CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208036Orig1s000

CHEMISTRY REVIEW(S)

NDA 208036
Review #1
Review Date: November 19, 2015

Drug Name/Dosage Form	E-Z-HD barium sulfate suspension / powder for suspension
Strength	98% w/w
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bracco Diagnostics, Inc.
US agent, if applicable	N/A

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505(b)(2)**

2. **RELATED/SUPPORTING DOCUMENTS:**

   A. **DMFs:**

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	REVIEWER
(b) (4)	Type III		(b) (4)	N/A		AMRussell, PhD
	Type III			N/A		AMRussell, PhD
	Type III			N/A		AMRussell, PhD
	Type III			N/A		AMRussell, PhD
	Type IV			adequate	27-Oct-2015	AMRussell, PhD
	Type IV			adequate	27-Oct-2015	AMRussell, PhD
						(b) (4)

   B. **Other Documents:** *IND, RLD, or sister applications*: N/A

3. **CONSULTS: N/A**

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	ONDP/DNDAPI
Drug Product	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Process	Li Shan Hsieh	OPQ/OPF/Process
Microbiology	Jessica Cole	OPQ/OPF/Microbiology
Facility	Thuy T. Nguyen	OPQ/OPF/DIA/BI
Biopharmaceutics	Assadollah Noory	OPQ/ONDP/DBP?Branch 3
Project/Business Process Manager	N/A	N/A
Application Technical Lead	Eldon Leutzinger	ONDP/Branch VII/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	Sharon Thomas	N/A
Environmental Assessment (EA)	N/A	N/A

Table 2 Documents

DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
EDR sequence 000	11-DEC-2014	Initial NDA submission	Drug Product/Anne Marie Russell, Ph.D./Martin Haber, Ph.D.
EDR sequence 002	11-JUN-2015	Response to IR#1	Drug Product/Anne Marie Russell, Ph.D./Martin Haber, Ph.D.
EDR sequence 005	22-JUL-2015	Response to IR#2	Drug Product/Anne Marie Russell, Ph.D./Martin Haber, Ph.D.

Executive Summary

I. Recommendations: APPROVAL

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

With risk mitigation, the overall Risk Assessment for E-Z-HD is reasonably low for safe use in adults. See the details of the overall risk assessment at the end of the Executive Summary.

DRUG SUBSTANCE:

Fundamental of the issues relating to establishment of drug product quality was the lack of characterization of barium sulfate drug substance, culminating in the absence of an understanding of (a) how **identity** will be confirmed in face of (b) (4), potentially occurring along with barium sulfate through association with the (b) (4) as it is obtained from the (b) (4), (b) (b) (4) (c) how **particle size (critical to clinical performance)** will be controlled. (b) (4)

[redacted] (b) (4)

To resolve the particle size issue, a comprehensive particle size distribution was determined, from which well-defined regions were derived and used to establish limits in the release specifications for [redacted] (b) (4) barium sulfate. **Based on resolution of these issues and others of less serious nature, it is concluded that the purity and quality of barium sulfate drug substance derived from the** [redacted] (b) (4) **satisfactory for use in the manufacture of E-Z-HD drug product**.

DRUG PRODUCT:
In finding a sound basis upon which to support the proposed E-Z-HD commercial product from the standpoint of drug product quality (affecting safety and efficacy), the looming problem was the absence of a "reference listed drug" and the absence of clinical studies. E-Z-HD was not available prior to 1980, but similar products were used during their development in the 1970's. Referenced literature was requested, consisting of 9 studies over the period 1976 – 2005. With a suitable **quality standards framework** (formulation, particle size, viscosity), the **proposed commercial product (E-Z-HD) was compared with the products used in the referenced studies**. Based on the results of these comparisons, **it is concluded that the proposed commercial E-Z-HD is comparable with the products used from the time of introduction in 1980 to 2005**. Inactive ingredients (other than flavorings) in the formulation of the proposed commercial E-Z-HD product already met acceptable quality standards. The quality of the flavorings were established subsequently with information provided as requested and through DMF's, thus completing the quality assurance of the formulation composition. An expiration date of 2 years at 25^0C is given to the proposed commercial E-Z-HD product on the basis of acceptability of the stability data provided.

The overall manufacturing process and controls for E-Z-HD (barium sulfate powder for suspension) is found to be satisfactory. No GMP deficiencies were identified in the preapproval inspections of [redacted] (b) (4) drug substance), E-Z-EM of Canada (part of release testing, stability testing, and final drug product). **All issues for drug substance and drug product are fully resolved. In conclusion, the proposed commercial E-Z-HD product meets acceptable quality standards for human use**.

2. Action letter language, related to critical issues such as expiration date
Suggested language: "we remind you of the commitment made to perform methods validation of [redacted] (b) (4) starting material, and to provide validation data, [redacted] (b) (4) ."

3. Benefit/Risk Considerations
In light of satisfactory resolution of the issues for characterization, along with strength in the release specifications for [redacted] (b) (4) barium sulfate, commitments, and with the proposed commercial E-Z-HD product meeting a suitable quality standards framework, relative to the historical product, the risk of not meeting the purity and quality for human use is reasonably low.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

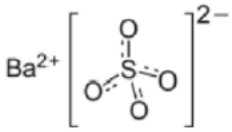
II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

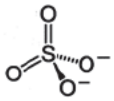
BARIUM SULFATE (INN; CAS 7727-43-7). It is described in the NDA as a white to lightly-colored powder (b) (4) with a characteristic odor. It has a molecular formula of $BaSO_4$ and molecular weight of 233.4. $BaSO_4$ defines the chemical composition of (b) (4) the drug substance is obtained. In its natural state, $BaSO_4$ is (b) (4) arises from the presence of trace amounts of elemental impurities (not an essential part of the chemical composition).

CHEMICAL STRUCTURE:

BARIUM SULFATE is the barium salt of tetrahedral polyatomic sulfate, and from the NDA is described with the following chemical structure:



Sulfate in this structure is shown possessing all partial S-O double bonds, and merits a brief discussion, since that by Pauling,



, is used in much of the chemical literature, and remains relevant from the standpoint of our conceptual view of an inorganic salt, including how Ba^{2+} and SO_4^{2-} ions (b) (4)

STRUCTURE / PROPERTIES RELEVANT TO DRUG PRODUCT QUALITY:

$BaSO_4$ is a relatively heavy substance, with a density of 4.50 g/cm^3, a physical property linked to how Ba^{2+} and SO_4^{2-} ions (b) (4) **This in turn relates to the particle packing properties in the drug product suspension, critical for quality of images**. $BaSO_4$ is practically insoluble in water [K_{sp} = 1.08 x 10^{-10} mol^2dm^{-6}; 0.0002448 g/100 mL at 20^0C and 0.000285 g/100 mL at 25^0C], **enabling coating of the bowel, as well as preventing systemic absorption of Ba^{2+} ions.** (b) (4)

(b) (4)

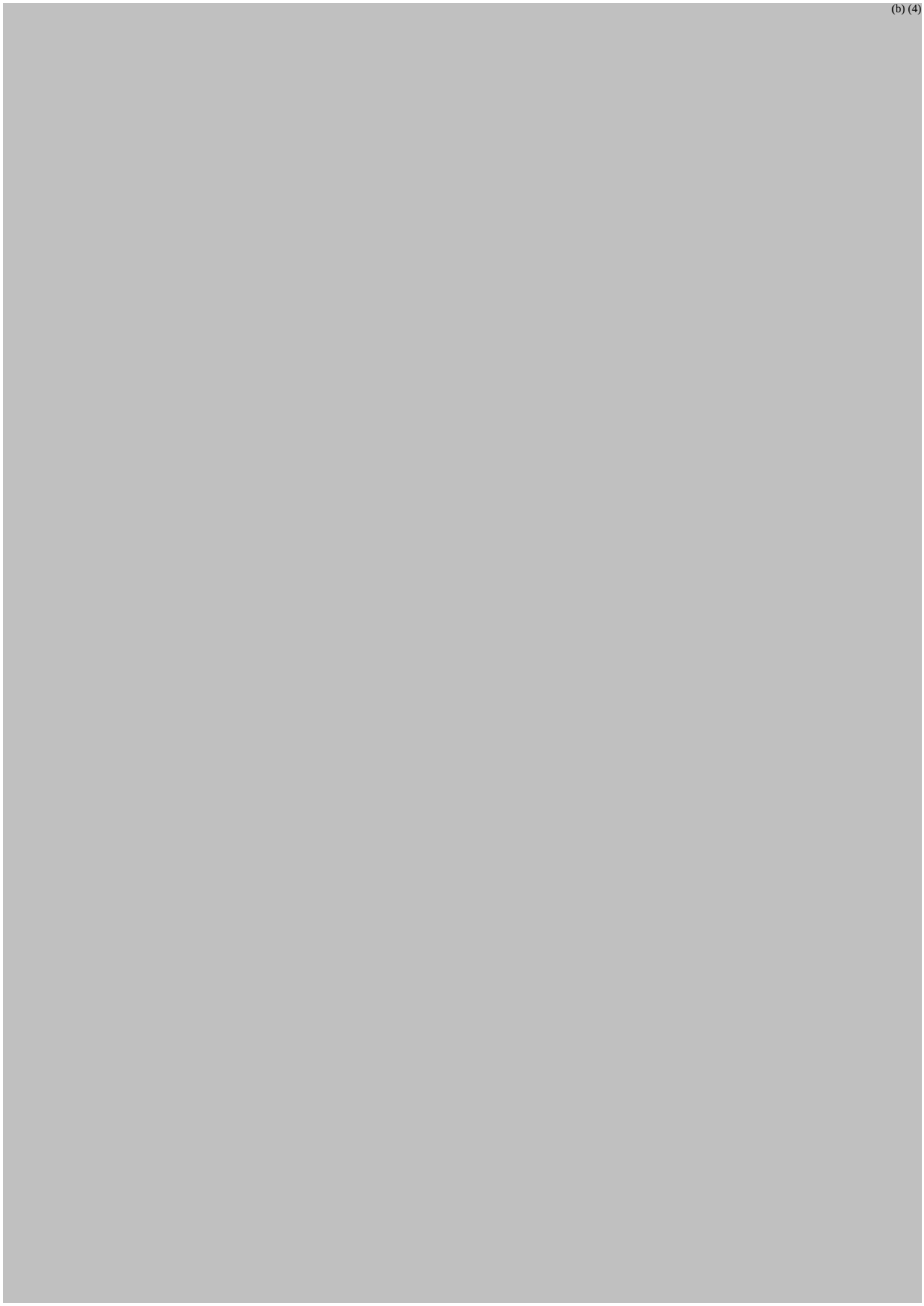
(b) (4)

PARTICLE SIZE – **as a CQA, particle size is fundamental to clinical performance of $BaSO_4$ suspensions**, as will be discussed under Drug Product. Barium sulfate is a (b) (4) particle, consistent with the structure (b) (4)

IMPURITY PROFILE – **a CQA of especial importance, since barium sulfate drug substance is obtained as the mineral,** (b) (4) **for which the only processing is purification by differential solubility in** (b) (4) .
Critical is the fact that (b) (4)

(b) (4)

(b) (4)


(b) (4)

B. Drug Product [Established Name] Quality Summary

The Drug Product (**E-Z-HD**) is presented as 340 g of formulated dry powder in a single use (b) (4) bottle closed with a white-threaded (b) (4) cap (b) (4) Details for the container closure are described in the drug product review (Ann Marie Russell, Ph.D.). E-Z-HD contains Barium Sulfate (b) (4) and *inactive ingredients* (Sorbitol, Gum Arabic, Carrageenan, Sodium Citrate (b) (4) Citric Acid, Simethicone, Polysorbate 80), (b) (Saccharin Sodium), and *flavoring agents* (Natural & Artificial Strawberry, Natural & Artificial Cherry)..

(b) (4) E-Z-HD (340 g of formulated dry powder in a single use (b) (4) bottle) is manufactured, packaged, labeled, quality-control tested and released by E-Z-EM Canada, Inc ((b) (4) Anjou Quebec, HIJ2Z4, Canada). It is used by reconstitution with 65 mL of water, yielding 140 mL of an oral suspension containing 2.38 g of barium sulfate per mL.

Quality Standards for E-Z-HD are established through the (1) quality of the ingredients, (2) batch history, and (3) stability.

INACTIVE INGREDIENTS:
Quality Standards for inactive ingredients (other than flavorings) are provided by (1) **USP specifications**, along with (2) **certificates of analysis**, both provided in the NDA.

FLAVORINGS:
Information on all flavorings is found in DMF's. Reviews of these DMF's (under separate cover; Anne Marie, Ph.D.) reveals no issues for quality.

BATCH HISTORY:
As a 505(b)(2) application, the problem for E-Z-HD is the absence of a reference listed drug, and the absence of clinical studies to support the proposed commercial E-Z-HD product. Consequently, Bracco is basing clinical efficacy and safety of their product on **historical use** and **published literature**. E-Z-HD was not available prior to 1980; but, similar products were used during the development period in the 1970's. The referenced literature consisted of 9 studies, extending from 1976 to 2005. The objective in establishing clinical efficacy and safety in the absence of formal clinical studies is to find a suitable **Quality Standards framework** by which current product can be compared with historical product. The **CQA's** within this framework were chosen to include (1) **formulation**, (2) **particle size** and (3) **viscosity**, and the product description for product used in the 9 referenced studies were compared with that in E-Z-HD. ***The conclusion is made, based on this product history, that E-Z-HD products manufactured from the time of its introduction (1980) to 2015 are comparable from the standpoint of quality***.

STABILITY:
Stability data provided in the NDA at the time of its submission was for batches not packaged in the proposed "NDA configuration," and as a consequence was considered to be secondary. In response to this issue, Bracco provided additional stability data. There were no discernible downward trends in the data provided. **Based on that stability data, Section 3.2.P.8.3 was amended with a 2-year expiration for E-Z-HD, when stored at 25^{0}C**. Bracco has committed

to conduct a post-approval stability program, and provided a stability protocol, which is deemed acceptable to extend the expiration date, post-approval. E-Z-HD is tested for Microbial Limits at Release and on Stability using a method consistent with USP Chapter <61>, <62> and <1111>. The Microbial Limits for E-Z-HD were determined to be acceptable from the Microbiology perspective (see review by Jessica Cole, Ph.D.).

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	E-Z-HD
Non Proprietary Name of the Drug Product	(barium sulfate) powder for suspension, 98%
Non Proprietary Name of the Drug Substance	Barium sulfate
Proposed Indication(s) including Intended Patient Population	In adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum (b) (4)
Duration of Treatment	One-time use
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: highly insoluble in water, and consequently a dissolution test for barium sulfate for suspension as an imaging agent is not necessary.
   - Drug Product: no biopharm issues are identified (see review by Assadollah Noory, Ph.D.).

2. Biowaivers/Biostudies N/A
   - Biowaiver Requests
   - PK studies
   - IVIVC

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

Some recommendations for labeling are provided in the drug product review (Anne Marie Russell, Ph.D., CMC Reviewer, DNDPII, Branch VII). However, labeling and package insert language is not final. Reviews of labeling, including revisions and negotiations will be handled through the clinical division (DMIP).

G. Process/Facility Quality Summary

The commercial site of manufacture (E-Z-HD, 340 g of formulated dry powder in a single use (b) (4) bottle) is E-Z-EM Canada, Inc., (b) (4) Anjou, Quebec, H1J2Z4, Canada. It is manufactured by (b) (4) packaged, labelled and release-tested at the same site. Based on the results from three validation batch runs, **it is concluded that the manufacturing process yielded a product consistently and reproducibly within the established product specifications, as well as CGMP requirements.**

H. Life Cycle Knowledge Information: N/A

Overall Drug Product Risk Assessment Summary					
From Initial Risk Identification			Review Assessment		
Attribute CQA	Factors that can impact CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments
Identity of $BaSO_4$	Association of $BaSO_4$ with (b) (4)	6	Evidence from (b) (4)	2	None
Heavy metals	Association of (b) (4)	3	(b) (4)	1	(b) (4)
Particle size	None, due to (b) (4) properties of $BaSO_4$	1	Establishment of well-defined particle size distribution (b) (4)	1	None
Comparability of proposed commercial product with unapproved historical product	Absence of "reference listed drug"	----------	Comparison of Quality Standards Framework" (formulation, particle size, viscosity) with products used in lit studies (1976 – 2005)	Low risk	None

Application Team Leader: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E. Leutzinger -S

Digitally signed by Eldon E. Leutzinger -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300054329, cn=Eldon E. Leutzinger -S
Date: 2015.11.19 15:24:58 -05'00'

Labeling & Package Insert: At this time, labeling and package insert language is not final. Labeling review, revisions and negotiations will be handled through the clinical team.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: E-Z-HD Established Name: (barium sulfate)	acceptable
Dosage form, route of administration	Dosage: for oral suspension Route:	acceptable
Controlled drug substance symbol (if applicable)	Not applicable	acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4)	Comment for applicant: Clarify the computation of 2.3 (b) (4) g BaSO4 per mL of reconstituted product as stated in Highlights DOSAGE FORMS AND STRENGTHS section of the label. Per our calculations, the value is 2.38 g BaSO4 per mL of reconstituted product as calculated from the following description: the container is filled with 340 g of powder for suspension, which contains 98% w/w of BaSO4. Prior to use, water is added to reconstitute the powder and form 140 mL of suspension. The calucation is (340 * 0.98)/140 = 2.38 g/mL

Conclusion: See comment above.

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	E-Z-HD is a barium sulfate powder for oral suspension, 98% w/w.	
Strengths: in metric system	(b) (4) [redacted]	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Change description to read: E-Z-HD is a **fine, white** barium sulfate powder for oral suspension, 98% w/w.

Conclusion: See assessment for change.

#11: Description (21CFR 201.57(c)(12))
(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	(b) (4)	Change to: E-Z-HD (barium sulfate) is a (b) (4) (b) (4) Its' (b) (4) BaSO4. (b) (4) molecular weight is 233.43 g/mol. E-Z-HD contains acacia, carrageenan, citric acid, ethyl maltol, natural and artificial cherry flavor, natural and artificial strawberry flavor, polysorbate 80, saccharin sodium, simethicone, sodium citrate, sorbitol. (b) (4)
Dosage form and route of administration	See above	Acceptable as revised above
Active moiety expression of strength with equivalence statement for salt (if applicable)	See above	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See above	
Statement of being sterile (if applicable)	Not applicable	
Pharmacological/ therapeutic class	See above	
Chemical name, structural formula, molecular weight	See above	
If radioactive, statement of important nuclear characteristics.	Opaque to x-rays – see above.	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not applicable	

Conclusion:

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))
(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	How Supplied E-Z-HD is supplied as (b) (4) a single (b) (4) HDPE plastic bottle containing 340 g of barium sulfate (b) (4). Provided as: 24 (b) (4) bottles (NDC 32909-764-01). Storage and Handling Store at USP Controlled Room Temperature 20 to 25°C (68 to 77° F). (b) (4)	acceptable
Available units (e.g., bottles of 100 tablets)	See above	acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	acceptable
Special handling (e.g., protect from light, do not freE-Ze)	See above	acceptable
Storage conditions	See above	acceptable

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for Bracco Diagnostics Inc. Monroe Township, NJ 08831 by E-ZEM Canada Inc Anjou (Quebec) Canada H1J 2Z4	acceptable

Conclusion:

2. Labels

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage (not required)		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

2) Cartons

(b) (4)

QUALITY REVIEW

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
"See package insert for dosage information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

Conclusion:

DP37

Author: Anne Marie Russell, Ph.D.

I. List of Deficiencies Communicated and teleconferences conducted during the review cycle

Drug Product Information Request #1:

1. Drug Substance particle size:
   a. Describe the function of [redacted] (b) (4) barium sulfate in the drug product formulation as regards performance, clinical efficacy and patient safety.
   b. Provide particle size distribution data for the barium sulfate drug substance lots [redacted] (b) (4) used to manufacture the commercial drug product lots submitted to the NDA [redacted] (b) (4) [redacted]

2. Drug Product specifications: In Section 3.2.P.5.1 "Table A Specification for E-Z-HD", identify the analytical method (i.e. [redacted] (b) (4)) as described in Section 3.2.P.5.2 Table A

3. Drug Product batch history:
   a. Provide a description of the manufacturing history for the E-Z-HD barium sulfate powder for suspension product – include product lot release data, number, size, manufacture date, type (e.g. development, commercial) and drug substance lot number. Identify the lots which were manufactured by the commercial process. Describe any differences from the submitted commercial process e.g. drug substance starting material, formulation, manufacturing procedure, site location, analytical methods, container and manufacturing scale. Include all lots submitted to the NDA – including stability batches. Tabulate the information wherever possible.
   b. Identify the lots of drug substance [redacted] (b) (4) used to manufacture the product batches submitted in the NDA (commercial validation lots# 65112, 65113, 65114, stability lots # 64159, 64160 and 66025). Provide drug substance batch anlysis data, if not already submitted, and identify the supplier of the [redacted] (b) (4) starting material.
   c. Provide quality information for the clinical product used in the published studies referenced for clinical safety and efficacy, including formulation, drug substance source, place of manufacuture, method of manufacture and specifications. Specifically, the product used in these two studies:
      i. Farber, E. et al, Published online 10.1148/radiol.2372041631 Radiology 2005; 237:535–540
      ii. 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.

4. Validation of Barium Assay [redacted] (b) (4): Clarify if the linearity validation tests were performed on the proposed product E-Z-HD or a different product [redacted] (b) (4) mentioned in the Validation Report ["The linearity was

performed during the validation of the assay of (b) (4) Provide justification for the linearity test as submitted or provide results conducted using the proposed E-Z-HD product.

5. Primary stability data for drug product: Be advised that the (b) (4) month data submitted for commercial lots #64159 and #64160 are considered secondary, not primary, since the drug product was not packaged in the NDA configuration and no stability test data were provided to demonstrate comparability to the NDA configuration. As per ICH, primary stability data from three lots of commercial product packaged in the NDA configuration are needed to support a proposed expiry. If the NDA is approved, an expiry will be granted based on the stability data provided to date. This expiry may be revised post-approval if you file a supplement with suitable primary stability data from three commercial lots packaged in the NDA configuration. We are providing advice at this time so that revisions to your stability program, if needed, can be made in a timely manner i.e. additional lots packaged in the NDA configuration.

6. Container:
   a. Provide two (2) container samples.
   b. Clarify if the containers used to package the commercial product are the same as the containers used for the HD-E-Z product sold in recent years. Provide a description of any differences and a timeline of production to support historical data as the basis of support for your proposed commercial product.

Teleconference:
A joint CMC/clinical teleconference was held with Bracco on 7-JUL-2015, at the Agency's request, to discuss substantiative CMC issues in N208036 (E-Z-HD) in an upcoming Information Request. The following talking points were provided to Bracco the day before the tcon. See teleconference meeting minutes in DARRTS for further details.

Talking points:

1. Historical batch information for E-Z-HD and Readi-Cat 2/Readi-Cat 2 Smoothie products.
   Additional quality information is needed on the historical barium sulfate products (i.e. formulation, release data including critical attribute such as particle size distribution) to establish the comparability of the proposed commercial products to the historical barium sulfate products which serve as the basis for demonstrating the safety and efficacy of your product.

2. Stability data Readi-Cat 2 Smoothies.
   Primary stability data are needed for the Readi-Cat 2 Smoothie products, one lot each flavor. Without this information, a shelf life cannot be established and granted.

3. Flavorings in E-Z-HD and Readi-Cat 2/Readi-Cat 2 Smoothie products.
   Additional quality information is needed on the flavorings used in the

formulations (cherry, strawberry, orange, vanilla, chocolate, coffee, berry and banana). Compliance with CFR 172.5 Flavoring agents and related substances.

Drug Product Information Request #2:

Comparability:

1. 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 E-Z-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 E-Z-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:

   b. 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(E-Z.HD 250% wt/vol from E-ZEM Westbury Co., New York) at Erasmus University, Rotterdam, The Netherlands.

2. 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 E-Z-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 –

d. 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.

e. Provide a statement confirming that all flavorings comply with the Code of Federal Regulations (CFR 172.5 "Flavoring Agents and related substances").

f. 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 E-Z-HD.

8. Drug Product specifications: revise the test column in Table A: Specification for

E-Z-HD to read "Identification 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, potassium, 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. sodium benzoate, sodium saccharine and sodium citrate).
    b. Report total content in grams for each (sodium, potassium, 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.

II. Attachments: Lifecycle Knowledge Management

Drug Product Risk Assessment Summary					
From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
None identified for drug product - all critical quality attributes were for drug substance	N/A	N/A	Drug product physical characteristics which are critical to clinical performance are 1. Barium sulfate particle size which is controlled (b) (4) specifications in the product.	Acceptable	none

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Drug Product Reviewer's Assessment and Signature:
Primary reviewer Anne Marie Russell, Ph.D

Supervisor Comments and Concurrence:
Secondary Reviewer Danae Christodoulou, Ph.D.

Note: additional reviewers can be added, as appropriate

Recommendation:
ANDA: Approvable, Minor/ Major/ Easily Correctable Deficiency

NDA 208036
Review #1
Review Date

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Introduction:

E-Z-HD™ is a barium sulfate powder for suspension (98% w/w) for oral administration. It is a fine, white to lightly colored with a high atomic number. Barium sulfate is highly insoluble; it is opaque to x-rays and therefore it is a good positive contrast agent for double contrast radiographic visualization of the esophagus, stomach and duodenum. Barium sulfate has been used as a contrast agent for diagnostic radiographic imaging of the gastrointestinal tract since the early 1900s.

Drug Product:

E-Z-HD™ is presented as 340 g in a single (b) (4) bottle. The formulation composition of E-Z-HD™ is shown in the following table.

Table A: Drug Product Composition

Component number	Component name	Percentage composition (% w/w)	Amount (g) per unit dose (340g)	Function	Grade
(b) (4)					(b) (4)
	Barium sulfate (b) (4)			(b) (4)	USP
	Sorbitol				USP/NF
	Acacia (b) (4				USP/NF
	Sodium citrate (b) (4				USP
	Simethicone				USP
	(b) (4) Citric acid				USP
	Polysorbate 80				USP/NF
	Carrageenan				USP/NF
	Ethyl maltol				USP/NF
	Saccharin sodium				USP
	Natural and artificial strawberry flavor[a]				Food grade
	Natural and artificial cherry flavor[b]				Food grade
					(b) (4)

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Barium sulfate is an inorganic compound with the chemical formula BaSO4. It is a white (b) (4) and highly insoluble in water.

Reviewer's Assessment:

Because barium sulfate is highly insoluble, it is not necessary to recommend a dissolution

test for this product.

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Reviewer's Assessment:

There are no dissolution data in the submission for this NDA and the briding, if any, will use comparisons of physicochemical properties.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Overall Assessment and Signature:

Dissolution test is not necessary for barium sulfate powder for suspension as an imaging contrast agent for NDA208036. There are no biopharm review issues for this NDA.

Assadollah Noory, Ph.D.
Primary Biopharmaceutics Reviewer
OPQ/ONDP/DBP/Branch 3

John Duan, Ph.D.
Secondary Biopharmaceutics Reviewer
& Branch Chief (Acting)
OPQ/ONDP/DBP/ Branch 3

cc Eldon Leutzinger, Paul Seo

Supervisor Comments and Concurrence: **Concur. John Duan**