

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208036Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208036

SUPPL #

HFD # 160

Trade Name E-Z-HD

Generic Name barium sulfate powder for oral suspension 98% (w/w)

Applicant Name Bracco Diagnostics Inc

Approval Date, If Known January 11, 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)

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# 006624

METABARIN SUSPENSION

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 to support the safety and effectiveness of E-Z-HD. 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

YES
Explain:

! NO
! Explain:

Investigation #2

!

!

YES
Explain:

! NO
! Explain:

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

YES NO

If yes, explain:

Name of person completing form: **Frank Lutterodt**
Title: **Senior Regulatory Project Manager**
Date: **10/25 /16**

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
10/25/2016

CHARLES J GANLEY
10/25/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research



DATE: 10/25/16

TO: E-Z-HD (Barium Sulfate) For Oral Suspension File (NDA 208036)

FROM: CDER Exclusivity Board

SUBJECT: Five-Year Exclusivity Recommendation for E-Z-HD (Barium Sulfate) For Oral Suspension (NDA 208036)

SUMMARY

This memorandum addresses whether E-Z-HD (barium sulfate) for oral suspension (NDA 208036), approved on January 11, 2016, comprises a drug substance that contains no active moiety that has been previously approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and thereby qualifies for 5-year new chemical entity (NCE) exclusivity.¹

Upon review of the regulatory documents related to NDA 208036 and other relevant documents, the Exclusivity Board (Board) within the Center for Drug Evaluation and Research (CDER) has determined that the drug substance (or active ingredient) contained in E-Z-HD, barium sulfate, contains the active moiety barium, which has been previously approved by FDA in an application submitted under section 505(b) of the FD&C Act. Accordingly, the Board recommends that E-Z-HD be deemed ineligible for 5-year NCE exclusivity.

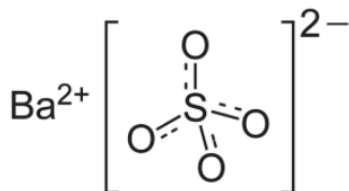
A discussion of the Board's reasoning follows.

I. FACTUAL AND PROCEDURAL BACKGROUND

On December 11, 2014, Bracco Diagnostics Inc. submitted NDA 208036 for E-Z-HD (barium sulfate) for oral suspension. E-Z-HD is a radiographic contrast agent indicated for use in double-

¹ See sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act; see also 21 CFR 314.108(a).

contrast radiographic examinations of the esophagus, stomach, and duodenum to help visualize the gastrointestinal (GI) tract in patients 12 years and older.² E-Z-HD is supplied as a fine white powder for oral suspension (98% w/w barium sulfate) for oral administration. The active ingredient, barium sulfate, is designated chemically as BaSO₄, with a molecular weight of 233.43 grams(g)/mole, and a density of 4.5 g/cm³.³ Barium sulfate is the sulfate salt of barium, an alkaline earth, divalent metal. The chemical structure is below.



Barium sulfate is classified pharmacologically as a radiologic contrast agent, (b) (4)
Due to its high atomic number, barium is opaque to X-rays and therefore acts as a positive contrast agent for radiographic studies.⁵ As described in the Cross-Discipline Team Leader (CDTL) Review of the E-Z-HD NDA, barium sulfate has been used to opacify the GI tract since the early 1900s.⁶

At least one drug product, Metabarin, containing barium sulfate as its active ingredient has been previously marketed under an NDA in the United States. On December 2, 1948, C.S.C. Pharmaceuticals, a division of Commercial Solvents Corporation, submitted an application (NDA 6624) for Metabarin under section 505(b) of the FD&C Act. The application became effective on December 9, 1948.^{7,8} As described in NDA 6624, Metabarin, an oral suspension, is a barium contrast medium used in the roentgenographic (X-ray) visualization of the esophagus, stomach, and intestinal tract.⁹ The NDA indicates that Metabarin contains 99.656% barium sulfate (USP) along with a suspending agent, intended to provide a high degree of dispersibility,

² See E-Z-HD Labeling, Section 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208036s000lbl.pdf.

³ See E-Z-HD Labeling, Section 11.

⁴ See NDA 208036, Division Director Summary Review (Jan. 4, 2016) at 2 and 6.

⁵ See E-Z-HD Labeling, Section 12.1.

⁶ NDA 208036, CDTL Review, (Jan. 4, 2016) at 2.

⁷ Under the FD&C Act in effect in 1948, NDAs submitted to FDA “bec[a]me effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpone[d] the effective date of the application to such time . . . as the Secretary deem[ed] necessary to enable him to study and investigate the application.” See section 505(c) of the FD&C Act of 1938 (Pub. L. 75-717). In the 1962 Amendments to the FD&C Act, such applications, which had “become effective” based, in part, on a demonstration of safety, were “deemed approved.” See section 107(c)(2) of the 1962 Amendments (Pub. L. 87-781).

⁸ A Notice of Opportunity for Hearing was published in 1970 proposing to withdraw approval of NDA 6624 (along with several other NDAs) on the grounds that the NDA-holders failed to make required reports under section 505(j) of the FD&C Act in effect at the time. 35 FR 2674 (Feb. 6, 1970). Receiving no requests for a hearing on the proposed withdrawal of approval of NDA 6624, later that year, FDA withdrew approval by notice in the Federal Register. 35 FR 11929 (July 24, 1970).

⁹ NDA 6624, Diagnostic Advantages, at 4; see also Metabarin Labeling.

and two flavoring agents.¹⁰ The Metabarin labeling states that Metabarin is (b) (4)

II. STATUTORY AND REGULATORY BACKGROUND

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an application submitted under Section 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective under the conditions of use described in the labeling.¹² The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) described abbreviated pathways for approval of drug products that allow an applicant to rely to the maximum extent possible on what is already known about a drug. These are described in sections 505(b)(2) (which established the 505(b)(2) application pathway) and 505(j) (which established the Abbreviated New Drug Application (ANDA) pathway) of the FD&C Act.¹³ At the same time, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation, including exclusivity to protect certain products from competition for specified periods of time.

Sections 505(j)(5)(F)(ii) and (c)(3)(E)(ii) of the FD&C Act describe a 5-year exclusivity period for certain drugs, during which 505(j) and 505(b)(2) applications may not be submitted for review (i.e., 5-year NCE exclusivity). Specifically, Section 505(j)(5)(F)(ii) of the FD&C Act provides, in relevant part, as follows:

If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section ¹⁴

FDA's regulations implementing the 5-year NCE provision of the Hatch-Waxman Amendments, at 21 CFR 314.108, provide that:

If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that

¹⁰ NDA 6624, Part 3 (A Full Statement of the Composition of Metabarin) at 1 and Part 4(a) (A Full Description of the Methods Used in the Manufacture, Processing, and Packing of Metabarin) at 1.

¹¹ NDA 6624, Diagnostic Advantages at 4.

¹² Section 505(b)(1) of the FD&C Act.

¹³ The precise nature of, and requirements established by, these pathways are not relevant to our analysis of and conclusions with regard to the issues discussed in this recommendation.

¹⁴ See also section 505(c)(3)(E)(ii) of the FD&C Act (containing the same language for 505(b)(2) applications).

contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application ¹⁵

The regulations define “new chemical entity” as:

[A] drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.”¹⁶

“Active moiety,” in turn, is defined as:

[T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.¹⁷

“Approved under section 505(b)” is defined as:

[A]n application submitted under section 505(b) and approved on or after October 10, 1962, or an application that was “deemed approved” under section 107(c)(2) of Pub. L. 87-781.¹⁸

In the Agency’s regulations governing new drug applications, FDA has defined “drug product” as:

[A] finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.¹⁹

In the same regulation, “drug substance” is defined as:

[A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.²⁰

III. DISCUSSION

The FD&C Act and FDA’s regulations preclude eligibility for 5-year NCE exclusivity when the drug contains an active moiety that has been previously approved in an application under section

¹⁵ 21 CFR 314.108(b)(2).

¹⁶ 21 CFR 314.108(a).

¹⁷ Id.

¹⁸ Id.

¹⁹ 21 CFR 314.3(b).

²⁰ Id.

505(b) of the FD&C Act. E-Z-HD contains barium sulfate, the sulfate salt of barium, as its active ingredient. The active moiety in E-Z-HD is barium.²¹ Likewise, barium sulfate is the active ingredient and barium is the active moiety in Metabarin. As noted above, the NDA for Metabarin became effective in 1948 and was deemed approved through the 1962 Amendments to the FD&C Act. FDA's regulations make clear that a drug product that is the subject of an application that was "deemed approved" under the 1962 Amendments is considered to be approved in an application under section 505(b) of the FD&C Act for purposes of determining whether certain products qualify for 5-year NCE exclusivity under section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act.²² Therefore, because the active moiety in E-Z-HD has been previously approved in an application under section 505(b) of the FD&C Act, i.e., the Metabarin NDA, E-Z-HD does not contain a new chemical entity and is not eligible for 5-year NCE exclusivity.

IV. CONCLUSION

For the reasons described above, and notwithstanding any prior assessments made,²³ the Board has determined that the active moiety in E-Z-HD has been previously approved. Accordingly, the Board recommends that E-Z-HD be deemed ineligible for 5-year NCE exclusivity. The Board further recommends that the Exclusivity Summary for E-Z-HD be revised to reflect the analysis in this memorandum.²⁴

Sanjay
Sitlani -A

Digitally signed by Sanjay
Sitlani -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Sanjay Sitlani -A,
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²¹ Under 21 CFR 314.108(a), the active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester or salt. Upon excluding the sulfate salt anion, the resulting active moiety is barium.

²² Id.

²³ See, e.g., NDA 208036, RPM Filing Review, classifying the NDA as Type 7 for Drug Already Marketed Without an Approved NDA.

²⁴ The application was based solely on published literature, marketing surveillance, and publicly available information on barium sulfate products; no preclinical or clinical studies were conducted or sponsored by the applicant for approval of this application. See NDA 208036, CDTL Review at 2. Therefore, this application is also not eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act.

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
10/25/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208036 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: EZ-HD Established/Proper Name: Barium Sulfate 98% w/w Dosage Form: Powder for 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 draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 1/8/16 <i>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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is January 11, 2016		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ 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) Assessment 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	☐ Rx-to-OTC full switch
☐ Rolling Review	☐ Rx-to-OTC partial switch
☐ Orphan drug designation	☐ Direct-to-OTC
☐ Breakthrough Therapy designation	

(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

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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 <i>(approvals only)</i>	☐ Yes ☐ No
❖ Public communications <i>(approvals only)</i>	
• 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 <i>(approvals only)</i>	☒ 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 11, 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	March 27, 2015 March 25, 2015
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: ☐ None DMEPA: ☐ None 07/06/2015 DMPP/PLT (DRISK): ☐ None OPDP: ☐ None 1/5/16 SEALD: ☐ None 12/23/2015 CSS: ☐ None Product Quality ☐ None 11/18/2015 Other: ☐ None DPMH 11/30/2015
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	December 21, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ 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 (<i>indicate date</i>) - If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) Date reviewed by PeRC <u>10/21/2015</u> 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) (<i>include only the completed template(s) and not the meeting minutes</i>) - CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ 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.) (<i>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</i>)	
❖ 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 (<i>indicate date of mtg</i>) - Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) - EOP2 meeting (<i>indicate date of mtg</i>) - Mid-cycle Communication (<i>indicate date of mtg</i>) - Late-cycle Meeting (<i>indicate date of mtg</i>) - Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	☒ N/A or no mtg ☐ No mtg 10/23/14 ☒ No mtg ☒ N/A ☒ N/A N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 1/11/15
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 1/04/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 1/04/16
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical	
❖ Clinical Reviews	

Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical review(s) (<i>indicate date for each review</i>)	08/23/15
Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ 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 (<i>indicate date of review/memo</i>)	08/23/15 see Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 08/27/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 08/12/15
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
- ADP/T Review(s) (<i>indicate date for each review</i>)	☐ No separate review 1/6/16
- Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
- Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 07/21/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☐ None 11/18/15
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None Drug Product-11/18/15 Drug Substance-11/18/15 Microbiology-07/23/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☐ None BioPharmaceutics 11/02/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/21/15
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ 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 (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done (<i>Send email to CDER OND IO</i>)
❖ 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 <i>Application Product Names</i> 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

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/s/

FRANK A LUTTERODT
01/19/2016

From: [Benson Melanie](#)
To: [Lutterodt, Frank A](#)
Subject: RE: PMC for EZ-HD
Date: Monday, January 11, 2016 3:01:39 PM

Dear Mr Lutterodt,

Bracco agrees to that stated below.

Best regards, Melanie

From: Lutterodt, Frank A [mailto:Frank.Lutterodt@fda.hhs.gov]
Sent: Monday, January 11, 2016 1:59 PM
To: Benson Melanie
Subject: PMC for EZ-HD
Importance: High

Dear Melanie,

We are proposing the following milestone date for Bracco's commitment to do the following:

Use the USP method to screen [REDACTED] (b) (4)
[REDACTED] for heavy metals, [REDACTED] (b) (4)

and provide data from your validation studies with revised specifications.

Final Report Submission: January 2017

Let us know ASAP if Bracco agrees.

Thank you,

Frank

Frank Lutterodt, M.S. | 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.

From: [Benson Melanie](#)
To: [Lutterodt, Frank A](#)
Subject: EZHD labeling
Date: Monday, January 11, 2016 11:36:11 AM

Hi Frank,

Bracco is in agreement with adding an additional bullet under Contraindications:

4 CONTRAINDICATIONS

E-Z-HD is contraindicated in patients:

- Known or suspected perforation of the GI tract
- **Known obstruction of the GI tract**
- At high risk of GI perforation such as those with a recent prior GI perforation, acute GI hemorrhage or ischemia, toxic megacolon, severe ileus, post GI surgery or biopsy, acute GI injury or burn, or recent radiotherapy to the rectum or prostate
- At high risk of aspiration such as those with prior aspiration, tracheo-esophageal fistula, or obtundation
- With known severe hypersensitivity to barium sulfate or any of the E-Z-HD excipients

Best regards, Melanie

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.

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/s/

FRANK A LUTTERODT
01/19/2016

From: [Lutterodt, Frank A](#)
To: [Benson Melanie \(Melanie.Benson@diag.bracco.com\)](mailto:Melanie.Benson@diag.bracco.com)
Subject: Recommendations for Barium Sulfate Container Label
Date: Monday, January 04, 2016 9:04:00 AM

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 11, 2014, received December 11, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Act for EZ-HD (barium Sulfate) powder for oral suspension 98% (w/w). We have the following information requests:

Container Label:

1. We recommend adding route of administration to the primary display panel which would state: "For Oral Use Only" due to wrong route of administration errors that have occurred with this drug (i.e., intravenous administration instead of oral), which could potentially inflict great harm.
2. We recommend changing the background color of the label as the label looks very similar to other barium sulfate products, such as Volumen and Readi-Cat 2 (Vanilla Smoothie), which may result in selection of the wrong product. In fact, post-marketing experience demonstrated that E-Z HD was confused with Readi-Cat 2.

Please submit the revised Label no later than Wednesday, January 6, 2015.

Sincerely,

Frank
Frank Lutterodt, M.S.,
Senior Regulatory Project Manager
Division of Medical Imaging Products
CDER
(301)-796-4251

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/s/

FRANK A LUTTERODT
01/04/2016

From: [Lutterodt, Frank A](#)
To: [Benson Melanie \(Melanie.Benson@diag.bracco.com\)](mailto:Melanie.Benson@diag.bracco.com)
Subject: Information Request for barium products
Date: Tuesday, December 15, 2015 2:41:00 PM
Importance: High

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 EZ-HD (barium sulfate for suspension, 98% (w/w) and Read-Cat (Read-Cat 2 and Read-Cat 2 Smoothie (barium sulfate suspension, 2%(w/v))).

We have the following information requests:

Readicat

You initially requested pediatric deferral in NDA 208143. In your Pediatric Development Plan submitted as an amendment to the NDA, you requested full pediatric assessment without updating product labeling. Please propose pediatric dosing and provide supporting evidence. For a starting point of labeling discussion, we listed here dosing information from your pediatric use survey. Please confirm or clarify whether these are your proposed pediatric dosing, and provide supporting evidence. A dose of 450 mL seems high for the younger pediatric patients (particularly 2-4 year olds). Provide information to support dosing, including any weight based dosing and data on gastric volumes and capacity in pediatric patients.

EZHD

Based on your pediatric survey, E-Z-HD is being used in clinical practice. We notice the survey does not distinguish between single contrast and double contrast studies. Please confirm or clarify. Please provide pediatric dosing recommendation for E-Z-HD and provide supporting evidence.

We request a prompt written response in order to continue our evaluation of your NDAs. Please respond no later than Friday, December 18, 2015.

Sincerely,

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

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/s/

FRANK A LUTTERODT
01/04/2016



NDA 208036

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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, 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).

On September 14, 2015, we received your major amendment to these applications. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 11, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 7, 2015.

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

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

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/s/

LIBERO L MARZELLA
09/17/2015



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 Read-Cat 2 and Read-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 (b) (4)
[REDACTED]
For use in Computed Tomography of the abdomen (b) (4)
[REDACTED]
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
Adrienne 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 (b)(4) 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 (b)(4) 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 (b)(4). 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 [REDACTED]

(b) (4)

[REDACTED]. 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. [REDACTED]

(b) (4)

[REDACTED] (b) (4)

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 ReadCat, 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 (b) (4) to the (b) (4) 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 (b) (4) 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 (b) (4) please use the teleconference information provided below:

Domestic: (b) (4)

Passcode: (b) (4)

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

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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 (b) (4)
[REDACTED]
For use in Computed Tomography of the abdomen (b) (4)
[REDACTED]

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
Adrienne 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 (b) (4) 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 (b) (4). 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 (b) (4) NDA for all barium products, we highly recommend that you submit results of the survey and your Pediatric Study Plan (PSP) to NDA 208036, (b) (4) 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 Read-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. (b) (4)

Does the FDA concur with Bracco plan?

FDA Response to Question 2

(b) (4)
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 (b) (4). 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>

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/s/

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

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/s/

LIBERO L MARZELLA
08/28/2015



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 (b) (4)
[REDACTED]
For use in Computed Tomography of the abdomen (b) (4)
[REDACTED]

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
Adrienne 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 (b) (4) 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 (b) (4). 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 (b) (4) NDA for all barium products, we highly recommend that you submit results of the survey and your Pediatric Study Plan (PSP) to NDA 208036, (b) (4) 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 Read-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. (b) (4)

Does the FDA concur with Bracco plan?

FDA Response to Question 2

(b) (4)
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 (b) (4). 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>

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/s/

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



NDA 208036

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 EZ-HD (barium sulfate for suspension, 98% (w/w)).

We have the following CMC information requests:

Drug Substance

1. Correct your revised [redacted] (b) (4)
2. Regarding a possible change in [redacted] (b) (4)
3. Regarding [redacted] (b) (4)
4. Provide batch data for [redacted] (b) (4) drug substance batches.
5. The particle size distribution specifications provided in the Quality Overall Summary differ from those in Module 3. Clarify what limits for D50 are proposed for the final DS specifications for both [redacted] (b) (4) and provide justification for the limits based on batch data. Add a numerical acceptance criteria for D10 and D90 to the specifications for [redacted] (b) (4) barium sulfate drug substances, as previously agreed with the

Agency. The current acceptance criteria “for information only” does not provide sufficient controls for the quality of this critical attribute.

Drug Product

1. Comparability: We reviewed your response to our request for quality information about the clinical E-Z-HD product used in the cited references (see below) and understand that the studies were not conducted with lots supplied by EZ-EM, but instead used the E-Z-HD product available on the market at the time. Therefore, provide quality information for the product available at the time (historical lots) to demonstrate comparability to your proposed commercial product.

Specifically, provide available quality information for the EZ-HD product on the market in the study regions (Israel, The Netherlands) during the timeperiod of the studies (1993, 2005). Include, in table format, barium sulfate source, barium sulfate particle size distribution, manufacturing sites (drug substance and drug product), product formulation (quantitative), product specifications (assay, pH, viscosity, loss on drying, suspendability, uniformity of dose and microbiology) and container/closure information. Describe differences compared to the proposed commercial product.

The referenced studies of interest are:

- a. Farber, E. et al, Published online 10.1148/radiol.2372041631 Radiology 2005; 237:535–540
- b. Ginai AZ, van Buuren HR, Hop WC, et al. Oesophageal varices: how reliable is a barium swallow? Br J Radiol 1993;66(784): 322–326.

The following information extracted from these publications provides details regarding the commercial product, market and timeframe to help narrow down the pertinent historical lots.

Farber: From November 2002 to May 2003, 61 patients were administered 50–100 mL of high-density barium sulfate, 60% wt/vol (E-Z HD; E-Z-Em, Westbury, NY) at Rambam Medical Center, Efron St, Haifa Israel.

Ginai: In the study published 1993, 119 patients were administered high-density barium sulphate(EZ.HD 250% wt/vol from EZEM Westbury Co., New York) at Erasmus University, Rotterdam, The Netherlands.

2. 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).

In addition to the quality information specific to the referenced studies (requested above), provide the following for E-Z-HD product:

- a. a timeline description of all the E-Z-HD (barium sulfate) powder for suspension 98% w/w for oral administration 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.).
3. To facilitate review of the batch data recently submitted for twenty seven (27) E-Z-HD product lots manufactured between 2011 and 2014 (Table D), tabulate the release test results as per Table B in file Batch Analysis in Section 3.2.P.5.4.
4. The data submitted on the E-Z-HD and barium sulfate lots in the Certificates of Analysis (COA) in Section 3.2.P.5.4 are not interpretable. Revise COAs to include a single typed page (not handwritten) which reports the test results from lot release testing per specification. Where several repeat measurements were made, report the average value. For example, refer to COA issued by (b) (4) for barium sulfate in Section 3.2.S.4.4 filename "Certificate of Analysis (b) (4)
5. Relocate the batch analysis data for the drug substance lots from the drug product section (3.2.P.5.4) to the drug substance section (3.2.S.4.4).
6. Drug Product Flavorings: Regarding the flavorings listed in Section 3.2.P.4.1 for E-Z-HD product –
 - 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 172.5 "Flavoring Agents and related substances").
 - c. Add CFR 172.5 compliance to each flavor specification (natural and artificial strawberry flavor, natural and artificial cherry flavor).
7. For the ongoing stability program and the post-approval stability program, provide a stability protocol, including storage conditions, timepoints and tests conducted, for the proposed shelf life of EZ-HD.
8. Drug Product specifications: revise the test column in Table A: Specification for E-Z-HD to read "Identification Barium Sulfate (FTIR)" , (b) (4) , "Suspendability (b) (4)" and "Barium Sulfate (b) (4)" to provide details regarding the test performed.

9. Describe the content of sodium, potassium and sorbitol in the barium sulfate products submitted in N208036 and N208143, including each flavor product (E-Z-HD, Readi Cat 2, and four flavors of Readi Cat 2 Smoothie).
 - a. Report total content for each (sodium, (b)(4) sorbitol) on a wt/vol basis and a wt/wt basis of the finished product. Sum the contributions from different sources in the formulation (e.g. (b)(4) sodium saccharine and sodium citrate).
 - b. Report total content in grams for each ((b)(4) sorbitol) in a single dose. Specify the dose used in the calculation.
 - c. Organize the information in tables where possible.
 - d. Include a minimum and maximum content based on the expected range of values in the excipients.
 - e. Describe the computation and inputs to the calculated content.

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

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/s/

LIBERO L MARZELLA
07/10/2015



NDA 208036

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 EZ-HD (barium Sulfate) powder for oral suspension 98% (w/w).

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

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/s/

LIBERO L MARZELLA
05/27/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208036

**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 11, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Barium Sulfate Powder for Suspension, 98% (w/w).

We also refer to your correspondence dated and received January 8, 2015, requesting review of your proposed proprietary name, E-Z-HD.

We have completed our review of the proposed proprietary name, E-Z-HD and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your January 8, 2015, submission are altered prior to approval of the marketing application, the proprietary name 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

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/s/

TODD D BRIDGES
03/27/2015



NDA 208-036

**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 E-Z-HD (barium sulfate for suspension, 98% (w/w)) powder for suspension, 98%w/w.

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 August 30, 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.

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

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/s/

LIBERO L MARZELLA
02/20/2015

**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

Meshawn Payne

George Greeley

Freda Cooner

Gregory Reaman

Peter Starke ([REDACTED] NON-RESPONSIVE)

Dionna Green

Belinda Hayes

Kevin Krudys

Maura O'Leary ([REDACTED] NON-RESPONSIVE)

Julia Pinto (Did not review [REDACTED] NON-RESPONSIVE)

Dianne Murphy

Andrew Mulberg (Did not review [REDACTED] NON-RESPONSIVE)

Agenda

9:00	NON-RESPONSIVE				
9:20	NON-RESPONSIVE				
9:30	NON-RESPONSIVE				
9:50	NON-RESPONSIVE				
10:10	NON-RESPONSIVE				
10:30	NON-RESPONSIVE				
10:50	NDA 208036	E-Z -HD (barium sulfate suspension) Assessment	DMP	Frank Lutterodt	Indicated for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum ^(b) ₍₄₎
11:00	NON-RESPONSIVE				
11:20	NON-RESPONSIVE				
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NON-RESPONSIVE

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 (b) (4)
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.

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
11/09/2015

From: Lutterodt, Frank A
To: [Benson Melanie \(Melanie.Benson@diag.bracco.com\)](mailto:Melanie.Benson@diag.bracco.com)
Subject: Information Request for Barium Sulfate NDA208036
Date: Thursday, October 01, 2015 12:04:00 PM

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 EZ-HD (barium sulfate for suspension, 98% (w/w)).

We have the following CMC information request:

Clarify the following discrepancy: (b) (4) your flavor supplier, submitted a Letter of Authorization to review their DMF (b) (4) for two flavors described as: (b) (4) cherry (b) (4) and (b) (4) strawberry (b) (4). However, your application provides specifications for these two flavors under a different description: natural and artificial cherry type flavor (code (b) (4)) and natural and artificial strawberry type flavor powder (code (b) (4)). The designation "natural and artificial" is not the same as (b) (4) as the formulations will contain different ingredients. Revise your flavor specifications description to harmonize with the supplier.

Please respond by close of business Wednesday, October 7, 2015.

Sincerely,

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

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/s/

FRANK A LUTTERODT
10/01/2015

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 23^(b)₍₄₎%) 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 Read-Cat 2 has been used commercially since market introduction in 1985.

The proprietary name Read-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: Ayalasonmayajula, Vasantha [<mailto:Vasantha.Ayalasonmayajula@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.ayalasonmayajula@fda.hhs.gov

From: Benson Melanie [<mailto:Melanie.Benson@diag.bracco.com>]
Sent: Friday, January 09, 2015 7:44 AM
To: Ayalasonmayajula, 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.

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/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 Read-Cat 2 has been used commercially since market introduction in 1985.

The proprietary name Read-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.ayalasangamajula@fda.hhs.gov

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

Dear Ms Ayalasangamajula,

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.

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/s/

VASANTHA S AYALASOMAYAJULA
01/23/2015



NDA 208036

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: E-Z-HD (barium sulfate for suspension, 98% (w/w)) powder for suspension, 98%w/w

Date of Application: December 11, 2014

Date of Receipt: December 11, 2014

Our Reference Number: NDA 208036

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 9, 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 Health Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature}

Alberta Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALBERTA E DAVIS WARREN
12/17/2014



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 [REDACTED] (b) (4)

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
Adrienne 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 (b) (4) Bracco indicated their intent to file 2 NDAs in December 2014, including drug substance information for (b) (4) barium sulfate. FDA concurred with this approach to file drug substance (b) (4) information as part of the initial NDA. This information would be cross-referenced in subsequent submissions for (b) (4) 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 ReadCat) to FDA in December 2014.

FDA: We have the following comments with respect to the Flow Charts of BaSO₄ manufacture, Figure 1 and Figure 2.

- 1. We do not agree with the designation of (b) (4) the processing steps you describe in Fig. 1 should be performed under GMPs.**

Post-meeting note: Note the edit of (b) (4) 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 (b) (4) barium sulfate drug substances. All other barium sulfate drug products (NDAs to be cross-referenced) are formulated using (b) (4) barium sulfate drug substance.

Bracco will file information for (b) (4) barium sulfate drug substance (b) (4) in the initial NDA. The sponsor clarified that processing for (b) (4)

2. Identify the suppliers of "(b) (4) BaSO4". Barium sulfate inorganic impurities may be varied based on the origin of the raw material (b) (4)

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 (b) (4) in the initial NDA. FDA further requested information, including address and FEI number for the (b) (4) Facility, and queried whether the facility was currently a registered establishment with FDA. Bracco acknowledged that the (b) (4) facility is located in (b) (4) and is currently a registered establishment with the FDA, and also indicated that this information for the (b) (4) facility will be included in the initial NDA.

3. Establish specifications for the incoming raw material, and the drug substance (b) (4)

BaS04, USP".

Bracco Response: We will plan to provide (b) (4) specifications for incoming raw material (b) (4) 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. (b) (4)

(b) (4)

(b) (4) 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 (b) (4) that may arise from the (b) (4) .

Bracco Response: We will plan to provide justification for our proposed specifications for the (b) (4) 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 (b) (4)

(b) (4)

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. (b) (4) 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 (b) (4)) for assay of your BaSO₄ (b) (4)

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, (b) (4) . FDA further acknowledged that these activities would require additional time and therefore this information would not be required in the initial ND (b) (4)

(b) (4)

FDA acknowledged this plan.

6. Provide a [REDACTED] ^{(b) (4)} 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 [REDACTED] ^{(b) (4)}

[REDACTED] Bracco acknowledged this recommendation from FDA and indicated their intent to follow-up in writing subsequent to the meeting.

END

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/s/

FRANK A LUTTERODT
11/21/2014