CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208143Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	01/12/2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA # **Supplement #**	208143 0
Applicant Name	Bracco Diagnostics Inc.
Date of Submission	12/18/2014
PDUFA Goal Date	01/15/2016
Proprietary Name / **Established (USAN) Name**	Readi-Cat 2 and Readi-Cat 2 Smoothie Barium sulfate
Dosage Form /	Suspension
Route of Administration	Oral
Strength/Dosing regimen	2% w/v barium sulfate
Indication	For use with computed tomography (CT) of the abdomen in adult and pediatric patients to delineate the gastrointestinal (GI) tract.
Recommended Action	Approval

Material Reviewed **OND Action Package, including:**			**Names of discipline reviewers**
Quality Microbiology Review		07/23/2015	Jessica Cole, PhD
Chemistry Manufacturing and Controls :	Drug Product Drug substance Process Facility Biopharmaceutics	12/19/2015	Anne Marie Russell, PhD Martin Haber, PhD Li Hsieh ,PhD Thuy Nguyen, PhD Assadollah Noory, PhD Fang Wu, PhD
Medical Officer Review		11/17/2015	Brenda Ye, MD
Pharmacology Toxicology Review		07/23/2015	Ronald Honchel, PhD
Statistical Review		01/06/2016	Satish Misra, PhD
Clinical Pharmacology Review	OCP/DCP-V	08/12/2015	Christy John, PhD
Labeling Reviews:	DMIP	01/11/2016	Nushin Todd, MD
	OSE/DMEPA OPDP	07/10/2015 01/05/2016	Leeza Rahimi, PharmD Adam George, PharmD
	OND/DPMH	11/23/2015 09/02/2015	Mona Khurana, MD Carrie Ceresa, MD
Cross Discipline Team Leader Summary		01/12//2016	Nushin Todd, MD

DCP-V = Division of Clinical Pharmacology V
DMEPA = Division of Medication Error Prevention and Analysis
DMIP = Division of Medical Imaging Products
DPMH = Division of Pediatric and Maternal Health
OCP =Office of Clinical Pharmacology
OND = Office of New Drugs
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Introduction

This review summarizes my assessment of the approvability of the 505(b)(2) New Drug Application (NDA 208143) by Bracco Diagnostics Inc. (the Applicant) for Readi-Cat 2 and Readi-Cat 2 Smoothie (2% barium sulfate suspension) for use with computed tomography (CT) of the abdomen in adult and pediatric patients to delineate the GI tract (b) (4)

This summary review references the following information:

1) Quality, preclinical and clinical data submitted by the Applicant to NDA 208036 for E-Z-HD

2) Quality, preclinical, clinical, and statistical reviews performed by the FDA reviewers listed above and filed to the E-Z-HD NDA.

3) FDA findings of safety and efficacy of NDA 208036 for E-Z-HD.

Barium sulfate drugs manufactured by US Pharmacopeia standards (USP) have been marketed in the US as radiologic contrast agents for use in GI imaging. Various preparations for use in different radiologic procedures have been developed. The products are formulated with different concentrations of barium sulfate (affecting radio-opacity), different viscosity (b) (4) stability and hydrophilicity (b) (4)

(b) (4)

As such a full review of all the applicable clinical studies was conducted at the time of the first NDA submission. The findings of that review are referenced for use (b) (4).
Given the nearly simultaneous submission of the E-Z-HD and Readi-Cat 2 NDAs, and the cross-referenced information the two applications were reviewed simultaneously and generally a single or similar review document was developed. The information specific to NDA 208143 included some product quality aspects and product labeling.

On December 11, 2014 the Applicant submitted a 505(b)(2) application for the approval of E-Z-HD (barium sulfate powder for suspension, 98% w/w) for use for double-contrast radiographic examination of the upper gastrointestinal (UGI) tract. On December 18, 2014 the Applicant submitted a 505(b)(2) application for the approval of Readi-Cat 2 and Readi-Cat 2 Smoothie (2% barium sulfate suspension) for use with computed tomography of the abdomen to delineate the GI tract.

On September 14, 2015 the applicant amended the applications by submitting the report of the results of the pediatric survey. FDA classified the amendment as major, determined that it would be reviewed during the present review cycle and that it would extend the PDUFA action date

Products

The drug product E-Z-HD contains [redacted] barium sulfate (33.4 g, 9.8% w/w) [redacted] E-Z-HD contains the following inactive ingredients: sorbitol, [redacted] arabic, carrageenan, sodium citrate [redacted], [redacted] citric acid, simethicone, polysorbate 80. E-Z-HD also contains [redacted] saccharin sodium and flavoring agents. E-Z-HD is reconstituted using 65 mL of water to yield 140 mL of a suspension (2.39 grams barium sulfate per mL) for oral administration. The recommended dose in adults is 65-135 ml of oral suspension. E-Z-HD is administered orally, for use in double contrast radiography of the upper gastrointestinal tract, [redacted] which release carbon dioxide gas and distend the UGI to enhance fluoroscopic visualization of the mucosa. This examination is used to visualize and locate normal and abnormal anatomy. By observing peristalsis one can evaluate the presence of functional abnormalities of the UGI.

The drug substance for all the other barium sulfate products is the [redacted] particle formulated at different concentrations with various excipients for specific radiologic imaging procedures.

The drug products Readi-Cat2 and Readi-Cat2 Smoothies are in ready to-use low concentration (2% weight /volume) barium suspension for oral administration and are provided in different flavors for patient acceptability. The products distend and increase the density of the bowel lumen and are used to differentiate collapsed bowel from surrounding structures such as abdominal masses. The contrast also helps detect thickening and bowel wall masses. At low concentrations, the barium sulfate contrast agents do not coat the mucosa, but simply fill the bowel lumen and do not hinder CT imaging by causing artifacts.

Barium sulfate is classified pharmacologically as a radiologic contrast agent. The mechanism of action of radiologic contrast is the attenuation of X-rays based on the high atomic number of these drugs. Barium is a heavy metal (atomic number =56) and has favorable K shell binding energy (37 keV) for absorption of diagnostic X-ray beams.

Clinical considerations

Barium sulfate allows visualization of the gastrointestinal tract during conventional X-ray and computed tomography examinations. Barium sulfate is used for a number of imaging procedures in the GI tract. The objective of the clinical review was to identify publications adequate for substantiation of the efficacy of at least one diagnostic use per region of the GI tract. The findings were then extrapolated to other indications based on similar mechanisms of action.

The following is a listing of radiologic procedures of the gastrointestinal tract and the corresponding barium sulfate products used for each.

1. Double Contrast Evaluation of the Upper Gastrointestinal Tract: E-Z-HD

2. Radiographic examinations of the esophagus, pharynx and hypopharynx. Swallowing studies: Varibar Thin Liquid, Varibar Nectar, Varibar Thin Honey, Varibar Honey, Varibar Pudding

3. Single-contrast radiographic examinations of the stomach. Small bowel follow-through after single-contrast or double-contrast upper GI studies or small bowel series: Liquid E-Z- Paque (Suspension), E-Z-Paque (Powder for suspension), Liquid Polibar Plus (Suspension), Entero-Vu 24%

4. Single and double-contrast radiographic examination of the colon: Liquid Polibar Plus (E-ZDose, Suspension)

5. Single-contrast radiographic examinations of the esophagus, pharynx, hypopharynx and cardiac series: E-Z-Paste

6. Detection of esophageal strictures (13mm or greater): E-Z-Disk (12.5 mm barium tablet).

7. Opacification of the Gastrointestinal Tract for CT of the Abdomen and Pelvis: E-Z-Cat Dry (powder for suspension), Readi-Cat 2 Suspension, Readi-Cat 2 Smoothies (Berry, Banana, Creamy Vanilla, Mochaccino)

8. Opacification of residual stool in the colon for CT colonography: Tagitol V.

The time for barium sulfate to produce adequate opacification of a GI segment varies according to the route of administration, the concentration, and the viscosity of the administered barium suspension. Maximum opacification of the esophagus, stomach, and duodenum occurs almost immediately after the oral administration of the barium sulfate suspension whereas opacification of the small bowel occurs between 15 and 90 minutes after oral administration of the barium sulfate suspension. Timing of opacification of the colon following rectal administration of the barium suspension (b) (4) depends on a number of factors such as positioning of the patient during the procedure, hydrostatic pressure, and rate of administration.

The two X-ray contrast media barium and iodine have similar physical characteristics (atomic numbers 56 and 55 respectively) and favorable K shell binding energy (37 and 33 keV, respectively) which is close to the mean energy of most diagnostic X-ray beams. Whereas iodine-based contrast agents are water soluble, barium based contrast agents formulations are resistant to dilution and provide greater and more homogeneous delineation of mucosal details in the GI tract.

Endoscopy is an alternative procedure used to visualize the mucosal detail of the gastrointestinal tract. In addition, magnetic resonance imaging (MRI) and sonography offer cross sectional imaging of the gastrointestinal tract.

Regulatory considerations

For 40 years E-Z-EM Inc. manufactured and marketed a total of 47 unapproved barium sulfate products produced following US Pharmacopeia Standards (USP). The products were marketed for use in the US as radiologic contrast agents for GI imaging. The Applicant acquired the manufacturer (E-Z-EM) in 2008 and continued to manufacture and market these barium sulfate products. The Applicant is presently the sole supplier of barium sulfate products in the United States.

(b) (4) The initial December 2014 submissions are NDA 208036 for E-Z-HD barium sulfate powder for suspension (98% w/w) and NDA 2081432 for Readi-Cat 2 and Readi-Cat 2 Smoothies barium sulfate oral suspension (2% w/v).

The FDA and the Applicant agreed that the E-Z-HD NDA would contain all the clinical study data in support of (b) (4) of barium sulfate

products in the US. As such a full review of all the applicable clinical studies was conducted at the time of the first NDA submission. The regulatory challenges posed by this application are the lack of a reference listed drug and the lack of clinical studies conducted by or for the Applicant with the proposed commercial products. In the case of E-Z-HD the referenced literature consists of studies published from 1976 to 2005. E-Z-HD became commercially available in 1980 and similar barium sulfate products had been under development and in in use in the 1970's. To bridge the current product with the historical product on which the published studies and other clinical experience is based, the CMC reviewers relied on a quality standards framework. The quality attributes within this framework included product formulation, drug substance particle size and viscosity.

The descriptions of the product used in the referenced studies were compared with the description in the E-Z-HD NDA. The CMC reviewers examined the manufacturing quality history and concluded, based on these data that E-Z-HD product manufactured from 1980 to 2015 are comparable from the standpoint of quality and are expected to have comparable clinical performance characteristics. A similar bridging approach was used for the Ready-Cat 2 products.

In the absence of a reference listed drug, the evaluation of the history of quality standards is the general approach to be used to evaluate the comparability of proposed commercial barium sulfate products and the unapproved historical products referenced in the literature.

A critical objective of the review of these marketed unapproved products is to verify the quality of the drug substances and final products and to ensure that the manufacturing process and controls yield a consistent product. Of particular importance is the assessment of potential impurities in the drug substance including related substances, degradants, inorganic impurities, residual solvents, reagents and genotoxic impurities.

Sources of clinical data.
Efficacy reports from the scientific literature. A total of 151 publications were selected for assessment of efficacy based on the review of each publication's abstract. A total of 103 publications were excluded based on inclusion and exclusion criteria. The remaining 48 publications were reviewed in detail and are included in this submission.

The focus of the clinical efficacy review of the literature was to verify the utility of the various barium sulfate products for enhancing the visualization of various region of the GI tract. Published studies of barium sulfate products evaluated the performance of barium sulfate in detection of normal and abnormal anatomy relative to a reference standard or to other diagnostic tests. Various study limitations and lack of access to patient-level data do not allow verification of quantitative performance of barium sulfate. Quantitative performance data are considered descriptive and supportive of the reliability of barium sulfate to provide for clinically useful delineation and visualization of GI structure.

Safety reports from the scientific literature and from practice guidelines. The Applicant conducted a review of the literature and also summarized the safety profile of barium sulfate described in the Manual on Contrast Media issued by the American College of Radiology (ACR), the Guidelines on Contrast Agents of the European Society of Urogenital Radiology, and the ACR Practice Parameters for performance of imaging procedures with barium sulfate**.**

Marketing data. The Applicant provided their safety database for the time period of 1/1/2009 to 7/31/2014 and historical records of spontaneous reports from 7/1/1997 to 12/31/2008.

Pediatric use survey. The Applicant conducted a survey among users and medical experts to obtain information about current methods of use and special precautions for all barium sulfate products in pediatric patients. On September 14, 2015 the applicant amended the pending applications by submitting the report of the results of the pediatric survey to (b) (4) E-Z-HD NDA before the Prescription Drugs User Fee Act (PDUFA) action date of October 11, 2015. FDA classified the amendment as major, determined that it would be reviewed during the present review cycle and that it would extend the PDUFA action date. FDA also agreed to use this information in considering requests for waiver or deferral of studies in pediatric patients (b) (4) .

Quality of clinical data
Given the long history of clinical use of barium sulfate, adequate and well controlled studies are not available in the literature and are not required in support of these NDAs. The available studies are primarily retrospective and therefore subject to selection bias; in addition independence of readers and blinding to clinical information including results of other diagnostic tests cannot be assured. Because most of the publications provided in the submission did not give details on the specific barium products used in the studies, the clinical reviewer conducted literature searches to identify studies that specifically used the applicant's barium products.

The clinical reviewer classified the quality of the studies into three categories: primary, supportive and evaluable for safety. The reviewer relied on the primary publications for the assessment of efficacy.

2. CMC

- I concur with the assessment made by the FDA microbiology reviewer, Dr. Cole, that this submission may be approved from the standpoint of product quality microbiology**.** The Microbial Limits specifications for E-Z-HD (Barium sulfate for suspension, 98% (w/w)) and Readi-Cat 2 and Readi-Cat 2 Smoothies (Barium sulfate suspension, 2% w/v) are acceptable from a product quality microbiology perspective.

- I concur with assessment by the FDA biopharmaceutics reviewer Dr. Noory and Wu that no biopharmaceutics issues are posed by either the drug substance or the drug product in the present applications.

- I concur with the assessments of the FDA process and facility quality reviewers (Drs. Hsieh and Nguyen) that based on the results of validation batch runs, the manufacturing process yields a product consistently and reproducibly within the established product specifications and within the CGMP requirements. The pre-approval inspection of the drug product manufacturer (E-Z-EM Canada, Inc.) and the drug substance manufacturer (Barium Sulfate USP producer (b) (4)) revealed no GMP deficiencies.

- I make reference to the drug substance information in NDA 208036 and to the review by Dr. Haber. I concur with Dr. Haber's assessment that from the drug substances perspective the CMC information provided in the application is satisfactory. The most important issue

identified in the drug substance quality review is the potential for trace metal impurities; the issue is summarized below. I agree with the assessments by the CMC and toxicology reviewers that the potential risks are minor and acceptable. I also concur with the proposed (b) (4) steps discussed below.

Barium sulfate has been manufactured at a commercial scale for several years. (b) (4)

(b) (4)

I agree with the CMC and the pharmacology/toxicology reviewers, (Drs. Haber and Honchel) that the proposed impurity limits in the report are reasonable for a single use product in adults.

Review of batch records by Dr. Haber showed that (b) (4)

The Applicant (b) (4) The applicant will develop these data and will provide the information post NDA approval. The Applicant agreed to establish and maintain a reference standard (b) (4)

(b) (4)

(b) (4)

- I concur with the assessment of the FDA drug product reviewer Dr. Russell that the application is approvable from the drug product perspective. I concur that E-Z-HD and Ready-Cat 2 products manufactured from the time of its introduction in 1980 until 2015 are comparable products from the quality perspective.

E-Z-HD

E-Z-HD is formulated containing (b) (4) These quality characteristics enhance the delineation of the mucosa in double-contrast examinations of the upper GI tract and are adequately controlled.

The E-Z-HD composition is based on established conventional formulations of barium sulfate preparations and complies with the USP Barium Sulfate for Suspension monograph. The formulation 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. **Table 1** lists the E-Z-HD drug substances and inactive ingredients and their functions.

Table 1. Composition of E-Z-HD

Component name	Percentage composition (% w/w)	Amount (g) per unit dose (340g)	Function	Grade
(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
Strawberry flavor[a]				Food grade
Cherry flavor[b]				Food grade
(b) (4)				

Dr. Russell determined that the quality of the inactive ingredients and flavorings is acceptable. 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.

Acceptable results were reported for release testing of the following attributes: description, pH, viscosity, loss on drying, screening, suspendability (sediment, supernatant), barium sulfate identification and assay, uniformity and microbiological testing. The attributes of viscosity and suspendability are controlled to assure the physical properties which affect performance, i.e. the proper texture and flow properties.

A critical objective of the product review was to establish comparability of the proposed commercial products to the historical unapproved barium sulfate products. For this purpose Dr. Russell examined the quality data for the historical barium sulfate products to compare quality attributes and identify important differences that might have been introduced to the drug substance, product formulation, or manufacturing processes.

Analysis of the E-Z-HD developmental milestones, history of formulation and drug substance, and product specification indicated that the critical quality attributes of barium sulfate particle size, formulation and viscosity were similar from the time of commercial introduction 1980 to the present. Before 1980, E-Z-HD was not commercially available, though clinical investigators had access to similar products during the development period in the 1970's. Consequently, Dr. Russell concluded that the E-Z-HD products manufactured from the time of introduction until the present are comparable products from the quality perspective.

The CMC review provides a listing of the maximum content of sodium ((b) (4)), potassium ((b) (4)) and sorbitol ((b) (4)) in a single dose of E-Z-HD. These amounts do not pose serious risks and do not justify the proposed statements in the "Warnings" section of the prescribing information.

Readi-Cat 2 and Readi-Cat 2 Smoothie

Readi-Cat 2 products are formulated with (b) (4) drug substance manufactured by (b) (4) and are white, low viscosity, flavored barium sulfate suspensions (2g/100 ml) presented as a single-use 450 mL fill in a (b) (4) HDPE bottle. The drug products were judged to be acceptable by the CMC reviewers.

Tables 2 and **3** list the drug substance, inactive ingredients and their functions, and the flavorings used for Readi-Cat 2 and Readi-Cat 2 Smoothies.

Table 2- Composition of Readi-Cat 2

Component Name	% w/v	Function	Grade
Barium sulfate (b) (4)	2.0898	Contrast Agent	USP
Xanthan Gum	(b) (4)		NF
Simethicone Emulsion			USP
Potassium Sorbate			NF
Sodium Benzoate			NF
Citric Acid (b) (4)			USP
Sorbitol Solution			USP
Saccharin Sodium			USP
Natural and Artificial Orange flavor[a]			N/A
Natural and Artificial Vanilla flavor[b]			N/A
Purified Water			USP
(b) (4)			

Table 3- Composition of Readi-Cat 2 Smoothies

Component Name	Function	Grade	Composition % w/v			
			Banana	Creamy Vanilla	Berry	Mochaccino
(b) (4)						(b) (4)
Barium sulfate	Drug Substance	USP	2.0898	2.0898	2.0898	2.0898
Xanthan Gum	(b) (4)	NF				(b) (4)
Simethicone Emulsion		USP				
Potassium Sorbate		NF				
Sodium Benzoate		NF				
Benzoic Acid		USP				
Citric Acid (b) (4)		USP				
Sodium Citrate		USP				
Sorbitol Solution		USP				
Purified Water		USP				
(b) (4)						
Saccharin Sodium		USP				
Artificial Vanilla Flavor		Food Grade				
(b) (4)		Food Grade				
Naturally (b) (4) Banana Flavor		Food Grade				
Natural and Artificial Blueberry Flavor		Food Grade				
Natural and Artificial (b) (4) Chocolate Flavor		Food Grade				
Natural and Artificial Coffee (b) (4) Flavor		Food Grade				

The Readi-Cat 2 products were developed and marketed between 1985 and 2009. Changes during this time period consist of source of barium sulfate, manufacturing site, formulation (preservatives, saccharin, citric acid/sodium citrate). However, the quality history indicates that key quality attributes of particle size and viscosity were similar from 1985 until 2015. Hence, Dr. Russell concluded that the quality of the proposed commercial Readi-Cat 2 products and historical products are comparable.

3. Nonclinical Pharmacology/Toxicology

I concur with the decision by the FDA Pharmacology/Toxicology reviewers to rely on the extensive clinical experience with barium sulfate and on the review of clinical safety by the FDA clinical disciplines. I agree with the position of the primary reviewer, Dr. Honchel, and the supervisory pharmacologist, Dr. Laniyonu, that this application cannot be approved from the pharmacology/toxicology discipline perspective due to the lack of support from standard nonclinical studies conducted in contemporary drug development. The Applicant did not conduct any new non-clinical studies. The Applicant's search of the scientific literature identified no pharmacology studies, and no toxicology studies to address repeat dose toxicity, genetic toxicology, carcinogenicity, or reproductive and developmental toxicology.

Nevertheless, barium sulfate is biologically inert and systemically absorbed barium sulfate is eliminated unchanged mainly in the feces and urine. Barium absorption is relatively low following high dose oral administration of barium sulfate with no additional absorption observed with increasing barium sulfate dose once the ability of gastric acid to liberate barium ions has been exceeded. Additionally, there are no nonclinical concerns with the inactive ingredients present in E-Z-HD or Ready-Cat 2 and Ready-Cat 2 Smoothies.

I reference the finding by the FDA clinical review disciplines that barium sulfate has a favorable benefit/ risk for its intended use (see Sections 6, 7 and 12 of this summary review) and their

recommend approval of the NDA. Consequently in the absence of clinical safety findings, The pharmacology toxicology reviewers concur with the recommendation to approve.

Dr. Honchel relied on the following publication: "Boyd EM, Abel M. The acute toxicity of barium sulfate administered intragastrically. Canad Med Assoc J 1966, 94: 849-853" for the assessment of single-dose toxicity. The LD50 of intragastrically administered barium sulfate (150% w/v) was 364 g/kg in young male CBL-Wistar albino rats. The cause of death was stomach rupture.

Dr. Honchel notes the presence of a number of impurities in the final product and evaluates the proposed impurity limits and the justification provided by the Applicant. The reviewer notes that the existing data for some of the impurities is limited and the methods used for determining safety were inconsistent. Nonetheless, the impurity limits proposed by the Applicant are judged to be acceptable. Most of the impurities are inert or are present in amounts that are probably safe based on the fact that they can also be present in similar quantities in water sources, foods, and drugs. For example, the impurity limit set for (b) (4) in the drug substance is NMT (b) (4)% w/w. Batch records show that (b) (4) are adequately controlled.

Two impurities present in (b) (4) are potentially concerning in regards to pregnancy. The highest recommended dose for E-Z-HD could contain up to (b) (4) g of (b) (4) and (b) (4) mg of (b) (4) based on specifications. There is concern that these impurities might be absorbed systemically by the mother and could result in fetal exposure (b) (4). As is the case for radioactive diagnostic agents, nonclinical reproductive toxicology studies are not recommended for barium sulfate products since their use would not be recommended during pregnancy given the risks posed by radiation exposure to the fetus. This issue was addressed in the product labeling. (b) (4)

4. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology reviewer Dr. John that the applications be approved with the recommended dosing regimens.

Dr. John noted the following in considering the available data. Barium sulfate is an insoluble compound and is biologically inert. The systemic absorption of barium sulfate is very low. Atomic absorption spectrometry has been used to measure urinary excretion of barium after oral and rectal administration of barium sulfate suspensions greater than 99.99% of the dose is not absorbed. Under physiological conditions, barium sulfate passes through the gastrointestinal tract in an unchanged form. There are no PK studies reported and none are needed due to barium's pharmacologic properties. CYP and transporter related interactions are not expected. There are no known interactions of barium sulfate with other medicinal products. Food will not render barium sulfate soluble. Barium sulfate may be taken with food for evaluation of gastric motility.

The pharmacologic effects of barium sulfate have been established through long clinical experience. Barium sulfate increases the attenuation of x-rays and enhances delineation of the GI tract. The mechanism of action is similar for the various barium sulfate products. To produce adequate opacification of a GI segment various radiologic procedures use formulations of barium sulfate that vary in concentration, density, viscosity, route and manner of administration. The barium suspension coats the mucosal surface of the GI tract and allows visualization of shape, distensibility, motion, integrity, continuity, location within the torso, relationship to other organs. At more dilute concentrations barium enhances the conspicuity of the GI tract to distinguish the GI tract from other abdominal organs in computed tomography examinations of the abdomen.

Enhanced delineation of the lumen and mucosa of the GI tract can be achieved by contrast provided by gas (ingested air or CO2-producing bicarbonate) in addition to the barium; this is called a double-contrast procedure. Osmotically active agents (b) (4) are also used to induce fluid accumulation and distention of the gut to enhance visualization.

Dr. John notes that transient ECG changes are known to occur during visceral stimulation and have been reported in association with gastroscopy and sigmoidoscopy. ECG abnormalities are more frequent in elderly patients with clinical history of cardiac disease. No QT study of the type recommended in FDA guidance has been performed. I agree with Dr. John that no such study is needed because the possibility that barium sulfate might affect cardiac repolarization is remote.

5. Clinical Microbiology

This section is not applicable to this submission.

6. Clinical/Statistical-Efficacy

- I concur with the recommendations by the statistical and clinical reviewers (Drs. Ye and Misra) that the two pending applications be approved: 1) NDA 208036 for E-Z-HD barium sulfate powder for suspension (98% w/w) for double contrast radiography of the upper GI tract; and 2) NDA 2081432 for Readi-Cat 2 and Readi-Cat 2 Smoothies for CT to opacify the GI tract. The findings of efficacy of barium sulfate for delineation of GI tract structure are based on the review of the scientific literature.

- I concur with Dr. Ye's assessment that the clinical data provided demonstrate the efficacy of the currently marketed barium sulfate products for the visualization of various regions of the GI tract using established radiologic procedures. Dr. Ye's review summarizes the literature evidence by type of radiologic examination, region of the GI tract examined, and barium formulations in clinical use. An important objective of the clinical review was the evaluation of the clinical utility of all the marketed barium sulfate products for the purpose of cross-referencing these findings (b) (4). The FDA and the Applicant agreed that the E-Z-HD NDA would contain the necessary clinical data to allow an evaluation of the safety and efficacy (b) (4) for the radiologic visualization of the GI tract. (b) (4)

- I concur with the recommendation by the clinical, statistical and labeling review teams that the scientific publications on which the findings of efficacy are based need not be cited in the products' prescribing information. The reviewers identified the following strengths and limitations in the data presented.

  Given the well-established clinical use of barium sulfate, adequate well controlled studies with current commercial product are not available. A product quality approach was used to establish the comparability of the commercial and historical product and bridge the clinical data submitted (see Section 2 of this summary review). For this reason new clinical studies with commercial product are not required for this submission.

  The pharmacologic/pharmacodynamic effects of barium sulfate have been established through long clinical experience (see Section 4 of this summary review). Radiologic contrast is necessary for the visualization of the GI tract. Barium sulfate increases the attenuation of x-rays and enhances the delineation of the GI tract. The clinical utility of enhanced visualization is considered self-evident. Nevertheless, Dr. Ye's review summarizes the evidence of the utility of barium sulfate for diagnostic purposes such as the detection of GI masses, ulcers, strictures, diverticula, inflammation, infection, altered motility.

  The objective of the clinical review was not to establish diagnostic performance characteristics for a specific radiologic procedure or for a comparative diagnostic procedure. Instead the evidence of diagnostic use was considered supportive of the proposed indication of (b) (4) delineation. The approach of Dr. Ye's review was to substantiate the efficacy of barium sulfate for at least one diagnostic use per region of the gastrointestinal tract. The findings are judged to be applicable to other diagnostic indications based on similar mechanisms of action.

  Quantitative data suitable for statistical analyses were limited and the summary data could not be verified at the patient level. Because of these and other study design issues the values of several available imaging parameters such as sensitivity and specificity reported in the clinical and statistical reviews are to be considered descriptive.

- I conclude that despite the limitations discussed above, the totality of the evidence demonstrates the clinical utility of bariums sulfate for visualization of the GI tract.

7. Safety

- I concur with the FDA Clinical Reviewer (Dr. Ye) that the safety profile of barium sulfate is well understood based on published reports of clinical use, marketing surveillance, and practice guidelines and that the risks are acceptable for patients requiring visualization of the GI tract.

  Marketing surveillance reports. As summarized by Dr. Ye, during the period from January 1, 2009 to July 31, 2014, approximately (b) (4) patients received barium sulfate products. A total of 308 spontaneous reports were considered related to the administration of barium sulfate; 50 of these reactions were classified as serious. The most common serious reactions were aspiration (n=14), barium impaction (n=4), and dyspnea (n=4). During the period from July 1, 1997 to

December 31, 2008, a total of 370 reports were considered related to the administration of barium sulfate; 70 of these reactions were classified as serious. The most common serious reactions were: aspiration (n=10); urticaria (n=7); large intestine obstruction (n=6); dyspnea (n=5); rectal perforation, vomiting, or aspiration pneumonia (n=4, each).

Practice guidelines. Practice guidelines also cite the following as serious risks: aspiration of orally administered barium with potential for fatal respiratory compromise or pneumonia; intestinal perforation or intravasation of barium from rectal administration due to procedural complications (including trauma, catheter misplacement, increased hydrostatic pressure) and associated with high mortality; rare hypersensitivity reactions to barium products; aggravation of toxic dilatation of the colon by barium; intestinal obstruction. Common non serious reactions to barium sulfate products are nausea and vomiting, abdominal pain, constipation, diarrhea, vasovagal reactions from viscous distention. The contraindications and warning sections of the labeling will address these risks.

8. Advisory Committee Meeting

A meeting of Advisory Committee was not considered necessary because the NDA did not raise new scientific or clinical issues.

9. Pediatrics

- I concur with the assessment and recommendations by the FDA Pediatric and Maternal Health Reviewer and the Clinical Reviewer (Drs. Khurana and Ye) that the efficacy of barium sulfate for delineation of the GI tract can be extrapolated from adults to pediatric patients. This conclusion is generally supported by the published literature (see Dr. Ye's summary of pediatric studies), practice guidelines by Radiology professional groups, and by the Applicant's pediatric use survey data.

  The low response rate limits the generalizability of the results of the pediatric survey conducted by the Applicant. Nevertheless the survey suggests that barium sulfate products are used in all pediatric age groups. Limitations of the use of barium sulfate products are not drug-specific but are imposed by procedural difficulties and need for patient cooperation.

  With regard to E-Z-HD there is limited applicability of use in the pediatric population (other than in adolescents) for the double contrast examinations of the upper GI tract. The radiologic studies are difficult to perform in pediatric patients and are associated with exposure to higher radiation doses. Therefore use in patients younger than 12 years of age is not recommended.

  With regard to Ready-Cat 2 products, the use is applicable to pediatric patients across all age groups.

- I concur with the assessment by Dr. Khurana that there are insufficient data on which to base dosing recommendations for barium sulfate in pediatric patients. In the absence of study data or clinical guidelines, institutional protocols have been in use. However I do not believe that further more comprehensive surveys of existing pediatric imaging protocols are needed. Dosing

recommendations would have to be based on medical expert review of the information. It is not clear if such consensus recommendations on barium sulfate dosing would provide an acceptable basis for drug labeling. Consequently labeling will recommend only scaling down the volume of barium sulfate to reflect the volume of the GI tract in the relevant pediatric age groups.

- I concur with the assessment by Dr. Ye that the safety profile of barium sulfate preparations is similar in pediatric patients and adults. The most commonly reported reactions in the Applicant's surveillance database are nausea, vomiting, abdominal pain, diarrhea, barium impaction, intestinal obstruction, barium aspiration, hypersensitivity reactions. Fluid overload might occur in pediatric patients with intestinal motility disorders. Perforation of the GI tract is a serious, rare complication

10. Other Relevant Regulatory Issues

No restrictions to ensure safe use are needed.

11. Labeling

The DMIP associate director for labeling Dr. Todd led the revisions of the prescribing information. To make it be consistent with current PLR format. (see appended final labeling).

.

12. Decision/Action/Risk Benefit Assessment

- I concur with the unanimous recommendation by the FDA reviewers that the pending applications be approved to provide an indication for E-Z-HD barium sulfate powder for suspension (98% w/w) for double contrast radiography of the upper GI tract in adult and adolescent patients and for Readi-Cat 2 and Readi-Cat 2 Smoothies for computed tomography to delineate the GI tract in adults and pediatric patients across all age groups.

- The totality of the data strongly supports the value of barium sulfate for visualization of the GI tract using various radiologic procedures. There are very few data on which to base recommendations for the doses of barium sulfate that have been in established clinical use. However, there is no evidence in the literature or marketing surveillance to suggest that new studies are needed to optimize or standardize dosing of barium sulfate products currently in use.

- The safety of barium sulfate is well established and serious reactions are uncommon. Serious adverse reactions are usually caused by complications related to the procedures required for the barium administration. These include mediastinitis or peritonitis due to perforation of the GI tract, respiratory distress and pneumonia due to aspiration of barium, and venous intravasation due to trauma or displacement of the barium enema tip. Other serious reactions related to the drug include anaphylactoid reactions to barium sulfate and excipients.

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

/s/

LIBERO L MARZELLA
01/13/2016