

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208143Orig1s000

OTHER REVIEW(S)

REQUIREMENTS UNDER SECTION 506B

3024-1 Use the USP method to screen the starting material

(b) (4)



Final Report Submission: January 2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 208143	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Readi-CAT 2 / Readi-CAT 2 Smoothie Established/Proper Name: Barium Sulfate Dosage Form: Oral suspension Strengths: 2% (w/v)		
Applicant: Bracco Diagnostics Inc.		
Date of Receipt: December 18, 2014		
PDUFA Goal Date: January 18, 2016		Action Goal Date (if different):
RPM: Frank Lutterodt		
Proposed Indication(s): For use in Computed Tomography of the abdomen (b) (4) 		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	All sections of labeling except section 11 Description and section 16 How Supplied

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is extremely limited (greater than 99.99% of the dose is not absorbed); it is not metabolized and is eliminated unchanged in the feces. Barium sulfate itself has no pharmacological effects.

The relied upon literature describes products that contain the same active ingredient (barium sulfate) and in similar dose ranges as that proposed by the applicant. In addition, the relied upon literature studies were conducted with an earlier product of similar quality attributes (E-Z-CAT product intended for dilution to a lower concentration for use). The critical quality attributes of the Read-Cat 2 products are barium sulfate particle size (b) (4) and low concentration (2% w/v) of the formulation. E-Z-CAT contains (b) (4) barium sulfate and is diluted to similar low concentration ((b) (4) 2.0% w/v). Based on OPQ evaluation, it was determined that the E-Z-Cat product used in the reference studies are comparable to the proposed Read-Cat 2 products based on similarity of the critical quality attributes of formulation and barium sulfate concentration, as well as other quality characteristics.

Regarding the historically available Read-Cat 2 products, OPQ determined that the critical quality attributes of barium sulfate particle size (b) (4) formulation, and viscosity were similar from the time of initial product introduction (1985), throughout the changes and until the current time. Critical drug product specifications for pH and viscosity were constant. Consequently, the Read-Cat 2 products manufactured from the time of introduction to the current time are comparable to the proposed products from a quality perspective.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

If "NO," proceed to question #5.

If "YES," list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
- YES ☐ NO ☒
- If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- N/A ☒ YES ☐ NO ☐
- If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*
- If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:
- a) Approved in a 505(b)(2) application?
- YES ☐ NO ☐
- If "YES", please list which drug(s).*
- Name of drug(s) approved in a 505(b)(2) application:
- b) Approved by the DESI process?
- YES ☐ NO ☐
- If "YES", please list which drug(s).*
- Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

If “YES”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer “N/A”
If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

If this application relies only on non product-specific published literature, answer “N/A”

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- ☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- ☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- ☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). If Paragraph IV certification was submitted, proceed to question #15.

- ☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- ☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- ☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

If “NO”, please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

If “NO”, please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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

/s/

FRANK A LUTTERODT
01/15/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: January 5, 2016

To: Frank Lutterodt
Regulatory Project Manager
Division of Medical Imaging Products (DMIP)

From: Adam George, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Amy Toscano, Pharm.D., RAC, CPA
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 208036 E-Z-HD (barium sulfate) injection, for oral suspension**

In response to your consult dated April 16, 2015, we have reviewed the draft prescribing information (PI) for E-Z-HD (barium sulfate) injection, for oral suspension (E-Z-HD). OPDP has reviewed the substantially complete version of the PI titled "BaSO4 EZ-HD labeling – LDT recommendations – 12 22 15" sent via email from Frank Lutterodt to OPDP on December 30, 2015. We had comments for sections 5.1, 5.6, 5.7, and 6 of the PI which are included directly on the attached copy of the labeling.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or adam.george@fda.hhs.gov.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ADAM N GEORGE
01/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: September 1, 2015

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst
Division of Pediatric and Maternal Health,
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Pediatric Team Leader
Division of Pediatric and Maternal Health,
Office of New Drugs

Tamara Johnson, M.D., M.S., Maternal Health Team
Leader, Division of Pediatric and Maternal Health,
Office of New Drugs

Lynne Yao, M.D., Director
Division of Pediatric and Maternal Health,
Office of New Drugs

To: Division of Medical Imaging Products (DMIP)

Drug: E-Z-HD (Barium Sulfate Suspension 98%)
READI-CAT2 & READI-CAT2 Smoothies (Barium
Sulfate Suspension 2%)

Application number: NDA 208036 and NDA 208143

Applicant: Bracco Diagnostics Inc.

Proposed Indication: E-Z-HD
for use in adults for double-contrast radiographic
examinations of the esophagus, stomach and duodenu

(b)
(4)

READI-CAT2 & READI-CAT2 Smoothies
For use in Computed Tomography of the abdomen (b) (4)

**Proposed Dosing
and Administration:**

E-Z-HD
between 65 and 135 mL (b) (4)

READI-CAT2
(b) (4) 450 and 900 m (b) (4)

READI-CAT2 Smoothie
(b) (4) 450 and 900 m (b) (4)

Consult Request:

DMIP requests Division of Pediatric and Maternal Health (DPMH) participation in the labeling discussions.

Materials Reviewed:

- Draft E-Z-HD (Barium Sulfate Suspension 98%) READI-CAT2 & READI-CAT2 Smoothies (Barium Sulfate Suspension 2%) labeling (December 11, 2014 & December 18, 2014)

BACKGROUND

Barium sulfate is a marketed unapproved contrast agent that has been used for decades in adult and pediatric patients for gastrointestinal imaging. E-Z-HD (NDA 208036) and READI-CAT2 (NDA 208143) are both oral barium sulfate products being reviewed as new NDA submissions that rely exclusively on evidence from published literature. Both NDAs have been submitted as part of the FDA Unapproved Drugs Initiative to work with applicants to provide a regulatory path to approval for previously unapproved marketed products such as barium sulfate when substantial evidence of efficacy and safety can be established.

E-Z-HD and READI-CAT2 both also contain the following excipients: benzoic acid, citric acid, potassium sorbate, saccharin sodium, simethicone emulsion, sodium benzoate, sorbitol solution, xanthan gum, natural and artificial flavoring and purified water. In addition, both products contain the following impurities: (b) (4) content. Of note, (b) (4) is a contaminant found in barium and

is limited by specification to not more than (b) (4) %.

(b) (4)

DISCUSSION

The DPMH labeling review will focus on edits to section 8.1 (Pregnancy), 8.3 (Nursing Mothers, now 8.2 [Lactation]) and 8.4 (Pediatric Use).

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR became effective on June 30, 2015; however, all applications pending on June 30, 2015, may voluntarily convert labeling to the PLLR format.

Pregnancy

There are no adequate and well-controlled studies with barium sulfate use during pregnancy. A search of published literature was performed and one article was found and is summarized below. Likewise, animal reproduction studies were not performed. Additionally, data demonstrate that the drug is not systemically absorbed; therefore, the following statement as outlined in the PLLR guidance is recommended for use in labeling:

“(Name of drug) is not absorbed systemically following (route of administration), and maternal use is not expected to result in fetal exposure to the drug.”

According to Han et al., the Korean Motherisk Program (KMR) conducted a study evaluating a group of pregnant women inadvertently exposed to barium and ionizing radiation while undergoing diagnostic upper gastrointestinal tract (UGT) fluoroscopic examination at 3.3 ± 1.5 (median: 3.3 weeks) gestation (2011). Forty-two women who were not aware they were pregnant during the diagnostic examination were included in the study. Doses of barium were variable. The control group consisted of 126 women. In the exposed group, there was 1 spontaneous abortion, 3 voluntary terminations, 2 ongoing pregnancies and 4 lost to follow-up. In the control group, there were 7 spontaneous abortions, 6 voluntary terminations, 8 ongoing pregnancies and 11 lost to follow-up. The final study results looked at 32 live-births (30 singletons, 1 twin birth) in

the exposed group and 94 live births (singletons) in the control group. The authors concluded that barium appears to be safe during pregnancy.

Reviewer comments:

- *DPMH believes that the study size is too small to make a drug-associated risk for teratogenicity and/or spontaneous abortions for the product.*
- *Per discussion with DMIP the heavy metal impurity levels contained in these products are not a concern given the one time use.*

Lactation

The Drugs and Lactation Database (LactMed)¹ was searched for available lactation data with the use of barium sulfate, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

There are no animal reproduction studies with regards to barium sulfate and lactation. Additionally, data demonstrate that the drug is not systemically absorbed by the mother; therefore, the recommended language for labeling is the following:

“(Name of drug) is not absorbed systemically by the mother following (route of administration), and breastfeeding is not expected to result in exposure of the child to (name of drug).”

Females and Males of Reproductive Potential

Infertility, contraception and pregnancy testing

There are no human or animal data available regarding the effects of barium sulfate on fertility. There are no safety concerns requiring the use of contraception or pregnancy testing.

Subsection 8.3 Females and Males of Reproductive Potential will be omitted from the barium sulfate label as there is no data to inform this subsection.

Pediatrics

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products granted pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

¹ United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

The applicant does not propose to indicate either NDA for the pediatric population. Thus, proposed labeling for both products simply states that the drug product is not indicated for pediatric use.

PREA Requirements

Submission of these two supplements trigger PREA because 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. The applicant did not submit an iPSP. DMIP filed the application without an agreed upon iPSP because of the need to review marketed unapproved drugs products. PREA requires that an agreed upon iPSP be submitted with a NDA or BLA submission that triggers PREA. Failure to include an agreed upon iPSP at the time of submission is a potential refuse-to-file action.

(b) (4)

For double contrast examination indication for the E-Z-HD (barium sulfate powder for suspension) formulation, the sponsor requests a full waiver based on limited applicability to the pediatric population for the proposed indication (i.e., studies would be impossible or highly impracticable). The applicant states that double-contrast examinations of the esophagus and upper gastrointestinal (GI) tract are very rarely performed in pediatric patients. The applicant also believes that double-contrast examinations of the esophagus and upper GI are more difficult to perform in pediatric patients because of the needs for patient cooperation, ingestion of an effervescent agent and the use of a high density barium contrast agent. In addition, double-contrast examinations are associated with higher radiation doses and are generally used in conditions less common to pediatric patients.

Reviewer comment: DMIP agrees with the applicant's plan for a full waiver for E-Z-HD.

(b) (4)

Reviewer comment: The applicant's use of terminology is incorrect. However, it appears that the applicant is (b) (4) to obtain additional information about the use of the product in pediatric populations. However, the application did not include a pediatric plan for deferred studies under PREA.

DPMH agrees with the division that a full waiver may be granted for the double-contrast barium examination because studies in pediatric populations would be impossible or highly impracticable because of the low incidence of conditions that would require double-contrast barium examination in pediatric patients. Endoscopy and other diagnostic procedures have largely replaced the need for double-contrast barium examinations. (b) (4)

Barium sulfate products are widely used in pediatric patients undergoing GI imaging, including UGI and CT scans. DPMH also notes that pediatric extrapolation of efficacy would likely be acceptable for this indication because the exposure response is likely to be similar between adult and pediatric patients and that the conditions in which adult and pediatric patients would require barium for CT imaging are also similar. Furthermore, there also appears to be sufficient clinical data in the public domain that would provide sufficient data on pediatric dosing and safety; obviating the need for additional clinical studies. Therefore, DPMH recommends that the applicant be asked to perform the literature review before the application is approved in order to consider whether the product may be fully labeled for use in all pediatric populations. (b) (4)

In order to request the additional pediatric information, the Division sent the following responses to questions submitted by the applicant related to their pediatric plan:

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.

In response to the May 27, 2015, information request the applicant submitted a Type A meeting request in order to discuss the iPSP. The following comments were sent to the applicant prior to the Type A meeting in response to their questions.

1.0 DISCUSSION

Question 1:

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

Does the FDA concur with the Bracco proposal?

FDA Response to Question 1

Since it has been agreed upon that all relevant clinical information be submitted to the (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)

FDA Response to Question 2

Do not submit labeling for other barium sulfate products for review under the current NDAs. However, we agree that you should submit data (e.g., use data, data on medical need, and availability of other products, etc.) that support plans to request waivers or deferrals for pediatric assessments under PREA. These data should be submitted as an initial pediatric study plan (iPSP) under the IND (b) (4)

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>

CONCLUSION

DPMH will review the information submitted by the applicant to support a full pediatric assessment and a decision about (b) (4) required studies under PREA will be made at that time. All assessments will be reviewed by the Pediatric Review Committee (PeRC). DPMH reminds the review division that DPMH and the PeRC are separate and distinct teams and that DPMH cannot make recommendations on behalf of the PeRC. However, the PeRC often provides recommendations that are consistent with advice provided by DPMH.

DPMH will provide labeling recommendations for subsection 8.4 Pediatric Use per 21 CFR 201.57(c)(9)(iv) at a later date. The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

DPMH will continue to participate in labeling meetings until final action is taken. DPMH refers to the NDA action for final labeling.

DPMH Labeling Recommendations

The following labeling recommendations are for subsection 8.1 and 8.2 only. Labeling recommendations for subsection 8.4 will be discussed at a later time.

READI-CAT 2 AND READI-CAT 2 SMOOTHIE LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

READI-CAT 2 and READI-CAT 2 Smoothie are not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

READI-CAT 2 and READI-CAT 2 Smoothie are not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the infant to READI-CAT 2 and READI-CAT 2 Smoothie.

E-Z-HD LABELING RECOMMENDATIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

E-Z-HD is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

E-Z-HD is not absorbed systemically by the mother following oral administration, and breastfeeding is not expected to result in exposure of the infant to E-Z-HD.

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

/s/

CARRIE M CERESA
09/01/2015

HARI C SACHS
09/01/2015

TAMARA N JOHNSON
09/01/2015

LYNNE P YAO
09/02/2015

LABEL AND LABELING OR HUMAN FACTORS PROTOCOL/RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 6 th , 2015
Requesting Office or Division:	Division of Imaging Products
Application Type and Number:	NDA 208143
Product Name and Strength:	Readi-Cat 2 and Readi-Cat 2 Smoothies (Barium Sulfate) 2% (w/v)
Product Type:	Multi- Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bracco Diagnostics
Submission Date:	January 8 th , 2015
OSE RCM #:	2015-116
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Yelena Maslov, Pharm.D.

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) requested that we review the Redi-Cat 2 and Redi-Cat 2 Smoothies (Banana, Berry, Creamy Vanilla and Mochaccino) [(Barium Sulfate) suspension, 2% (w/v)] current container and carton labels and proposed Prescribing Information for areas that may lead to medication error.

Redi-Cat 2 and Redi-Cat 2 Smoothies have been in the US Market since 1985. However, the FDA has never approved this product. As a result, on January 8th, 2015 Bracco submitted an NDA for Redi-Cat 2 and Redi-Cat 2 Smoothies and proposed proprietary name review for the product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA analyzed medication errors that occurred with the currently marketed Redi-Cat 2 products. Our review identified two cases of wrong route of administration (intravenous instead of oral) , and one case of wrong drug use (Redi-Cat 2 instead of E-Z-HD). In terms of wrong route of administration error cases, accidental intravenous administration of the drug can lead to potentially fatal complications including death. See Appendix C for additional details regarding medication error cases and our analysis of the cases.

Additionally, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors.

Furthermore, we have communicated with the clinical team regarding the labeling concerns we had with the product related to the usage of percentages versus concentration in milligrams, the presence of the GI image on the display panel, and providing measuring markings on the label. Please refer to Appendix D for that discussion.

Due to post-marketing experience and analysis of labels and labeling, we recommend the carton and container labeling can be improved to enhance readability of important information and avoid any potential medication errors. Thus, DMEPA will provide its standard recommendations in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Full Prescribing Information:

1. Remove the trailing zero from 2.0 % (w/v) in all the sections to avoid a ten-fold misinterpretation per ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designation that lists dosing designations of trailing zeros as dangerous¹.
2. Section 16 How Supplied/Sotrage And Handling: Add “Orange” next to Read-Cat 2 to indicate it has flavor.

¹ <https://www.ismp.org/tools/errorproneabbreviations.pdf> [Accessed last on March 18, 2015].

4.2 RECOMMENDATIONS FOR THE BRACCO DIAGNOSTICS

We recommend the following be implemented prior to approval of this NDA:

A. Carton and Container Label for REDI-CAT 2 and REDI-CAT 2 Smoothies:

1. Remove the trailing zero from (2.0 % w/v) per per FDA guidance on Container and Carton, April 2013 (lines 469-472)². Additionally, ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designation lists dosing designations of trailing zeros as dangerous¹.

B. Container Labels for REDI-CAT 2 Smoothies (Creamy Vanilla, Berry, Banana, Mochaccino):

1. Consider reducing the images that represent the flavors such as banana, berry, and etc. to make other important information such as the established name and route of administration more prominent. Per Draft Guidance: Container and Carton, April 2013 (line 219-222).

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Read-Cat 2 that Bracco Diagnostics submitted on January 8th, 2015.

Table 2. Relevant Product Information for Read-Cat 2 and Read-Cat 2 Smoothies	
Initial Approval Date	N/A
Active Ingredient	Barium Sulfate 2%
Indication	For use in Computed Tomography of the abdomen (b) (4)
Route of Administration	Oral
Dosage Form	Oral suspension
Strength	2% (w/v)
Dose and Frequency	Dose can range from 450-900mL of product
How Supplied	Read-Cat 2 (Orange Flavor) Provided as a unit dose in a single use HDPE plastic bottle containing 450 mL of 2% barium sulfate. 24 x 450 mL bottles. Read-Cat 2 Smoothies are provided in 4 flavors, Banana, Berry, Creamy Vanilla, and Mochaccino. All are provided as a unit dose in a single use HDPE plastic bottle containing 450 mL of 2% barium sulfate 24 x 450 mL bottles
Storage	USP Controlled Room Temperature 20 to 25 degrees Celsius (68 to 77 degrees F)

APPENDIX B. ISMP NEWSLETTERS

B.1 Methods

On June 23rd, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community Care
Search Strategy and Terms	Match Any of the Words: Read-Cat 2

B.2 Results

Our search did not identify any reports.

APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

C.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 19th, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.³

Table 3: FAERS Search Strategy	
Date Range	January 01, 1980 or March 19 th , 2015
Product	Barium Sulfate
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT]

C.2 Results

Our search identified 17 cases, of which three described errors relevant for this review.

Wrong Route of Administration (n=2):

- Once case, FAERS Case # 3570318 (v1) reported that the patient told the CT technologist that she had a feeding tube. She did not tell her it was an IV feeding tube. The tech gave her the Read-Cat product with instructions to inject the Read-Cat into the "feeding tube" to prepare for her CT exam. This was done at home. When the patient's daughter injected the first syringe of 12 cc of barium into the IV feeding tube (pick line) the patient reacted immediately. She had difficulty breathing and began to lose consciousness. She was subsequently taken to a nearby hospital for three days.
- One case, FAERS Case # 7306307 (v2) reported that Read-Cat 2 was administered via a gastrostomy tube, "barium ended up in the peritoneal cavity", possibly through a perforation. The reporter stated the patient was going into the operating room, but did not state the reason for this. Follow-up information was received from the reporting physician on 02-Apr-2010: The barium leaked from the stomach to the peritoneal cavity from the stoma for the gastrostomy tube. There was no perforation of the stomach. The barium was irrigated from the peritoneal cavity with sterile water in the operating room laparoscopically in Feb-2010. The patient did fine and there were no complications.

³ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Wrong Drug Dispensed (n=1)

- One case (n=1) reported that wrong product dispensed, patient received E-Z-HD (Barium Sulfate) Powder for Suspension 98% (w/w) instead of Redi-Cat Smoothie (Barium Sulfate) oral suspension 2% w/v. It was reported that a male in-patient (already being hospitalized) was scheduled to have a CT with Redi-Cat 2 Berry Smoothie on (b) (6). Instead, the floor was supplied with the wrong barium product and the patient was given E-Z-HD Barium Sulfate for Suspension (98% w/w). The patient drank one bottle of the E-Z-HD at midnight on (b) (6) and another bottle at 6am the morning of exam on (b) (6). The exam was never completed. The facility became aware and administered enema and Go-Lytely and patient was able to eliminate the barium sulfate and did not need surgery.

We excluded 14 cases because they described non-specific barium sulfate products.

C.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Identified FAERS Case Numbers and Corresponding Manufacturer Control Numbers Summarized in Review			
FAERS CASE NUMBER	FAERS CASE VERSION	MANUFACTURER CONTROL NUMBER	DATE
3570318	1	2432460-2000-00035	11/21/2000
7306307	2	US-BRACCO-004121	3/5/2010
6216978	1	2411512-2006-00004	12/29/2006

C.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX D. Communication between DMEPA and DMIP in regards to labeling.

From: Rahimi, Leeza

Sent: Friday, May 08, 2015 12:08 PM

To: Orzach, Harris; Fejka, Richard

Cc: Todd, Nushin F

Subject: EZ-HD and Read-Cat 2 NDA 208036 and NDA 208143

Hello Dr. Orzach,

I am DMEPA's safety evaluator for the barium sulfate products. We had some questions concerning labeling, and we would appreciate any feedback on the following items:

1. Do you ever rely on the percentages (i.e. 98% for EZ-HD and 2% for Read-Cat) or do you think concentration of mg/ml or weight expressed in mg would be better?
2. The pictures of GI system on the bottles; are they helpful for identifying the area of use? We want to get your opinion if they really accurately represent the areas which product is supposed to be used in.
3. Lastly, do you find it helpful if the bottles have markings for measurements? Since the dosing is between 65mL-135 mL for E-Z-HD and 450-900mL for Read-Cat 2, how are the doses measured? In the pharmacy it is dispensed as the entire bottle, but we wanted to get your input if it would be easier to have some type of markings to facilitate administration?

Thank you in advance.

Sincerely,

Leeza

From: Orzach, Harris

Sent: Tuesday, May 12, 2015 2:27 PM

To: Rahimi, Leeza

Subject: RE: EZ-HD and Read-Cat 2 NDA 208036 and NDA 208143

Hi Leeza,

Sorry about the delay. In answer to your questions:

1. We customarily rely on percentages. E-Z-HD comes as powder- 98%w/w, in a (b) (4) container. It is reconstituted by adding (b) (4) water, yielding 135 ml barium

sulfate suspension, (b) (4) %w/v. Ready-CAT2 comes as a premade suspension, 2.0% w/v, 450 ml per container.

2. At this time, I only have access to the E-Z-HD label. It highlights the esophagus, stomach and duodenum, which are the appropriate areas of usage.
3. To reconstitute the E-Z-HD, one adds (b) (4) water to the barium sulfate powder in the bottle. Having a marking on the container might simplify this, but is not absolutely necessary. The Ready-CAT2 comes as a liquid barium sulfate suspension, 450 ml/container, ready to use.

I hope this satisfactorily answers your questions. Please let me know if more information is needed. Thank you.

Harris

From: Rahimi, Leeza

Sent: Tuesday, May 12, 2015 4:32 PM

To: Orzach, Harris

Subject: RE: EZ-HD and Read-Cat 2 NDA 208036 and NDA 208143

Hi Harris,

Thank you so much for the response. We will take the answers into consideration when addressing the labeling recommendations.

Just to clarify question number 3, per your knowledge and experience do you know how does a healthcare provider measure the exact amount of E-Z-HD after reconstitution? Since not all the patients will receive the entire bottle (135mL), is it measured in a separate measuring device and then given to the patient?

Thank you.

Leeza

Leeza,

We encourage full size adults to drink the entire 135 ml, if they can. But it is not an exact science. We watch the stomach fluoroscopically, and if it is 1/3 to 1/2 full, that is enough for a good double contrast study. If the stomach empties more rapidly, they may have to drink more of the 135 ml. Sometimes they will drink what we initially believe is sufficient, but we may have to give more later in the study, to get the views we need, or demonstrate the pathology that we see.

Every UGI ends with single contrast esophagram using liquid E-Z Paque (60%w/v)(usually 1/3 to 1/2 bottle,) and some patients will drink an additional bottle of E-Z-Paque, if they require a small bowel follow-through. This additional barium can also be used to further evaluate the stomach, if necessary.

I hope this answers your questions. Thank you.

Harris

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

/s/

LEEZA RAHIMI
07/09/2015

YELENA L MASLOV
07/10/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208143 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Readi-Cat 2 Established/Proper Name: barium sulfate suspension, 2% (w/v) Dosage Form: suspension Strengths: 2% (w/v)		
Applicant: Bracco Diagnostics Inc. Agent for Applicant (if applicable):		
Date of Application: 12/18/2014 Date of Receipt: 12/18/2014 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 18, 2015		Action Goal Date (if different):
Filing Date: February 16, 2015		Date of Filing Meeting: January 21, 2015
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☒ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): (b) (4) 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	☐ 351(a) ☐ 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification: <i>The application will be a priority review if:</i> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): PIND115090				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	☒	☐		

to the supporting IND(s) if not already entered into tracking system.					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:		☐	☐		
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application (check daily email from UserFeeAR@fda.hhs.gov): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
User Fee Bundling Policy <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (Check the 356h form,		☒	☐		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:																					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		☐	☒																		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		☐	☒																		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>																					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☒																		
If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>						Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																					
Exclusivity		YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm		☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		☐	☐	☒																	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes , # years requested: <i>Note: An applicant can receive exclusivity without requesting it;</i>		☐	☒	☐																	

<i>therefore, requesting exclusivity is not required.</i>		☒		
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☒	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☐	
<i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ <i>If not, explain (e.g., waiver granted).</i>	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	☒	☐		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☐	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☐	☒		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☐	☒		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	☒	☐		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	☐	☐	☒	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	☐	☒		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	☒	☐	☐	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	☐	☐	☒	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☐	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☐	☐	☐	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s):	☐	☐	X	
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 11/14/2014, 11/21/14	☒	☐		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☐	X	
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 21, 2015

BACKGROUND: On December 18, 2014, Bracco Diagnostics Inc., submitted NDA 208-0143 (Readi-Cat2, Readi-Cat 2 Creamy Vanilla Smoothie, Readi Cat 2 Berry Smoothie, Readi-Cat 2 Banana Smoothie, Readi-Cat 2 Mochaccino Smoothie (barium sulfate suspension, 2%(w/v) for use in computed Tomography to opacify the gastrointestinal tract. (b) (4)

(b) (4)
This submission is the second
Barium Sulfate and makes reference to NDA208-036. (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frank Lutterodt	Yes
	CPMS/TL:	Kyong Kang	Yes
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		Y
Division Director/Deputy	Libero Marzella		Y
Office Director/Deputy	Charles Ganley		Y
Clinical	Reviewer:	Harris Orzach	Y
	TL:	Libero Marzella	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (for antimicrobial products)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Satish Misra	Y
	TL:	Jyoti Zalkikar	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ronald Honchel	Yes
	TL:	Adebayo Lanionu	
Statistics (carcinogenicity)	Reviewer:	N/A	N
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Anne-Marie Russell Matin Haber	Y
	TL:	Eldon Leutzinger	Y
Biopharmaceutics	Reviewer	N/A	
	TL:		
Quality Microbiology	Reviewer:	Jessica Cole	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Nushin Todd—ADL Jagjit Grewal-ADRA Charles Ganley- Office Director		

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain: M-010 in Module 3.3.P.5.2 was provided in French. Request will be in Day 74 letter	☐ YES ☒ NO
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) Is the product an NME?	☐ YES ☒ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> Was the Microbiology Team consulted for validation of sterilization? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility Inspection</u> - Establishment(s) ready for inspection? - Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) - Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? - If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
What late submission components, if any, arrived after 30 days?	
Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Charles Ganley- Office Director Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments: This product is a Type 7 NDA not in the “Program”	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA's completed: September 2014

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
02/17/2015