

## Summary Review for Regulatory Action

<b>Date</b>	10/13/2016
<b>From</b>	Libero Marzella MD, PhD
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	208844
<b>Supplement #</b>	0
<b>Applicant Name</b>	Bracco Diagnostics Inc.
<b>Date of Submission</b>	12/14/2015
<b>PDUFA Goal Date</b>	10/14/2016
<b>Proprietary Name / Established (USAN) Name</b>	Varibar Pudding (barium sulfate) paste Barium sulfate
<b>Dosage Form</b>	Paste
<b>Route of Administration</b>	Oral
<b>Strength/Dosing regimen</b>	40% w/v barium sulfate
<b>Indication</b>	VARIBAR PUDDING is a radiographic contrast agent indicated for use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients 6 months of age and older
<b>Regulatory Action</b>	Approval

<b>Material Reviewed</b>		<b>Names of discipline reviewers</b>
<b>OND Action Package, including:</b>		
Chemistry Manufacturing and Controls : OPQ/ONDP/DivII OPQ/OPF OPQ/OPF/DMA	Drug Product Facility Microbiology	Anne Marie Russell, PhD Brian Ryan Jessica Cole, PhD
Pharmacology Toxicology	OND/ODEIV/DMIP	Ronald Honchel, PhD Adebayo Lanionu, PhD
Clinical	OND/ODEIV/DMIP	Brenda Ye, MD
Labeling Reviews:	OND/ODEIV/DMIP	Michele Fedowitz, MD
	OSE/DMEPA OPDP	Michelle Rutledge, PharmD Adam George, PharmD
	OND/ODEIV/DPMH	Mona Khurana, MD Carol Kasten, MD

DMA = Division of Microbiology Assessment  
 DMEPA = Division of Medication Error Prevention and Analysis  
 DMIP = Division of Medical Imaging Products  
 DPMH = Division of Pediatric and Maternal Health  
 ODEIV = Office of Drug Evaluation IV  
 OND = Office of New Drugs  
 OPDP = Office of Prescription Drug Promotion  
 OPF = Office of Process and Facilities  
 OPQ = Office of Pharmaceutical Quality  
 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 208844) by Bracco Diagnostics Inc. (the Applicant) for Varibar Pudding, barium sulfate paste 40% w/v, for use in modified barium swallow examinations to evaluate the oral and pharyngeal function and morphology in adult and pediatric patients 6 months of age and older.

This summary review references the following information: 1) quality, preclinical and clinical data submitted by the Applicant to NDA 208036 for E-Z-HD, barium sulfate powder for suspension, 98% w/w; and 2) quality, preclinical, clinical, and statistical FDA reviews and findings based on that information.

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

(b) (4). The FDA and the Applicant agreed that the first NDA for barium sulfate E-Z-HD NDA would contain all the clinical study data in support of (b) (4) applications for marketing authorization of barium sulfate products in the US. Therefore, a complete review of all the clinical information was conducted at the time of the first NDA submission. The findings of that review are referenced for use by (b) (4) subsequent NDAs.

#### Products

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.

On January 11, 2016 E-Z-HD (barium sulfate powder for suspension, 98% w/w) was approved for use for double-contrast radiographic examination of the upper gastrointestinal tract. On January 16, 2016 Read-Cat 2 and Read-Cat 2 Smoothie (2% barium sulfate suspension) was approved for use with computed tomography of the abdomen to delineate the GI tract.

The drug product E-Z-HD contains (b) (4) barium sulfate (33.4 g, 9.8% w/w) (b) (4). The drug substance for all the other barium sulfate products is the (b) (4) particle formulated at different concentrations with various excipients for specific radiologic imaging procedures.

The drug product Varibar Pudding (barium sulfate paste, 40% w/v) for use in the modified barium swallow examination is a viscous formulation administered orally by spoon or syringe for use in the fluoroscopic evaluation of the oropharynx and cervical esophagus. Other Varibar formulations with the same strength but differing in viscosity are provided to simulate the consistency of various fluids and foods.

#### 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 modified barium swallow procedure is used for fluoroscopic evaluation of oral and pharyngeal phases of swallowing in adult and pediatric patients with dysphagia to identify functional and structural abnormalities. The typical adult dose is 5mL and pediatric dose is 1-3 ml. Multiple doses may be administered in a single examination.

Fiberoptic endoscopy is an alternative procedure used to visualize the mucosal detail of the gastrointestinal tract and to assess swallowing. 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 according to USP standards. 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.

The FDA and the Applicant agreed on a 505(b)(2) process [REDACTED] (b) (4)  
[REDACTED] The FDA and the Applicant agreed that the E-Z-HD NDA would contain all the clinical study data in support of [REDACTED] (b) (4) applications for marketing authorization of barium sulfate products in the US.

A full review of all the applicable clinical studies was conducted at the time of the first NDA submission. The regulatory challenges posed by these applications 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. Varibar became commercially available in the year 2000. 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 Varibar NDA. The CMC reviewers examined the manufacturing quality history and concluded based on these data that products manufactured from 2000 to 2016 are comparable in quality and are expected to have comparable clinical performance characteristics.

#### Sources and quality of clinical data.

*Efficacy reports from the scientific literature.* The focus of the clinical 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 did not allow verification of the quantitative diagnostic performance of barium sulfate.

*Safety reports from marketing data, the scientific literature and from practice guidelines.* The Applicant reviewed their safety database, 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.

*Pediatric use survey.* The Applicant conducted a survey among clinical users and medical experts to obtain information about current methods of use and special precautions for all barium sulfate products in pediatric patients. FDA also agreed to use this information in considering requests for waiver or deferral of studies in pediatric patients for all barium sulfate NDAs and sNDAs.

*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.

## 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 microbiological quality of the drug product is controlled via upstream controls and a suitable testing protocol.

Varibar Pudding is a non-sterile, preserved barium sulfate paste (40% w/v) with pudding-like consistency for oral administration. It is supplied in a 230 mL multiple-dose, polyethylene tube. The product is tested for microbial limits at release using acceptable methods. The drug product will also be tested for microbiological quality at expiry as part of the post approval stability protocol. I agree with the recommendation by Dr. Cole that the Applicant consider including antimicrobial effectiveness testing at expiry.

- I reference the previous assessment by the FDA biopharmaceutics and CMC reviewers that no biopharmaceutics issues are posed by the drug substance and that from the drug substances perspective the CMC information provided is satisfactory.
- I reference the previous favorable assessments of the FDA process and facility quality reviewers. I concur with the present assessment of the facility reviewers that there are no significant risks to the manufacturing process or final product based on the evaluation of the listed facilities, previous inspection results, and recent experience. The facilities are determined acceptable.

The drug substance manufacturer (b) (4) has no GMP deficiencies. (b) (4) will perform (b) (4) testing of barium sulfate drug substance and is acceptable based on inspectional history. Multiple inspections of the drug product manufacturer and tester (E-Z-EM Canada, Inc.) are considered acceptable.

- I concur with the assessment of the FDA drug product reviewer Dr. Russell that the application is approvable from the drug product perspective. Since market introduction in 2000, Varibar Pudding has been manufactured under the (b) (4) specifications, formulation, manufacturer, and process. I therefore agree that based on

the available product manufacturing history, the to-be-marketed product is comparable to the unapproved product. Varibar Pudding contains the following excipients all of which are adequately controlled: [REDACTED] (b) (4)

The Varibar products include five textures and consistencies that range from liquid (thin liquid, nectar, honey, spoon-thick) to food (purees, pastes). The products consist of powder for suspension (Varibar Thin Liquid), ready-to-use suspensions (Varibar Nectar, Varibar Thin-Honey and Varibar Honey) and ready-to-use paste (Varibar Pudding).

Dr. Russell determined that the specifications and analytical procedure for the drug product are acceptable. Three commercial product lots were manufactured and validated. Stability data were provided to support the 24 month shelf life and the 21 day in-use period at room temperature.

### 3. Nonclinical Pharmacology/Toxicology

- I reference the decision by the FDA Pharmacology/Toxicology reviewer to rely on the extensive clinical experience with barium sulfate and on the review of clinical safety by the FDA clinical disciplines. I note the reviewer's assessment that in the absence of clinical safety findings, from the pharmacology toxicology perspective the application can be approved.

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 testing.

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. 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.

### 4. Clinical Pharmacology/Biopharmaceutics

- I reference 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. 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. There are no known interactions of barium sulfate with other medicinal products.

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, and relationship to other organs.

## **5. Clinical Microbiology**

This section is not applicable to this submission.

## **6. Clinical/Statistical-Efficacy**

- I reference the previous recommendations by the FDA statistical and clinical reviewers 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 summarized the literature evidence by type of radiologic examination, region of the GI tract examined, and barium formulations in clinical use.
- I reference 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. A product quality approach was used to establish the comparability of the commercial and historical product and bridge the clinical data submitted.

The pharmacologic/pharmacodynamic effects of barium sulfate have been established through long clinical experience. 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. Dr. Ye's review summarized the evidence of the utility of barium sulfate for diagnostic purposes such as the detection of GI masses, ulcers, strictures, diverticula, inflammation, infection, and altered motility.

## 7. Safety

- I reference the FDA clinical reviewer's assessment that the safety profile of barium sulfate is well understood based on published reports of clinical use, marketing surveillance data, and practice guidelines and that the risks are acceptable for patients requiring visualization of the GI tract.

## 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 reviewers 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), by the Applicant's pediatric use survey data and by practice guidelines by Radiology professional groups. The pediatric survey conducted by the Applicant, 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.

Modified barium swallow fluoroscopy is useful for the functional and structural examination of the oropharynx and upper esophagus and for the visualization of aspiration of material in the airway in pediatric and adult patients. Five Varibar formulations are provided with the same strength (40% w/v) but differing viscosity. The consistency and texture of these formulations range from liquid to soft food-like. The number and order of presentation of these formulations in a patient with dysphagia varies by age and condition evaluated.

The pediatric and maternal health reviewer and the clinical reviewer (Drs. Khurana and Ye) point out that the volume and consistency of the barium sulfate need to be age appropriate. The typical volume of Varibar Pudding to be presented to pediatric patients ranges from 1 to 3 mls. Multiple swallows may be necessary for radiologic visualization. The consistency of Varibar Pudding makes it unsuitable for use in infants younger than 6 months of age.

- I concur with the assessment by The Pediatric Review Committee (PeRC, August 31, 2016) that studies of Varibar Pudding be waived in patients less than 6 months of age as suitable Varibar formulations are available for infants unable to take solid foods.
- I reference 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.

- I note that there are no clinical concerns with the inactive ingredients present in Varibar Pudding in the indicated pediatric population (age 6 months or greater). With specific reference to Polysorbate 80, the Supervisory Pharmacologist finds that  $\leq 3$  mg/kg of body weight per day of the excipient administered intravenously is considered safe for use in neonates. A single oral pediatric dose of Varibar Pudding (1-3 ml) contains (b) (4) mg of Polysorbate 80.

## 10. Other Relevant Regulatory Issues

No restrictions to ensure safe use are needed.

## 11. Labeling

- The DMIP associate director for labeling Dr. Fedowitz led the revisions of the prescribing information to make it consistent with current Physician Labeling Rule (PLR). I concur with the appended final labeling.
- The DPMH reviewer Dr. Kasten revised the labeling with respect to the format and content of the pregnancy and lactation labeling rule. I concur with those revisions.
- I concur with the Office of Prescription Drug Promotion that the trade name does not misbrand the product. The reviewer recommended a number of changes to the prescribing information that were adopted by the Applicant.
- I concur with the Division of Medication Errors Prevention and Analysis that from a safety and misbranding perspective the proprietary name is acceptable.

In conducting the assessment DMEPA's reviewers (Dr. Rutledge) considered the components of the name. Varibar suggests the availability of various viscosities of barium and Pudding is a distinguishing descriptor for one of the consistencies (puree/paste) as defined by national guidelines for assessment of dysphagia. Phonetic and orthographic analyses and searches of the FDA's adverse event reporting system did not raise concerns with name confusion errors. The reviewers also noted that changing the proprietary name may introduce confusion among the medical community given the recognition of this product name among radiologists and reliance on the dosage form descriptor to distinguish among various Varibar products.



## 12. Decision/Action/Risk Benefit Assessment

- I concur with the unanimous recommendation by the FDA reviewers that the pending application be approved.

The totality of the data strongly supports the value of barium sulfate for visualization of the GI tract using various radiologic procedures. The modified barium swallow procedure is useful for fluoroscopic evaluation of oral and pharyngeal phases of swallowing in adult and pediatric patients with dysphagia to identify functional and structural abnormalities. The typical adult dose is 5ml and pediatric dose is 1-3 ml. Multiple doses may be administered in a single examination.

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 hypersensitivity reactions to barium sulfate and excipients.

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LIBERO L MARZELLA  
10/14/2016