie** (barium sulfate) suspension, 2.0% (w/v), Bracco is requesting to maintain the use of these names as they are well recognized (have been in use since market introduction in 1985 and 1998, respectively), there are no current data to indicate medication errors or name confusion with other named drugs (please see E. Applicant's Assessments of Proprietary Name, Packaging, and/or Labeling of the Request for Proprietary Name Review document for additional information). The proprietary name combines the readiness for use of the product (READI), the modality of use for the product (Computed Tomography (formerly known as Computed Axial Tomography), (CAT) and the concentration of the product, 2% (2). For the SMOOTHIE line, the modifier is suggestive of the appearance and taste similar to smoothie beverages.

Please let me know if this addresses your request. As the information is already in the respective Request for Proprietary name Review documents submitted under the respective NDAs, please also let me know if it is still necessary to resubmit this information to each request.
Please contact me if you have any further questions or require additional information in support of these reviews.
Best regards,
Melanie Benson
Bracco Diagnostics Inc.

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Monday, January 26, 2015 1:56 PM
To: Benson Melanie
Subject: Information Request: Bracco Proprietary Name Requests

Ms.Benson,

For each proposed proprietary name you intend to submit for Agency's review of barium sulfate products, please provide a rationale for using these proposed trade names.

Please submit this information to each of the proprietary name review request in addition to email submission.

We kindly ask to submit this information by closing of business day on Tuesday, January 27th, 2015.

Thank You.

****

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Friday, January 23, 2015 7:57 AM
To: Ayalasomayajula, Vasantha
Subject: RE: Bracco Proprietary Name Requests

You are very welcome.

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Friday, January 23, 2015 7:55 AM
To: Benson Melanie
Subject: RE: Bracco Proprietary Name Requests

Thank you Ms.Benson.
Vasantha

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Friday, January 23, 2015 7:51 AM
To: Ayalasomayajula, Vasantha
Cc: Jenkins, Darrell; Flowers, Louis
Subject: RE: Bracco Proprietary Name Requests

Dear Ms Ayalasomayajula,

Thank you for your correspondence. This information requested in your email is provided herein. All submissions will include this information in section *3. Derivation of Proprietary Name* of the Request for Proprietary Name Review document, going forward. We will also include this information in the cover letter for complete transparency.

The proprietary name E-Z-HD has been used commercially since market introduction in 1980.

The proprietary name Readi-Cat 2 has been used commercially since market introduction in 1985.

The proprietary name Readi-Cat 2 Smoothie has been used commercially since 1998. (Banana was the first flavor, introduced in 1998.)

Please contact me if you have any further questions or require additional information in support of these reviews.
Best regards,
Melanie Benson
Bracco Diagnostics Inc.

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Thursday, January 22, 2015 5:12 PM
To: Benson Melanie
Cc: Jenkins, Darrell; Flowers, Louis
Subject: RE: Bracco Proprietary Name Requests

Dear Ms. Benson,

DMEPA would like to know that for each proposed proprietary name that you intend to submit to submit for Agency's review for barium sulfate products, please provide information regarding how long those products have been on the market in US bearing these names? For example, you submitted the proposed proprietary name E-Z HD. How long was the product used in US under this name?

Thanks,

****

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)
Email: Vasantha.ayalasomayajula@fda.hhs.gov

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Friday, January 09, 2015 7:44 AM
To: Ayalasomayajula, Vasantha
Subject: Bracco Proprietary Name Requests

Dear Ms Ayalasomayajula,

Please find attached courtesy copies of the two proprietary name requests submitted to the respective NDAs yesterday, through the FDA portal.

The PIND submissions were withdrawn on January 7, 2015 (paper); if you would like a courtesy of the withdrawal letters, please let me know. Please contact me if you have any questions.

Best regards,
Melanie Benson
Bracco Diagnostics Inc.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

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

/s/

VASANTHA S AYALASOMAYAJULA
01/28/2015

From: Benson Melanie
To: Ayalasomayajula, Vasantha
Cc: Jenkins, Darrell; Flowers, Louis
Subject: RE: Bracco Proprietary Name Requests
Date: Friday, January 23, 2015 7:51:05 AM

Dear Ms Ayalasomayajula,

Thank you for your correspondence. This information requested in your email is provided herein. All submissions will include this information in section *3. Derivation of Proprietary Name* of the Request for Proprietary Name Review document, going forward. We will also include this information in the cover letter for complete transparency.

The proprietary name E-Z-HD has been used commercially since market introduction in 1980.

The proprietary name Readi-Cat 2 has been used commercially since market introduction in 1985.

The proprietary name Readi-Cat 2 Smoothie has been used commercially since 1998. (Banana was the first flavor, introduced in 1998.)

Please contact me if you have any further questions or require additional information in support of these reviews.
Best regards,
Melanie Benson
Bracco Diagnostics Inc.

From: Ayalasomayajula, Vasantha [mailto:Vasantha.Ayalasomayajula@fda.hhs.gov]
Sent: Thursday, January 22, 2015 5:12 PM
To: Benson Melanie
Cc: Jenkins, Darrell; Flowers, Louis
Subject: RE: Bracco Proprietary Name Requests

Dear Ms. Benson,

DMEPA would like to know that for each proposed proprietary name that you intend to submit to submit for Agency's review for barium sulfate products, please provide information regarding how long those products have been on the market in US bearing these names? For example, you submitted the proposed proprietary name E-Z HD. How long was the product used in US under this name?

Thanks,

****

Sincerely,
Vasantha Ayala
Senior Regulatory Project Manager
Office of Surveillance and Epidemiology | Project Management Staff
Ph: 240-402-5035 (O)

Email: Vasantha.ayalasomayajula@fda.hhs.gov

From: Benson Melanie [mailto:Melanie.Benson@diag.bracco.com]
Sent: Friday, January 09, 2015 7:44 AM
To: Ayalasomayajula, Vasantha
Subject: Bracco Proprietary Name Requests

Dear Ms Ayalasomayajula,

Please find attached courtesy copies of the two proprietary name requests submitted to the respective NDAs yesterday, through the FDA portal.

The PIND submissions were withdrawn on January 7, 2015 (paper); if you would like a courtesy of the withdrawal letters, please let me know. Please contact me if you have any questions.

Best regards,
Melanie Benson
Bracco Diagnostics Inc.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

The information contained in this e-mail and any attachments is confidential and may also be privileged. If you are not the named recipient please notify the sender immediately and delete it from your files. Do not disclose the contents to any other person, use it for any purpose, or store or copy the information in any medium.

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

/s/

VASANTHA S AYALASOMAYAJULA
01/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208143

NDA ACKNOWLEDGMENT

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Rd.
Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Readi-Cat2, Readi-Cat 2 Creamy Vanilla Smoothie, Readi Cat 2 Berry Smoothie, Readi-Cat 2 Banana Smoothie, Readi-Cat 2 Mochaccino Smoothie (barium sulfate suspension, 2%(w/v)

Date of Application: December 18, 2014

Date of Receipt: December 18, 2014

Our Reference Number: NDA 208143

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2015 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling 21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Mr. Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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/

ALBERTA E DAVIS WARREN
12/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND115, 090

MEETING MINUTES

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
259 Prospect Plains Road, Bldg. H-
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Barium Sulfate Medical Imaging Agents.

We also refer to the teleconference between representatives of your firm and the FDA on Thursday, October 23, 2014. The purpose of the meeting was to discuss your plan to submit CMC information for barium sulfate drug substance in the initial NDA filing in December, 2014.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: Thursday, October 23, 2014, 2:00-3:00PM
Meeting Location: Teleconference

Application Number: PIND115090
Product Name: Barium Sulfate Imaging Products
Indication: Barium Sulfate is localized, and provide contrast to help detect and evaluate abnormalities of the esophagus, the stomach, and/or the small intestine
Sponsor Name: Bracco Diagnostics Inc.

FDA ATTENDEES
Libero Marzella, M.D.,Ph.D., Director, Division of Medical Imaging Products (DMIP)
Alexander Gorovets, M.D., Deputy Director, Division of Medical Imaging Products (DMIP)
Brenda Ye, M.D.,Clinical Team Leader, Division of Medical Imaging Products (DMIP)
Eric Duffy, Ph.D., Director, DNDQA III
Danae Christodoulou, Ph.D., Acting Branch Chief, DNDQA III
Harris Orzach, M.D., Medical Officer, Division of Medical Imaging Products (DMIP)
Kyong (Kaye) Kang, Pharm. D., Chief, Project Management Staff, DMIP
Frank Lutterodt, M.S., Regulatory Project Manager

SPONSOR ATTENDEES
Andrew Betournay, Head, Global Regulatory Affairs
Maria Luigia Storto, M.D., Executive Director, Medical Planning and Management
John Spaltro, Ph.D., Senior Director, Global Regulatory Affairs
Adrianne Setton, Ph.D., Associate Director, Regulatory Affairs

1.0 BACKGROUND

On September 26, 2014, Bracco Diagnostics Inc., requested a meeting to discuss their plan and receive feedback on filing CMC information for barium sulfate drug substance in the initial NDA filing to be submitted in December 2014. FDA provided preliminary response to several questions in the Type A meeting request, dated September 26, 2014 and following interactions on October 13 and October 16; FDA also offered further comment on proposed manufacturing process flow diagram(s) provided in the Type A meeting request.

The following section constitutes the discussions at the teleconference and clarification of items in FDA's October 22, 2014 preliminary responses.

2. DISCUSSION

Following introductions, Bracco (the sponsor) began the meeting discussion by thanking FDA for granting the requested meeting and for providing preliminary response to questions posed in the submitted meeting requests. The sponsor then proceeded to review their understanding of several key points as indicated in FDA Meeting Preliminary Comments. The responses to FDA's Preliminary comments and a summary of meeting discussion are detailed below.

FDA CMC Comments (Preliminary Response):

We acknowledge your e-mail communication of October 16, 2014 in which you stated that Chemistry, Manufacturing and Controls (CMC) information regarding the drug substance Barium Sulfate (BaSO4) will be submitted in your initial NDA and cross referenced to your subsequent applications. This is acceptable.

Bracco Response: We acknowledge FDA acceptance of our proposed approach to file barium sulfate drug substance information in our initial NDA and that this information will be cross referenced in subsequent submission.

Meeting Discussion: FDA agreed to the proposed approach to filing the drug substance information as part of the NDA, FDA also indicated that use of a Drug Master File (DMF) or NDA Rolling Review could enable earlier review of the drug substance information and scheduling of a pre-approval inspection of the Cimbar site located in Chatsworth, GA. Bracco indicated their intent to file 2 NDAs in December 2014, including drug substance information for both 1 micron and 10 micron pharmaceutical grade barium sulfate. FDA concurred with this approach to file drug substance (1 micron and 10 micron) information as part of the initial NDA. This information would be cross-referenced in subsequent submissions for all barium sulfate products.

The sponsor acknowledged the FDA recommendation to consider Rolling Review for the submitted NDAs, however they intend to proceed with their plan to submit 2 entire NDAs (E-Z-HD and ReadiCat) to FDA in December 2014.

FDA: We have the following comments with respect to the Flow Charts of BaS04 manufacture, Figure 1 and Figure 2.

1. **We do not agree with the designation of "10 mm Pharmaceutical Grade BaS04, USP" as the starting material and the micronized "1 mm Pharmaceutical Grade BaS04, USP" as the drug substance. The starting (raw) material should be incoming 10 mm Industrial Grade BaS04 and the processing steps you describe in Fig. 1 should be performed under GMPs.**

   Post-meeting note: Note the edit of "mm" to "µm" in the FDA response above.

Bracco Response: The drug product E-Z-HD (which is the drug product included in the original NDA) is formulated with a blend of 1micron and 10 micron pharmaceutical grade barium sulfate drug substances. All other barium sulfate drug products (NDAs to be cross-referenced) are formulated using 1 micron pharmaceutical grade barium sulfate drug substance.

Bracco will file information for two (2) barium sulfate drug substances (10 micron pharmaceutical grade and1micron pharmaceutical grade) in the initial NDA. The sponsor clarified that processing for each drug substance, from "Industrial Grade Starting Material" to final drug substance (1 micron and 10 micron pharmaceutical grade barium sulfate) as indicated in Figure 1 and 2 are currently performed under GMPs and that they will provide a process description for each drug substance beginning with incoming industrial grade 10 micron barium sulfate as Starting Material in the initial NDA.

2. **Identify the suppliers of "Industrial Grade BaSO4". Barium sulfate inorganic impurities may be varied based on the origin of the raw material, which is most likely mined.**

   Bracco Response: We currently plan to provide this information as part of the drug substance information included in the initial NDA.

   Meeting Discussion: FDA acknowledged the Bracco's plan to provide information on the origin of source raw materials (barite) in the initial NDA. FDA further requested information, including address and FEI number for the CIMBAR Facility, and queried whether the facility was currently a registered establishment with FDA. Bracco acknowledged that the CIMBAR facility is located in Chatsworth, GA and is currently a registered establishment with the FDA, and also indicated that this information for the CIMBAR facility will be included in the initial NDA.

3. **Establish specifications for the incoming raw material, and the drug substance "10mm Pharmaceutical Grade BaS04, USP" and micronized "1 mm Pharmaceutical Grade BaS04, USP".**

   Bracco Response: We will plan to provide specifications for incoming raw material, 1 micron and 10micron pharmaceutical grade barium sulfate as part of the drug substance information included in the initial NDA.

   Meeting Discussion: FDA acknowledged the Bracco's plan to provide this information in the initial NDA.

4. **We consider testing of BaS04 according to the USP monograph the minimal quality requirements for the drug substance. Provide additional specifications, including limits of heavy metals, e.g., As, Cd, Pb, Hg, other divalent metals, e.g., Ca, Sr, Fe, Ni,**

Co, monovalent Na, K and limits if ions e.g., sulfites ($SO_3^{2}\cdot$), sulfides (S^{2-}),), chlorides (Cl^-), Nitrates (NO3) and phosphates ($PO4^{3-}$) to control inorganic impurities that are likely to be present. Consider American Chemical Society specifications and USP<232> and USP <233> . Provide justification for your proposed specifications with a risk assessment for potential inorganic impurities. For example, in Fig. 2, monitor the levels of Zirconium in your micronized drug substance that may arise from the ZrO beads used in the process.

Bracco Response: We will plan to provide justification for our proposed specifications for the 1 micron and 10 micron pharmaceutical grade barium sulfate drug substances as part of the initial NDA. A risk assessment for potential inorganic impurities, supporting our proposed drug substance specifications will also be included in the initial NDA.

Routine testing of zirconium levels is currently performed for the 1 micron pharmaceutical grade barium sulfate that is micronized using zirconium beads. This zirconium level data, in addition to data on propylene glycol levels (added as a processing aid for 1 micron pharmaceutical grade barium sulfate), is included as part of the justification supporting proposed specifications for the 1 micron pharmaceutical grade barium sulfate.

Meeting Discussion: FDA acknowledged the Bracco plan to provide justification for proposed specifications and a risk assessment to address potential inorganic impurities as part of the initial NDA. FDA indicated preference for testing of heavy metals using Inductively Coupled Plasma (ICP) methodology. Bracco indicated that method has been used to characterize elemental impurities in incoming raw material and that they intend to provide this information as part of the initial NDA. FDA acknowledged this plan.

5. **We strongly encourage you to develop HPLC (high performance ion chromatography with electrochemical detection) for assay of your $BaSO_4$ aud detection of sulfite and sulfide ions.**

Bracco Response: We will take the FDA recommendation to develop an HPLC method for assay of barium sulfate under advisement at this time. A currently performed chromatographic method may be extendable to other analytes as indicated by FDA, yet further assessment, method development and validation will be required prior to implementation. We will initiate this activity yet expect that this will not be part of the initial NDA filing.

Meeting Discussion: FDA acknowledged the Bracco plan to perform further assessment of the existing HPLC method for assay of barium sulfate, sulfite and sulfide ions. FDA further acknowledged that these activities would require additional time and therefore this information would not be required in the initial NDA, but could be submitted as a supplement to the initial NDA filing. Bracco will plan to file the initial NDA without this information and will plan to provide information on a new HPLC method as a supplement to the initial NDA. FDA acknowledged this plan.

6. **Provide a three-point particle size distribution for yourmicronized drug substance.**

Bracco Response: We will to provide this data as part of the drug substance information included in the initial NDA.

Meeting Discussion: FDA indicated that D10, D50, D90 particle size distribution data was adequate to fulfill this request. Bracco acknowledged that this information would be provided in the initial NDA.

FDA Additional Comments

The Pediatric Research Equity Act (PREA) requirements will need to be fulfilled for the proposed barium sulfate NDAs. Please comment on your plan toward PREA fulfillment at the meeting.

Bracco Response: In order to fulfill pediatric requirements we intend to use the same approach as used to support use in adult populations. Our plan is to provide published literature and post-marketing information in support of pediatric use as part of module 5 for FDA review. For barium sulfate products not relevant for use in pediatric population(s), we intend to seek full-waiver of pediatric requirements as defined under PREA.

Meeting Discussion: Bracco provided further detail with regard to the current plan to support pediatric use of barium sulfate products with the same literature and guidelines-based approach used in adults and making specific reference to guidelines issued by the American College of Radiology (ACR) in collaboration with the Society of Pediatric Radiology (SPR); feed-back from experts is being considered in some specific areas. Bracco is considering pursuing a full waiver for barium products which do not cover a clinical need in pediatric patients (such as products for fecal tagging during CT colonography, commonly used in screening programs of colorectal cancer). FDA indicated that Bracco should include, as part of the rationale for waiver of pediatric requirements, an assessment of alternative imaging modalities that are currently used in pediatric patients that eliminate the need for barium sulfate products. FDA also offered recommendation to Bracco to consider a request for deferral of pediatric requirements under PREA in the initial NDA. Bracco acknowledged this recommendation from FDA and indicated their intent to follow-up in writing subsequent to the meeting.

END

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

/s/

FRANK A LUTTERODT
11/21/2014