CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208844Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application, 505(b)(2)
Application Number(s)	NDA 208036
Priority or Standard	Standard
Submit Date(s)	December 11, 2014
Received Date(s)	December 11, 2014, September 14, 2015
PDUFA Goal Date	January 11, 2016
Reviewer Name(s)	Brenda Ye, M.D.
Review Completion Date	November 16, 2015
Established Name	Barium sulfate powder for suspension
(Proposed) Trade Name	E-Z-HD
Therapeutic Class	Oral contrast agent
Applicant	Bracco Diagnostics Inc.
Formulation(s)	98% w/w powder for suspension
Dosing Regimen	Volume administered varies based on clinical condition, and anatomic characteristics.
Indication(s)	Double contrast examination of the esophagus, stomach and duodenum under fluoroscopic guidance.

Intended Population(s) Adults

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 5

1.1 Recommendation on Regulatory Action 5
1.2 Risk Benefit Assessment 5
1.3 Recommendations for Post-market Risk Management Activities 6
1.4 Recommendations for Post-approval Studies/Clinical Trials 6

2 INTRODUCTION AND REGULATORY BACKGROUND 6

2.1 Product Information 6
2.2.1 Uses of Currently Available Barium Sulfate Products for X-ray Gastrointestinal Tract Imaging 10
2.3 Availability of Proposed Active Ingredient in the United States 12
2.4 Important Safety Issues With Consideration to Related Drugs 12
2.5 Summary of Pre-submission Regulatory Activity Related to Submission 13

3 ETHICS AND GOOD CLINICAL PRACTICES 13

3.1 Submission Quality and Integrity 13
3.2 Compliance with Good Clinical Practices 14
3.3 Financial Disclosures 14

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 14

4.1 Chemistry Manufacturing and Controls 14
4.2 Preclinical Pharmacology/Toxicology 14
4.3.1 Mechanism of Action 14
4.3.2 Pharmacokinetics and Pharmacodynamics 15

5 SOURCES OF CLINICAL DATA 15

5.1 Tables of Studies/Clinical Trials 15
5.1.1 Esophagus and Upper Gastrointestinal Studies 15
5.1.2 Barium Enema Studies 23
5.1.3 Small Bowel Studies 33
5.1.4 Modified Barium Swallow Studies 38
5.1.5 Fecal Tagging Studies 41
5.1.6 Pediatric Barium Enema Studies 42
5.1.7 Pediatric Small Bowel Studies 43
5.1.8 Pediatric Modified Barium Swallow Studies 44
5.2 Review Strategy 45

6 REVIEW OF EFFICACY 45

6.1 Esophagram and Upper Gastrointestinal Series 45
(b) (4) 49
..... 53
6.4 Modified Barium Swallow (MBS) Examination 57
6.5 Opacification of the Gastrointestinal Tract in Computed Tomography (CT) of the Abdomen/Pelvis 58
(b) (4) 61
6.7 Analysis of Clinical Information Relevant to Dosing Recommendations 64

7 REVIEW OF SAFETY 67

Safety Summary 67
7.1 Methods 67
7.2 Adequacy of Safety Assessments 67
7.3 Major Safety Results 68

7.3.1 Safety Results from Bracco Post-Marketing Surveillance Data (PMS) 68
7.3.2 Safety Findings from Literature 68
7.3.3 Safety Results from Practice Guidelines 71
7.4 Safety Findings in the Pediatric Population 73

8 PEDIATRIC RESEARCH EQUITY ACT (PREA) REQUIREMENTS 74

Bracco Survey - Barium Sulfate Pediatric Usage Data 74
8.1 Esophagus and Upper Gastrointestinal Studies 75
(b) (4) 77
..... 79
8.4 Opacification of the Gastrointestinal Tract in Computed Tomography (CT) of the Abdomen/Pelvis 81
8.5 Modified Barium Swallow (MBS) Examination 83

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is a 505(b)(2) New Drug Application (NDA) for E-Z-HD Barium Sulfate powder for suspension (98% w/v) for use in double contrast radiography of the upper gastrointestinal tract (esophagus, stomach and duodenum). (b) (4)

The present submission contains the clinical data needed to evaluate the safety and efficacy of all the Barium Sulfate drug products for use as contrast agents in various radiologic procedures for the opacification of the GI tract. The objective of this review is to evaluate the clinical utility of the marketed Barium Sulfate products and to permit the data and the FDA findings from this review to be cross-referenced in subsequent applications to be filed for barium sulfate products (b) (4)

The clinical reviewer recommends approval of the two pending applications: E-Z-HD barium sulfate powder for suspension (98% w/w) for use in double contrast radiography of the upper gastrointestinal tract (esophagus, stomach and duodenum), and Readi-Cat2 for computed tomography to opacify the gastrointestinal tract.

1.2 Risk Benefit Assessment

This is a literature-based 505(b)(2) submission, utilizing information from peer reviewed papers and review articles retrieved from the literature, as well as post-marketing surveillance (PMS) database, based on an estimated exposure of more than (b) (4) patients worldwide, in the period between January 1, 2009, to July 31, 2014. It also relies on Guidelines and appropriateness criteria issued by the American College of Radiology, and Guidelines on the safety of contrast agents issued by the European Society of Urogenital Radiology (ESUR).

The safety of Barium Sulfate products has also been evaluated during the more than 100 years of clinical use. Serious adverse reactions are usually caused by complications related to the procedure required for the barium administration. These include mediastinitis or peritonitis due to perforation of the GI tract, respiratory distress and pneumonia due to aspiration, and venous intravasation due to trauma or displacement of the enema tip. Other serious reactions related to the drug include anaphylactoid reactions to barium sulfate and excipients.

The most common adverse reactions are nausea, vomiting, abdominal cramping or discomfort, constipation and colonic retention of barium.

1.3 Recommendations for Post-market Risk Management Activities

None

1.4 Recommendations for Post-approval Studies/Clinical Trials

None

2 Introduction and Regulatory Background

Barium has been used for medical imaging exams since the early 1900's. With passage of the Federal Food and Drugs Act of 1906, it was considered a drug and was subject to regulations imposed on drugs. In 1910, pharmaceutical companies decided to purify barium to United States Pharmacopeia (USP) standards and make it available to the medical community. Since that time, barium sulfate suspensions have been used for opacification of the GI tract with the development of different formulations, based on the type of imaging required. EZ-EM marketed up to 47 different barium sulfate products in the United States prior to 2008. Bracco made several inquiries to the FDA regarding the regulatory requirements for these products. It did not pursue any New Drug Applications, based on an understanding that it was not necessary at the time, and that the class of drugs would be reviewed at a future date under the Drug Efficacy Study Implementation (DESI) Program. The Canadian EZ-EM manufacturing facility has undergone several FDA inspections, the latest in September, 2011, all of which have been acceptable to allow shipment of barium sulfate commercial products to the United States.

Bracco acquired EZ-EM in 2008. Bracco has manufactured and distributed barium products since that time, and is now the only supplier of barium sulfate products in the United States. Bracco initiated contact with the FDA to discuss bringing barium products under an approved New Drug Application, and contacted the Division of Medical Imaging Products. Bracco proposes to bring barium sulfate products into the approval process.

This submission is the (b) (4) 505(b)(2) NDA submission for E-Z-HD barium sulfate powder for suspension (98% w/v), which is the first (b) (4) filed with FDA for barium sulfate products. The (b) (4) NDA for E-Z-HD will be cross-referenced in subsequent barium sulfate applications to be filed with FDA (b) (4)

2.1 Product Information

Bracco barium sulfate drug products submitted in the NDAs (b) (4) are composed of (b) (4) E-Z H-D is a Barium sulfate powder for suspension.

E-Z-HD is administered orally, for use in double contrast radiography of the upper gastrointestinal tract (esophagus, stomach and duodenum), typically along with sodium bicarbonate effervescent granules, which release carbon dioxide gas, to obtain distension of the upper gastrointestinal tract, to enhance visualization of the mucosa. This allows double contrast fluoroscopic evaluation, in order to locate and outline normal structures, distinguish between normal and abnormal anatomy. One can also observe peristalsis, and therefore diagnose functional abnormalities of the upper gastrointestinal tract.

Esophagus and Upper Gastrointestinal Series

The applicant provided 16 publications supporting the use (b) (4) barium sulfate. These product quality attributes are tailored to specific pharmacologic activities due to differences in interactions with the GI mucosa. For example a high viscosity dosage form is useful to coat the esophageal or gastric mucosa, which, when used with effervescent sodium bicarbonate powder, gives a double contrast view of the intestinal mucosa and sub-mucosal folds. In some publications, high density barium alone was used; in others, low density or both were used, yielding a single contrast or biphasic examination. Most of the publications did not specifically describe specific product, concentration or volume administered.

Products which may have been used in the studies:
E-Z-HD: For double contrast examinations of the esophagus, stomach and duodenum.
E-Z-Paque: For single contrast examinations of the esophagus, stomach, and small bowel.
Liquid E-Z-Paque: For single contrast examination of the stomach.
Liquid Polibar Plus: May be used for single contrast examination of the entire gastrointestinal tract.

The publications are generally representative of the clinical uses and imaging outcomes for this procedure. However the focus of most publications is on diagnostic performance characteristics with the use of barium sulfate. No data were provided to support the independent verification of performance characteristics of barium sulfate and no such data were needed. For the purpose of this review evidence of diagnostic performance will be used as support for the finding that barium sulfate for use in opacification of the GI tract enhances structural delineation and provides useful clinical information about normal and abnormal GI structure. Demonstration of enhanced visualization in a well defined clinical setting in at least one anatomic region was considered adequate for the purpose of generalization to the various clinical uses in the same anatomic region.

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Visualization of the Gastrointestinal Tract, in Conjunction with CT

The publications are generally representative of the clinical uses and imaging outcomes for this procedure. However the focus is on diagnostic performance characteristics. This type of evidence will be used as support for the finding that barium sulfate enhances structural delineation and provides new clinical information about normal and abnormal structure. Enhanced visualization in a specific clinical setting was considered adequate for the purpose of generalization to the various clinical uses in this anatomic region.

Oral contrast agents are commonly administered to patients undergoing CT scan of the abdomen and pelvis. They can be divided into positive, negative and neutral contrast agents, depending on the extent of attenuation of the x-ray beam.

Routine abdominal and pelvic CT uses positive contrast agent, which increase the density of the bowel lumen. This contrast provides opacification and distension of the GI lumen, and may help differentiate collapsed bowel from surrounding structures such as abdominal masses, lymph nodes and abscesses. The contrasts also helps detect mural or fold thickening and bowel wall masses. The contrats is provided by low concentration 1% to 2% weight /volume barium suspensions. At these low concentrations, the barium sulfate contrast agents do not coat the mucosa, but simply fill the bowel lumen, and do not cause significant CT artifact which may hinder diagnosis. The Bracco barium sulfate products used for CT examination of the abdomen are as follows:

- Readi-CAT2
- Readi-CAT2 Smoothies
  E-Z-CAT Dry

The above products are in powder for suspension, or in ready to-use suspension form, and are provided in different flavors for patient acceptability.

Negative contrast agents include air and carbon dioxide, and are used to obtain gaseous distension of the colon for CT Colonography.

Neutral contrast agents such as water, methylcellulose and VoLumen, provide distension and water-like attenuation of the GI lumen, with improved evaluation of mucosal, mural and serosal

pathology. VoLumen contains a small amount of barium sulfate (b) (4)

Another barium sulfate product used during CT examinations of the abdomen is Tagitol V, which is specifically used during CT colonography to opacify residual stool, and therefore reduces false positive cases. This is called "fecal tagging".

2.2.1 Uses of Currently Available Barium Sulfate Products for X-ray Gastrointestinal Tract Imaging

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-Z-Dose, Suspension)

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

6. To assess the esophagus for significant 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-Cat2 Suspension, Readi-Cat 2 Smoothies (Berry, Banana, Creamy Vanilla, Mochaccino)

8. Opacifying residual stool in the colon for CT Colonography: Tagitol V.

Table 1 below provides the same information by product.

Table 1: Uses of Barium Sulfate Products in Various Examinations of the Gastrointestinal Tract

Product Names	Dose Form	Route of Administration	Type of Examination and Target Segment of GI
Radiography/Fluoroscopy (Conventional X-ray)			
E-Z-HD	Powder for suspension	Oral	Double-contrast radiographic examinations of the esophagus, stomach and duodenum
Varibar Thin Liquid	Powder for suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Nectar	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Thin Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Varibar Pudding	Paste	Oral	Radiographic examinations of the esophagus, pharynx and hypopharynx / Swallowing studies
Liquid E-Z-Paque	Suspension	Oral	• Single-contrast radiographic examinations of the stomach • Small bowel follow-through after single-contrast or double-contrast upper GI study
E-Z-Paste	Paste	Oral	Single-contrast radiographic examinations of the esophagus, pharynx, hypopharynx and for cardiac series
Entero Vu 24%	Suspension	Oral	For use in small bowel radiographic examinations
Liquid Polibar Plus	Suspension	Oral	Radiographic examinations of .esophagus (undiluted for double contrast), cardiac series, stomach (single- and double-contrast) and small bowel series.
Liquid Polibar Plus (E-Z-Dose)	Suspension	Rectal	Single- and double-contrast radiographic examinations of the colon
E-Z-Disk	Tablet	Oral	Radiographic examinations of the esophagus for detection of esophageal strictures
E-Z-Paque	Powder for suspension	Oral	Single-contrast radiographic examinations of the esophagus, stomach, duodenum and small bowel
CT Exams – Opacification of GI Tract at CT Imaging			
E-Z-Cat Dry	Powder for suspension	Oral	CT examinations of the abdomen
Readi-CAT2	Suspension	Oral	CT examinations of the abdomen
Readi-CAT2 Smoothies: **a. Berry** **b. Banana** **c. Creamy Vanilla** **d. Mochaccino**	Suspension	Oral	CT examinations of the abdomen
Tagitol V	Suspension	Oral	For use in opacifying residual stool in the colon at CTC
GI: gastrointestinal; CT: computed tomography; CTC: CT colonography.			

An additional product, **VoLumen Oral Suspension**, is available, (b) (4) although it does contain a small quantity of barium. This product is utilized for CT Enterography.

2.2.2 Currently Available alternative X-ray contrast agents for Gastrointestinal Imaging

Iodinated water-soluble contrast media can be used for opacification and X-ray visualization of the GI tract.

Diatrizoate meglumine/diatrizoate sodium is a marketed water-soluble iodinated high-osmolar contrast agent, suitable for GI opacification. This contrast agent is indicated for radiographic examination of segments of the GI tract (esophagus, stomach, proximal small intestine and colon) and for distinguishing normal loops of bowel from adjacent organs in CT examinations of the body. The contrast agent is administered orally or rectally, is hypertonic, and may lead to hypovolemia and hypotension due to fluid loss from the intestine.

Iohexol is another marketed iodinated contrast agent suitable for GI imaging. Although generally utilized intravenously, this contrast agent is indicated for oral use for examination of the GI tract. In dilute concentrations, iohexol is administered orally as a bowel marker for CT examinations of the abdomen.

It should be emphasized that various formulations of barium sulfate are necessary for GI imaging because of properties such as resistance to dilution and optimal coating of the mucosal surface of the GI tract. For these reasons, water soluble contrast agents are generally used only in situations that preclude the use of barium sulfate for example in patients with suspected bowel perforation or leak, or likely small bowel obstruction and in whom need for surgery is anticipated.

2.2.3 **Currently Available Alternative Imaging Modalities for Gastrointestinal Visualization**
Endoscopy is becoming widely available to visualize the mucosal detail of the gastrointestinal tract. In addition, magnetic resonance imaging (MRI) and sonography offer a cross section imaging of the gastrointestinal tract.

2.3 Availability of Proposed Active Ingredient in the United States

Barium Sulfate, the active ingredient in EZ-HD, and all of the other barium formulations, has been used for medical imaging examinations since the early 1900s. Since that time, barium sulfate suspensions have been used for opacification of the GI tract, with the development of different formulations based on the type of imaging required.

EZ-EM marketed 47 different formulations of barium sulfate products in the United States prior to 2008. Bracco acquired EZ-EM in 2008 and has manufactured and distributed barium products since that time.

2.4 Important Safety Issues With Consideration to Related Drugs

The marketed, water soluble, high osmolar contrast agent indicated for radiographic examination of GI tract, is a solution comprising 660 mg/ml diatrizoate meglumine, and 100 mg/ml diatrizoate sodium, which contain 367 mg of iodine per ml. Safety issues include the following:
1. Hypersensitivity (anaphylactoid) reactions to iodine.
2. If aspirated, may cause life-threatening pulmonary edema.
3. Alterations in thyroid function tests for variable periods of time.

4. Since they are hypertonic, may cause hypovolemia and/or hypotension, especially in very young or elderly patients.
5. Transient bacteremia has been shown to occur in patients undergoing single contrast enemas.

Iohexol administered orally may induce hypersensitivity reactions , other reported reactions include diarrhea, nausea , vomiting, and abdominal pain.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

(b) (4)

(b) (4)

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of this submission is satisfactory.

3.2 Compliance with Good Clinical Practices

The sponsor has complied with good clinical practices.

3.3 Financial Disclosures

This application contains no covered clinical studies, and is supported by information from peer reviewed literature, textbooks and guidelines. Therefore, this requirement is not applicable to this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This new drug application is a 505(b)(2) literature based application. However no reference listed drug (RLD) was included or available. The absence of a RLD makes the chemistry, manufacturing and control review difficult, because it is not possible to evaluate the quality of the commercial product against the RLD to determine comparability and provide assurance that the commercial product will perform as labeled. The manufacturer did not provide quality information for any of the clinical studies as they had not supplied the product to the study's investigators. To bridge the quality of the historical product to the commercial product, the strategy of the CMC reviewers was to examine quality data for product on the market at the time that specific clinical studies were conducted. In addition the reviewers examined information on the history of the product' use as formulated in the NDA. The chemistry review team concluded that Bracco's historical products were all comparable to their proposed commercial products.

4.2 Preclinical Pharmacology/Toxicology

The Applicant stated that there was no pharmacology data available in the literature. The lack of preclinical pharmacology/toxicology data, does not importantly affect the assessment of the product safety. The clinical safety experience is sufficient for this purpose.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Barium sulfate is a contrast agent that enhances visualization of the GI tract by increasing the absorption of x-rays by the soft tissues. Barium sulfate has no pharmacological activity. It is essentially not absorbed from the GI tract and it is not metabolized. Barium sulfate is used to fill

the gastrointestinal tract lumen or to coat the mucosal surface and is administered orally, rectally, or by instillation into indwelling enterostomy tube or catheter. Barium sulfate is a heavy metal with a high atomic number (Z=56) and a K shell binding energy (K-edge of 37.4 keV) close to the mean energy of most diagnostic x-ray beams. Barium is therefore ideal for absorption of x-rays.

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. The barium suspension coats the mucosal surface of the GI tract so that its shape, distensibility, motion, integrity, continuity, location within the torso, relationship to other organs can be examined for diagnostic purposes. In this manner various masses such as benign or malignant tumors, ulcers, strictures, diverticula, inflammation or infection, altered motility, displacement and other pathology can be identified.

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 (e.g. sorbitol) are also used to induce fluid accumulation and distention of the gut to enhance visualization.

4.3.2 Pharmacokinetics and Pharmacodynamics

Barium sulfate is poorly soluble in water and demonstrates negligible absorption from the GI tract following either oral or rectal administration. It is excreted, unchanged, in the feces, the rate of excretion being dependent on the route of administration and the status of the patient's normal peristaltic activity and GI motility. In normal subjects, orally administered barium sulfate is generally excreted within 24 hours. Rectally administered barium sulfate is eliminated with evacuation of the enema.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

5.1.1 Esophagus and Upper Gastrointestinal Studies

Study Title	Study Design	Study Results
Kimura Y, Sugiura M, Kato T, Makino N, Ohmae Y, Kishimoto S. Value of barium swallow studies in predicting	To assess the usefulness of barium swallow studies for diagnosis of laryngopharyngeal reflux	The barium swallow was used to assess changes in LPRD in response to treatment.

the response to rabeprazole in elderly patients with laryngopharyngeal reflux disease and nonerosive reflux disease in particular. Ann Otol Rhinol Laryngol. 2010 Sep;119(9):631-5.	disease (LPRD). Study subjects were 59 patients of at least 60 years of age with LPRD suspected on laryngoscopic findings. Esophageal clearance was evaluated using a barium swallow study and the upper GI tract endoscopic findings of GERD according to the revised Los Angeles classification, and correlated these findings with the effect of rabeprazole, a proton pump inhibitor. Brand of barium product was not specified (10 mL of 130% w/v barium sulfate)	*Reviewer's comments: The study was not designed to evaluate the diagnostic performance of barium sulfate. The reviewer considers the use of barium sulfate to detect change from baseline in the appearance of the esophageal mucosa supportive of the clinical usefulness in structural delineation*
Fornari F, Gurski RR, Navarini D, Thiesen V, Mestriner LH, Madalosso CA. Clinical utility of endoscopy and barium swallow X-ray in the diagnosis of sliding hiatal hernia in morbidly obese patients: a study before and after gastric bypass. Obes Surg. 2010 Jun;20(6):702-8.	The aim was to assess the role of endoscopy and X-ray in the diagnosis of sliding hiatal hernia (SHH) in morbidly obese patients before and after gastric bypass (GBP) surgery. 92 patients underwent reflux symptoms evaluation, upper GI endoscopy, and barium swallow X-ray before and 6 months after banded GBP. The performance of endoscopy in diagnosing SHH was assessed, taking X-ray as reference. Endoscopy and X-ray were tested as predictors of SHH with GERD. Barium product was not specified (200 mL of diluted barium)	The study was designed to evaluate the clinical course of patients treated with GBP. *Reviewer's comments The study provides useful information regarding the ability of barium swallow to identify SHH. The radiographic technique has the advantage of evaluating the position of the GE junction which is more challenging to assess using endoscopy.*
Melman L, Quinlan JA, Hall BL, Brunt LM, Pierce RA, Halpin V, et al. Clinical utility	This study aimed to evaluate the use of routine barium esophagram after laparoscopic	Routine protocol barium esophagrams performed for 236 patients were used to

of routine barium esophagram after laparoscopic anterior esophageal myotomy for achalasia. Surg Endosc. 2009 Mar;23(3):606-10	anterior esophageal myotomy for achalasia. The records of 260 consecutive patients who underwent laparoscopic anterior esophageal myotomy for achalasia from May 1996 to August 2007 were reviewed from a prospective institutional review board-approved database. Barium sulfate product or dosing was not specified.	evaluate response to surgery. The surgeon relied on the radiographic findings to resume feeding. Acceptable flow of contrast was considered evidence of recovery of function. An abnormal barium esophagram (contrast retention or pooling, delayed emptying) led to delay in initiation of a diet. *Reviewer's comment The reviewer considered the clinical use of these functional assessments as supportive evidence of the utility of barium for structural delineation*
Linke GR, Borovicka J, Schneider P, Zerz A, Warschkow R, Lange J, et al. Is a barium swallow complementary to endoscopy essential in the preoperative assessment of laparoscopic antireflux and hiatal hernia surgery? Surg Endosc. 2008 Jan;22(1):96-100.	The objective of this study was to investigate the effective value of a barium swallow if complementary to the commonly recommended endoscopy before laparoscopic antireflux and hiatal hernia surgery. This study prospectively evaluated 40 consecutive patients who were tested with preoperative barium swallow and endoscopy before laparoscopic surgery for gastroesophageal reflux disease and/or symptomatic hiatal hernia. Results regarding the presence and the type of hiatal hernia found by barium swallow and endoscopy were correlated with the intraoperative finding as the reference standard. Barium sulfate product or	Intraoperative findings revealed 21 axial, 7 paraesophageal, and 12 mixed hiatal hernias. Barium swallow and endoscopy allowed the diagnosis of hiatal hernia in 75% and 98%, respectively. The correct classification of hiatal hernia was confirmed in 50% by barium swallow and 80% by endoscopy.

	dosing was not specified.	
Nawaz M, Jehanzaib M, Khan K, Zari M. Role of barium meal examination in diagnosis of peptic ulcer. J Ayub Med Coll Abbottabad. 2008 Oct-Dec;20(4):59-61.	The objective of this study was to compare the use of a barium meal examination in the diagnosis of peptic ulcer diseaseto endoscopy. Between Nov 2000 and March 2004, a total of 115 patients with signs and symptoms of peptic ulcer disease were selected for this study and underwent a barium meal examination. The diagnosis of benign/malignant peptic ulcer was made by barium meal examinations. In all these patients the diagnosis was later on confirmed by endoscopy and or surgery. Barium sulfate product or dosing was not specified. *Reviewer's comments: Strength of the study included prospective design and the use of a robust standard of truth (biopsy from endoscopy).*	Of the 115 patients, 80 were male and 35 were female patients. Their ages ranged from 27-75 years with mean age of 49 years. 52 patients had duodenal ulcer, 30 patients gastric ulcer, and 33 patients had normal radiological findings. In 6 out of 30 patients with gastric ulcer had radiological evidence of malignant gastric ulcer. The sensitivity of barium meal in diagnosing peptic ulcer was 97%, specificity 100%.
Chen BB, Liang PC, Liu KL, Hsiao JK, Huang JC, Wong JM, et al. Preoperative diagnosis of gastric tumors by three-dimensional multi-detector row CT and double contrast barium meal study: correlation with surgical and histologic results. J Formos Med Assoc. 2007 Nov;106(11):943-52.	The accuracy of multi-detector row CT (MDCT) was compared with double contrast barium meal (DCBM) for detection and differentiation (mucosal versus submucosal lesion) of gastric tumors. In addition, MDCT findings were correlated with surgical and pathologic results in gastric cancers for T and N stages. 79 patients with gastric tumors identified by gastric optical endoscopy were admitted for preoperative evaluation. All	Among the 79 patients with gastric tumors, there were 24 cases of early gastric cancer, 40 cases of advanced gastric cancer, 12 cases of GI stromal tumor, and 3 cases of gastric lymphoma.. The diagnostic accuracies of MDCT and DCBM were similar in differentiating mucosal and submucosal lesions as well as classification of Borrmann type in advanced gastric cancer.

	patients received DCBM study and abdominal MDCT with 3D reconstruction before surgery Study drug dosing: E-Z-HD (200-250 mL)	
Caylakli F, Yavuz H, Erkan AN, Ozer C, Ozluoglu LN. Evaluation of patients with globus pharyngeus with barium swallow pharyngoesophagography. Laryngoscope. 2006 Jan;116(1):37-9.	The objective of this study was to determine the value of barium swallow pharyngoesophagography in the investigation of patients with globus pharyngeus who had no known disease, no history of surgery in the head and neck region, and no thyroid pathology. The clinical presentation and radiologic findings were compared, to assess the diagnostic accuracy of barium swallow in such patients. Clinical records and radiologic reports of 194 patients with globus pharyngeus, were retrospectively reviewed. Barium sulfate product or dosing was not specified	Consistent with the clinical presentation, barium swallow findings showed no pathology. The majority of patients had benign radiologic findings, the remainder had completely normal examinations.
Kunisaki C, Ishino J, Nakajima S, Motohashi H, Akiyama H, Nomura M, et al. Outcomes of mass screening for gastric carcinoma. Ann Surg Oncol. 2006 Feb;13(2):221-8.	The objective of this retrospective study was to compare the detection of gastric cancer in 364 patients undergoing screening to 686 patients with a cancer scheduled for gastrectomy. Patient characteristics, therapeutic results, and prognostic factors were compared in the 2 groups. Barium sulfate product or dosing was not specified	The screened patients tended to be younger and male, with tumors in the middle third of the stomach that were of a macroscopically superficial type, with a smaller diameter, and at an earlier stage. They had fewer metastatic lymph nodes and underwent more frequent curative resection. Among the screened patients with curatively resected disease, tumors tended to be of a smaller diameter, and there were fewer metastatic lymph

		nodes in both early and advanced cases. Disease-specific survival was higher in the screened cases among all registered and curatively resected patients.. Multivariate analysis revealed that mass screening was an independent prognostic factor, together with depth of invasion, lymph node metastasis, age, and tumor diameter.
Hajioff D, Lowe D. The diagnostic value of barium swallow in globus syndrome. Int J Clin Pract. 2004 Jan;58(1):86-9.	The aim of this two-center retrospective study was to assess the diagnostic yield of barium swallow in patients (N=2854) with globus syndrome. Barium sulfate product or dosing was not specified.	Of 2854 barium swallows, 2514 (88%) were normal, 195 (7%) revealed minor abnormalities not requiring further intervention and 145 (5%) revealed potentially significant abnormalities.
Ukrisana P, Wangwinyuvirat M. Evaluation of the sensitivity of the double-contrast upper gastrointestinal series in the diagnosis of gastric cancer. J Med Assoc Thai. 2004 Jan;87(1):80-6.	To evaluate the use of the double-contrast UGI series in the diagnosis of gastric cancer, using pathological findings as the gold standard. Retrospective assessment of UGI exams in 84 patients with suspected gastric cancer and pathological confirmation by gastric biopsies and/or surgery. Barium sulfate dosing not specified (high density barium suspension and effervescent powder).	48 patients had gastric cancer at pathology. At UGI series, there were 45 true positive, 28 true negative, 8 false positive, and 3 false negative cases. The present findings indicate that the double-contrast UGI series has value for visualization.
Drudi FM, Trippa F, Cascone F, Righi A, Iascone C, Ricci P, David V, Passariello R. Esophagogram and CT vs endoscopic and surgical specimens in the diagnosis of esophageal carcinoma. Radiol	The aim of this retrospective study was to compare diagnostic imaging (barium and iodine contrast based with endoscopic examination in 39 patients with esophageal cancer.	Esophagogram identified neoplasm in 38 patients out of 39 supporting the ability of barium to visualize tumors

Med. 2002 Apr;103(4):344-52.	Barium sulfate dosing not specified (high-density barium suspension for double contrast esophagram; low density barium suspension for single-contrast esophagram)	
Le Blanc-Louvry I, Köning E, Zalar A, Touchais O, Savoye Collet C, Denis P, et al. Severe dysphagia after laparoscopic fundoplication: usefulness of barium meal examination to identify causes other than tight fundoplication--a prospective study. Surgery. 2000 Sep;128(3):392-8.	The aim of this study was to evaluate a barium meal examination in postoperative patients with (n=20) or without (n=31) severe dysphagia. A barium meal examination was interpreted by 3 independent blinded observers . Barium sulfate dosing not specified.	Barium meal examination revealed characteristic features in the symptomatic patients including cardial narrowing, mediogastric plication, and gastric volvulus. After laparoscopic fundoplication when upper endoscopy and esophageal manometry are normal, results of a barium meal examination can explain the cause of dysphagia. *Reviewer's comments: The study is useful in demonstrating the value of structural delineation for assessment of postoperative dysphagia.*
Schwickert HC, Schadmand-Fischer S, Jaeger U, Staritz M, Klose P, Uberschaer B, Thelen M. Motility disorders of the esophagus: diagnosis with barium-rice administration. Eur J Radiol. 1995 Dec 15;21(2):131-7	To evaluate the use of barium-rice administration in patients with dysphagia and esophageal motility disorders. 60 healthy volunteers and 218 patients with various esophageal disorders (achalasia, scleroderma and other connective tissue diseases, neurologic diseases, esophagitis and others) were examined both by a conventional barium study and by a barium-rice study. The barium-rice meal consisted of barium sulfate and boiled rice, mixed half and half. The time required for esophageal	Normal esophageal transit time was estimated in healthy controls for both methods. In patients, the transit time was greater than in controls. The proportion of patients with prolongued transit time was higher with the use of barium rice than with the conventional barium study, across all the underlying disease. This study supports the value of barium for structural delineation of the esophagous and suggests that this information has functional implications.

	clearance of one sip was measured. Barium sulfate product was not specified (high-density barium sulfate suspension; highdensity barium sulfate suspension mixed with boiled rice)	
Nellemann H, Aksglaede K, Funch-Jensen P, Thommesen P. Bread and barium. Diagnostic value in patients with suspected primary esophageal motility disorders. Acta Radiol. 2000 Mar;41(2):145-50.	To evaluate the use of bread and barium studies as a supplement to manometric studies for assessment of esophageal function in patients with suspected esophageal motility disorders. 89 patients underwent simultaneous roentgenologic and manometric investigations during wet and solid barium swallow, and during continuous drinking. Barium sulfate product was not specified: -10 mL barium suspension (0.4 g/mL barium sulfate); 2 wet swallows -barium paste (0.7 g/mL barium sulfate) mixed with bread and liver pate'; 6 g, -180 mL of barium suspension (0.4 g/mL barium sulfate) through a straw, twice	All patients with normal esophageal clearing (n=31) on barium swallow had normal manometry. Patients with delayed esophageal clearing on barium swallow (n=58) showed abnormal findings at manometry. *Reviewer's comments: The study provides evidence that visualization of the esophagus with barium mixed with food provides functional information that is consistent with information provided by manometry.*
Bender GN, Makuch RS. Double-contrast barium examination of the upper gastrointestinal tract with nonendoscopic biopsy: findings in 100 patients. Radiology. 1997 Feb;202(2):355-9.	To evaluate the use of double contrast barium examination of the upper gastrointestinal tract augmented with non-endoscopic gastric mucosal biopsy. 126 patients (aged 9-81 years) underwent double-contrast barium examination of the	19 of the patients with negative barium studies had a positive biopsy specimen, and 4 of the patients with positive barium studies had negative biopsy specimens. The results show that double-contrast barium examination of the upper GI tract can

	upper GI tract and nasogastric biopsy. Pathology reports were recovered for 100 patients. These patients' records were searched for procedural complications, sufficiency of biopsy tissue, diagnoses among various age groups, and radiographic findings. Barium sulfate product or dosing not specified.	provide useful information.
Admassie D. Relative sensitivity of barium swallow examination in the diagnosis of oesophageal pathology. East Afr Med J. 1996 Mar;73(3):201-3.	To evaluate barium swallow findings relative to surgical, histological, and esophagoscopic findings in 668 patients with dyspahagia 668 patients with dysphagia underwent barium swallow examination; 173 of them had either histologically confirmed diagnoses and/or surgical diagnoses or oesophagoscopic diagnoses. Barium sulfate product or dosing not specified.	The histological, oesophagoscopic and surgical diagnoses were: malignant tumours, achalasia, diverticula, peptic strictures, non-specific oesophagitis, Barium swallow findings were consistent with nearly all histological, oesophagoscopic and surgical diagnoses. A weakness of this study is the very small number of confirmatory tests. While performance results are not reliable, the study supports the value of barium sulfate for visualization and characterization of normal and abnormal anatomy

5.1.2 Barium Enema Studies

Study Title	**Study Design**	**Study Results**
Ferrucci JT. Double-contrast barium enema: use in practice and implications for CT colonography. AJR Am J Roentgenol. 2006 Jul;187(1):170-3.	This study examines the use and yield of DCBEs for colorectal polyp detection in current clinical practice outside the research setting. The authors retrospectively	A total of 244 double-contrast barium enemas were performed over the 4-year period. Overall, only 14 of the 244 studies gave positive reports for polyps, and of these, 5 were shown to be

	reviewed adult DCBE studies performed in routine clinical practice at a single academic institution from 2001 through 2004 by reviewing the official radiology and colonoscopy reports. Data were collected on indications for a DCBE, number of positive and negative DCBE reports, results of a DCBE after failed colonoscopy, and professional profiles of the radiologists who performed the DCBEs. Correlation for colon polyp detection was made by reviewing reports of colonoscopy performed within 12 months before or after a DCBE. Barium sulfate product or dosing not specified.	false-positive at later colonoscopy. Only 6 polyps 10 mm or larger were positively detected during the entire study, which is approximately one per 60 studies. In 104 patients who had negative DCBEs after failed or inconclusive colonoscopy, more than 50 subcentimeter polyps had been detected and removed, yet not one additional polyp was detected by a DCBE.
Frenette CT, Strum WB. Relative rates of missed diagnosis for colonoscopy, barium enema, and flexible sigmoidoscopy in 379 patients with colorectal cancer. J Gastrointest Cancer. 2007;38(2-4):148-53.	This study was designed to determine relative rates of failures for these tests when applied to diagnosis of colorectal cancer. Failures of diagnosis of colorectal cancer by colonoscopy, barium enema, and flexible sigmoidoscopy have been demonstrated using various techniques. A database of patients with colorectal cancer diagnosed between 2000 and 2005 was created. Records were reviewed for the results of colonoscopy, barium enema, and flexible sigmoidoscopy in the 3 years prior to diagnosis. An examination that was negative for cancer with no	379 patients, who had 421 examinations, were analyzed. The diagnosis of colorectal cancer failed in 60 of 379 patients (16%). These 60 patients had 71 examinations that failed to make the diagnosis: 25 of 282 colonoscopies (9%), 16 of 79 barium enemas (20%), and 30 of 60 flexible sigmoidoscopies (50%). *Reviewer's comments: Study is retrospective in design. It only assessed patients with cancer, rather than a patient population undergoing cancer screening. It did not assess diagnostic performance characteristics.*

	immediate follow-up was defined as a failure of diagnosis, either from inaccurate observation, failure to examine the entire colon, or failure of timely follow-up. The failure rates were compared. Barium sulfate product or dosing not specified.	
Kung JW, Levine MS, Glick SN, Lakhani P, Rubesin SE, Laufer I. Colorectal cancer: screening double-contrast barium enema examination in average-risk adults older than 50 years. Radiology. 2006 Sep;240(3):725-35.	The study's objective was to retrospectively determine the diagnostic yield of double-contrast barium enema (DCBE) examinations performed for colorectal cancer screening of neoplasms 1 cm or larger or advanced neoplastic lesions of any size in average-risk adults older than 50 years. Computerized databases revealed 276 DCBE examinations performed for colorectal cancer screening in average-risk adults older than 50 years. Radiographic and pathologic reports were reviewed to determine the number of patients who had polypoid lesions 1 cm or larger, polyps smaller than 1 cm, or advanced neoplastic lesions of any size. 45 (16%) of the 276 patients underwent follow-up sigmoidoscopy or colonoscopy. Medical, endoscopic, and pathologic records were reviewed as the standard of truth and compared with radiographic findings.	The results of DCBE examination revealed 74 of 276 patients with 104 polypoid lesions in the colon, including 32 patients with 41 polypoid lesions 1 cm or larger, 15 patients with 19 polyps 6-9 mm, and 27 patients with 44 polyps 5 mm or smaller. Endoscopy was performed in 24 of 32 patients, the results of which confirmed 23 (72%) of 32 radiographically diagnosed lesions 1 cm or larger in 16 (67%) of 24 patients. In 2 of these individuals, the polyps were hyperplastic. The remaining 14 patients had a total of 21 neoplastic lesions 1 cm or larger. The diagnostic yield of screening DCBE examination was 5% (14 of 276 patients) for neoplastic lesions 1 cm or larger and 6% (17 of 276 patients) for advanced neoplastic lesions of any size.

	Barium sulfate product was Liquid Polibar Plus, but its dosing was not specified.	
Tawn DJ, Squire CJ, Mohammed MA, Adam EJ. National audit of the sensitivity of double contrast barium enema for colorectal carcinoma, using control charts For the Royal College of Radiologists Clinical Radiology Audit Sub-Committee. Clin Radiol. 2005 May;60(5):558-64.	This study audited the sensitivity of double contrast barium enema (DCBE) for colorectal carcinoma, as currently practiced in UK departments of radiology. As part of its program of national audits, the Royal College of Radiologists Clinical Radiology Audit Sub-Committee undertook a retrospective audit of the sensitivity of DCBE for colorectal carcinoma during 2002. The following targets were set: demonstration of a lesion ≥ 95%; correct identification as a carcinoma ≥90%. Barium sulfate product or dosing not specified.	Across the UK, 131 departments took part in the audit, involving 5454 examinations. The mean demonstration rate was 93% and the diagnosis rate was 86%, slightly below the targets set. The equivocal rate (lesion demonstrated, but not defined as malignant) was 7%, the perception failure rate was 3% and the technical failure rate was 4%. *Reviewer's comments: the study is retrospective in design and has a selection bias since less than half of the departments responded (hence selection bias: a self-selection). The study only intends to measure sensitivity and does not assess specificity. Nonetheless the strength of the study is its large scale multi-center design. Most of the other publications submitted in the NDA are single center studies.*
Johnson CD, MacCarty RL, Welch TJ, Wilson LA, Harmsen WS, Ilstrup DM, et al. Comparison of the relative sensitivity of CT colonography and double-contrast barium enema for screen detection of colorectal polyps. Clin Gastroenterol Hepatol. 2004;2:314-21	The main objective of the study aimed to compare the relative sensitivity and specificity of CT colonography with DCBE for detection of colorectal polyps in an asymptomatic low prevalence population. This prospective, blinded study comprised 837 asymptomatic subjects at higher than average risk for colorectal cancer who	The sensitivity of DCBE varied between 39% and 56% for the 31 polyps ≥1 cm. Relative specificity for polyps ≥1cm on a per patient basis ranged from 99%-100% at DCBE. CT colonography and DCBE had similar performance in full structural examinations when interpreted by a single examiner. *Reviewer's comments: strength of the study included*

	underwent CT colonography followed by same-day DCBE. Examinations with polyps ≥5 mm in diameter were referred to colonoscopy. Barium sulfate product (high-density barium [80% w/v]) or dosing not specified	*prospective design with blinded readers. The study population (asymptomatic subjects undergoing cancer screening) was appropriate. The study father assessed the performance characteristics including sensitivity and specificity of DCBE.*
Tan KY, Seow-Choen F, Ng C, Eu KW, Tang CL, Heah SM. Which colorectal cancers are missed by double contrast barium enema? Tech Coloproctol. 2004 Nov;8(3):169-72.	This study aims to evaluate the accuracy of DCBE as read by the initial consultant radiologist for detection of colorectal cancers in patients presenting with large bowel symptoms. To identify type and characteristics of lesions missed at DCBE. Clinical data were reviewed for all patients who underwent DCBE within the 6 months prior to surgical resection of colorectal cancer between April 1989 and April 1999. Patient demographics and tumor characteristics were analyzed for their effects on the likelihood of the lesions being missed at DCBE. Barium sulfate product or dosing not specified.	There were 706 patients included in the study. A total of 29 DCBE examinations failed to detect the colorectal cancer subsequently found on endoscopic evaluation (4% of 706 examinations). Conversely, DCBE detected 96% of all cancers. Tumors less than 3 cm in length and with lesser extent of circumferential involvement were more likely missed at DCBE. The mean follow-up was 65 months.
Ota Y, Matsui T, Ono H, Uno H, Matake H, Tsuda S, Sakurai T, Yao T. Value of virtual computed tomographic colonography for Crohn's colitis: comparison with endoscopy and barium enema. Abdom Imaging. 2003 Nov-Dec;28(6):778-83.	In this study the visualization ability of CTC was compared with that of BE and colonoscopy. A total of 42 lesions in 33 patients with Crohn's disease were examined by virtual computed tomographic colonography (CTC) and barium enema (BE). 22 patients also were examined by colonoscopy.	In the visualization of elevated lesions, the performances of CTC, BE and colonoscopy were similar. CTC enabled identification of serious lesions in the colon proximal to the stenosis in 9 patients and was superior to BE and colonoscopy in terms of its ability to visualize the proximal site of the stenosis. BE visualized a higher number

	Barium sulfate product or dosing not specified.	of elevated lesions and ulcerative lesions than CTC.
Chong A, Shah JN, Levine MS, Rubesin SE, Laufer I, Ginsberg GG, Long WB, Kochman ML. Diagnostic yield of barium enema examination after incomplete colonoscopy. Radiology. 2002 Jun;223(3):620-4.	The objective of this study was to determine the use of BE examination for neoplastic lesions larger than 1 cm in diameter in the nonvisualized portion of the colon after incomplete colonoscopy. A review of computerized gastroenterology and radiology databases identified 355 patients who underwent incomplete colonoscopy; subsequent BE examination was performed in 158 of them. The radiographic reports were reviewed and compared with the endoscopic reports by 1 author to identify neoplastic lesions larger than 1 cm in the nonvisualized colon after incomplete colonoscopy. Barium sulfate product or dosing not specified.	BE examination depicted 6 possible lesions in the nonvisualized colon after incomplete colonoscopy; 5 were found to be true-positive radiographic findings, and 1 was found to be a FP finding. The 5 true-positive findings included 2 annular lesions (both adenocarcinomas) and 3 polypoid lesions (all tubulovillous adenomas, with high grade dysplasia in one). Thus, neoplastic lesions larger than 1 cm were found on BE images in the nonvisualized colon in 5 (3%) of 158 patients after incomplete colonoscopy. These findings suggest that BE is a useful test for detecting clinically important colorectal neoplasms in this group of patients with incomplete colonoscopy.
Ciatto S, Castiglione G. Role of double-contrast barium enema in colorectal cancer screening based on fecal occult blood. Tumori. 2002 Mar-Apr;88(2):95-8.	The present study evaluated the contribution of DCBE in detecting neoplastic lesions of the colon in fecal occult-blood positive subjects with incomplete colonoscopy. Subjects with a positive fecal occult-blood test were invited to undergo total colonoscopy. Incomplete colonoscopy prompted DCBE. Type and rate of neoplastic lesions detected by endoscopy or DCBE as single methods or combined were evaluated. A total of 38,829 subjects	. DCBE was useful in detecting colorectal cancer beyond the range reached by incomplete colonoscopy. The diagnostic contribution observed in the present survey confirms the usefulness of DCBE as a routine adjunct to incomplete colonoscopy.

	underwent fecal occult-blood testing in the period 1993-2000. Overall, 1542 were positive. Assessment was refused by 235 subjects. Out of 1307 subjects accepting assessment, total colonoscopy was attempted in 1294; of these, total colonoscopy was not possible in 343 cases, and DCBE was advised and performed in 261 subjects. Barium sulfate product or dosing not specified.	
Blakeborough A, Chapman AH, Swift S, Culpan G, Wilson D, Sheridan MB. Strictures of the sigmoid colon: barium enema evaluation. Radiology. 2001 Aug;220(2):343-8.	This study aims to assess the role of radiologic interpretation, in the absence of clinical information, in the differentiation of benign and malignant sigmoid strictures at BE examination. On 2 occasions, 4 independent observers retrospectively assessed examination findings in 78 patients with documented sigmoid strictures. Each stricture was graded by using a 5-point scale (definitely malignant to definitely benign). Barium sulfate product or dosing not specified.	There were 43 benign and 35 malignant strictures. Consensus findings indicated agreement among at least 3 of the 4 observers in 68 (87%) and 66 (85%) cases at the first and second assessments, respectively.
Brown AL, Skehan SJ, Greaney T, Rawlinson J, Somers S, Stevenson GW. Value of doublecontrast barium enema performed immediately after incomplete colonoscopy. AJR Am J Roentgenol. 2001 Apr;176(4):943-5.	The purpose of this study was to evaluate the ease, completeness, and clinical utility of DCBE performed immediately after incomplete colonoscopy. During a 30-month period, a prospective study was performed in 103 patients to	DCBE revealed the entire colon in 97 patients (94%). Incomplete DCBE was a result of obstruction and incontinence in 3 patients each. The mean score for ease of performing DCBE was 5.0. In 14 patients (14%), significant additional diagnostic information was

	determine the ease and completeness of DCBE immediately after failed colonoscopy and any additional useful information provided by the enema. The ease with which DCBE was performed was graded from 1 (easy) to 10 (difficult). Barium sulfate product was Polibar Plus (E-Z-EM). Barium sulfate dosing was not specified.	provided by the immediate DCBE. In 8 patients, abnormalities were identified on DCBE that had not been seen at colonoscopy (5 malignant neoplasms, 1 diverticular mass, 2 extrinsic masses, and multiple strictures). In 4 patients, a suspected colonoscopic abnormality was excluded with DCBE findings; and in 2 patients, a colonoscopic abnormality was further characterized with DCBE.
Gillespie JS, Kelly BE. Double contrast barium enema and colorectal carcinoma: sensitivity and potential role in screening. Ulster Med J. 2001 May;70(1):15-8.	The aim of this study is to assess the usefulness of DCBE for detection of colorectal carcinoma and consider its possible role as a suitable imaging method in screening for this disease. A total of 160 patients with a histopathologically proven diagnosis of colorectal carcinoma over a 2-year period were reviewed. Subsequently 112 of the 160 patients were identified as having undergone DCBE, the results of which were analyzed to determine its sensitivity for detecting colorectal carcinoma. Barium sulfate product or dosing not specified.	Colorectal carcinoma was missed in 4 of the 112 BEs performed. This corresponds to a sensitivity of 97% with a FN rate of 4%. This study correlates with previous studies showing a FN rate for DCBE of 3.5%. Colonoscopy also fails to detect small numbers of tumors with FN rates reported as high as 10%..
McDonald S, Lyall P, Israel L, Coates R, Frizelle F. Why barium enemas fail to identify colorectal cancers. ANZ J Surg. 2001 Nov;71(11):631-3.	The aim of the present study was to determine the cause and clinicopathological factors associated with the failure of BEs to detect colorectal cancers.	There were 967 patients with colorectal cancers treated during the study period 1991-1995. Matching of these patient details with all BE records revealed 313 patients

	A histopathological database was used to identify all patients with a diagnosis of colorectal cancer between 1991 and 1995. These records were matched with the records from patients who underwent BE examinations between 1990 and 1995. Those patients who had a colorectal cancer histologically diagnosed within 24 months of a barium enema in which no carcinoma was seen, were identified. Where possible the radiology was reviewed. Failure to identify a carcinoma was then attributed to either simple failure, technical, interpretive or perceptive difficulties. Barium sulfate product or dosing not specified.	who had BEs and histologically proven colorectal cancer. There were 21 (7%) patients in whom a carcinoma was missed. On review, 11 carcinomas could not be identified (9 due to technical error: poor coating (n = 1), overlapping loops (n = 3), SCBE (n = 4), fecal residue (n = 1)); and 7 could be seen on review of the films (2 interpretation errors, 1 technical and perceptive error, and 4 perceptive errors). In 3 cases films could not be found for review. In 16 of the 21 missed lesions the patient had a double contrast barium enema (DCBE) while 5 patients had single contrast barium enema (SCBE). The cuse of barium enema for diagnosis of colorectal malignancy is dependent on strict quality control. The most common reason for missed tumors was technical.
Smith GA, O'Dwyer PJ. Sensitivity of double contrast barium enema and colonoscopy for the detection of colorectal neoplasms. Surg Endosc. 2001 Jul;15(7):649-52.	The aim of this study was to evaluate the sensitivity of DCBE and colonoscopy for the detection of colorectal cancer and neoplastic polyps ≥1 cm. All patients undergoing DCBE (1389) or colonoscopy (1081) as the primary investigation for large bowel symptoms or for cancer or polyp surveillance in the first 9 months of 1997 at a large teaching hospital were included in this study. At 1	In the DCBE group, 47 patients (4%) had a cancer diagnosed; 8 of them had been missed at the primary investigation (sensitivity 83%). Neoplastic polyps ≥1 cm were diagnosed in 2% of the DCBE group. 9 patients had a FP diagnosis of cancer in the DCBE group. The sensitivity of colonoscopy was 98%. Due to study design limitations the performance values are considered descriptive.

	and 2 years following investigation, a computerized search of appropriate diagnosis and procedure codes to detect any missed cancers or polyps was performed for all patients with a normal investigation. Barium sulfate product or dosing not specified.	
Civelli EM, Gallino G, Mariani L, Cozzi G, Biganzoli E, Salvetti M, et al. Double-contrast barium enema and computerized tomography in the pre-operative evaluation of rectal carcinoma: are they still useful diagnostic procedures? Tumori. 2000 Sep-Oct;86(5):389-92.	A retrospective analysis of the parameters obtained with DCBE and endorectal balloon CT was conducted to assess their diagnostic performance. 53 consecutive patients with adenocarcinoma of the distal half of the rectal ampulla underwent DCBE examination, CT of the pelvis with endorectal balloon, and surgery. On the basis of the DCBE and CT assessment the following were evaluated: 1) the distance between the cranial extremity of the anal canal and the distal margin of the neoplasm; 2) the radial diffusion of the tumor; 3) the metastatic involvement of the perirectal and inferior mesenteric lymph nodes. Imaging data were compared with pathology information. Barium sulfate product or dosing not specified.	CT and DCBE measurements of tumor distal margin were similar, although both techniques tended to overestimate the measurement when compared to the pathologic examination. The discrepancy between imaging and pathology could be explained with the fixation of surgical specimens in formalin which causes axial shortening of the viscera. The diagnostic information provided by the radiological examinations is comparable to that of clinical and instrumental methods currently employed for local staging of rectal carcinoma (transrectal ultrasound and endoscopic ultrasound).
Segal R, Khahil A, Leibovitz A, Gil I, Annuar M, Habot B. Barium enema in frail elderly patients. Gerontology. 2000 Mar-Apr;46(2):78-82.	The purpose of this study was to evaluate the role of barium enema (BE) in hospitalized frail elderly patients.	192 (41%) BE examinations were considered inadequate because of inappropriate preparation (n=150; 32%); or inability to retain contrast

	472 elderly patients hospitalized for different reasons underwent BE examinations. The medical charts and radiological reports were retrospectively reviewed. Single contrast barium enema was performed in 98% of the patients. Barium sulfate product or dosing not specified.	material. The characteristics associated with unsuccessful BE examination were the patient's functional status, presence of dementia, the mean number of medical problems, the mean number of scheduled medications and in particular the long-term use of laxatives or antiparkinsonian drugs.
Sayer JM, Donnelly MT, McIntyre AS, Barton JR, Grundman MJ, Vicary FR, Long RG. Barium enema or colonoscopy for the investigation of iron deficiency anaemia? J R Coll Physicians Lond. 1999 Nov-Dec;33(6):543-8.	The study evaluated the role of double contrast barium enema (DCBE) for excluding carcinoma of the colon in patients with iron deficiency anemia. Prospective audit. 123 patients with iron deficiency anemia. All patients had upper GI endoscopy, duodenal biopsy and DCBE. Malignant disease and other GI pathology were treated. Patients with recurrent or persistent anemia at follow-up were colonoscoped. Barium sulfate product or dosing not specified.	GI lesion contributing to anemia and 11 colon cancers were found in 71% of patients, all identified on barium enema. Two pre-cancerous conditions were missed on barium enema examination.

5.1.3 Small Bowel Studies

Study Title	**Study Design**	**Study Results**
Rajesh A, Sandrasegaran K, Jennings SG, Maglinte DD, McHenry L, Lappas JC, Rex D. Comparison of capsule endoscopy with enteroclysis in the investigation of small bowel disease. Abdom Imaging. 2009 Jul;34(4):459-66.	The objective of the study is to compare results of capsule endoscopy with those of barium enteroclysis or CT enteroclysis. Retrospective review of hospital records revealed 65 patients who had an	Patients with obscure GI bleeding (n = 37) or suspected Crohn disease (n = 17) were enrolled. Radiologic studies included CT enteroclysis (n = 30), and fluoroscopic barium enteroclysis (n=35). The diagnostic yield of capsule endoscopy and barium-carbon

	enteroclysis and small bowel capsule endoscopy. The diagnostic yield of capsule endoscopy was compared with the enteroclysis. Barium sulfate product or dosing not specified. Barium was used with either methylcellulose or carbon dioxide under fluoroscopic enteroclysis.	dioxide enteroclysis were similar.
Amitai MM, Arazi-Kleinman T, Hertz M, Apter S, Portnoy O, Guranda L, et al. Multislice CT compared to small bowel follow-through in the evaluation of patients with Crohn disease. Clin Imaging. 2008 Sep-Oct;32(5):355-61.	A comparison of the findings on CT and Small Bowel Follow-Through (SBFT) in patients with Crohn disease (CD) was performed. The CT and SBFT studies were reviewed of 41 patients with CD. The findings were evaluated by 3 experienced abdominal imagers. Barium sulfate product or dosing not specified. Gastrografin for CT.	The detection of mural involvement of the small bowel was similar for the two radiologic procedures.
Solem CA, Loftus EV Jr, Fletcher JG, Baron TH, Gostout CJ, Petersen BT, et al. Small bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial. Gastrointest Endosc. 2008 Aug;68(2):255-66.	The objective of the study was to compare capsule endoscopy, CT enteroclysis (CTE), ileocolonoscopy, and Small Bowel Follow-Through (SBFT) in the diagnosis of small bowel Crohn's disease. Prospective, blinded trial. Sensitivity, specificity, and accuracy of each test to detect active small-bowel Crohn's disease. The standard of truth was a consensus diagnosis based upon clinical presentation and all 4 studies. Liquid E-Z-Paque for SBFT	41 CTE examinations were performed, 40 patients underwent colonoscopy, 38 had SBFT studies, and 28 had capsule endoscopy examinations. Small-bowel Crohn's disease was active in 51%, absent in 42%, inactive in 5%, and suspicious in 2% of patients. The sensitivity of SBFT for detecting active small-bowel Crohn's disease was 65% and similar to that of the other modalities. SBFT was numerically higher than capsule endoscopy in

		specificity.
Angriman I, Scarpa M, Ruffolo C, Pomerri F, Filosa T, Polese L, et al. Double contrast small-bowel radiography in the preoperative assessment of Crohn's disease: is it still useful? Surg Today. 2008;38(8):700-4.	The study evaluated the usefulness of double contrast Small Bowel Radiography (SBR) in the preoperative assessment of patients with Crohn's disease. 39 consecutive patients who underwent surgery for Crohn's Disease between 2000 and 2004, preceded by a preoperative small-bowel series evaluation, were enrolled in the study. The radiologic findings were compared with the intraoperative findings. Barium sulfate product not specified. 120- 160 mL of diluted barium suspension followed by 1500- 2000 mL of aqueous suspension of methylcellulose through a nasogastric tube	The detection of stenosis was numerically higher than the detection of internal fistulas.
Minordi LM, Vecchioli A, Guidi L, Mirk P, Fiorentini L, Bonomo L. Multidetector CT enteroclysis versus barium enteroclysis with methylcellulose in patients with suspected small bowel disease. Eur Radiol. 2006 Jul;16(7):1527-36.	The purpose of this study was to evaluate the diagnostic accuracy of Multi-Detector CT (MDCT)-Enteroclysis versus barium enteroclysis with methylcellulose (B-Ent) in clinically selected patients with suspected small bowel disease. 52 patients who underwent noncontrast and postcontrast MDCT (16 rows) after administration of 2-2.5 L of methylcellulose by naso-jejunal tube were prospectively studied. B-Ent was performed after administration of barium 60%	In total, barium enteroclysis (B-Ent) identified 30 patients with Crohn's disease. Sensitivity and specificity of B-Ent using endoscopy as reference standard was 96% and 100%, respectively. Early stages of Crohn's disease are better evaluated by B-Ent.

	w/v (200-250 mL) and methylcellulose (1-2 L). 28 patients also underwent endoscopy. Barium sulfate product not specified. 200- 250 mL 60% w/v suspension of 60% barium sulfate, followed by 1000-2000 mL (mean: 1200 mL) 0.5% methylcellulose infusion for B-Ent	
Buchman AL, Miller FH, Wallin A, Chowdhry AA, Ahn C. Videocapsule endoscopy versus barium contrast studies for the diagnosis of Crohn's disease recurrence involving the small intestine. Am J Gastroenterol. 2004 Nov;99(11):2171-7.	This study was undertaken to evaluate Videocapsule endoscopy (VCE) relative to Small Bowel Follow-Through (SBFT) in the assessment of active disease in patients with known Crohn's disease. 30 subjects with prior diagnosis of Crohn's disease and clinical suspicion of recurrent disease were assessed in a prospective, blinded comparative study of VCE versus SBFT. SBFT was performed first; subjects with stricture and proximal bowel dilation were excluded from further evaluation. SBFT was scored as grade 0 (normal), grade 1 (minimal nodularity, ulcerations, normal luminal diameter, <5 cm involved), grade 2 (more extensive ulcers, minimal luminal narrowing, 5-10 cm involved), or grade 3 (fistula, skip areas, extensive ulceration, >10 cm involved). E-Z-Paque (1000 mL) was the barium sulfate study drug.	Active Crohn's disease was visualized in 20 of 30 patients with SBFT. SBFT found mucosal disease in 20 of 30 patients and VCE found mucosal disease in 21 of 30 patients. SBFT showed Crohn's disease in 5 patients (all grade 1) with normal VCE. SBFT may be required to detect strictures as the videocapsule may not pass.
Eliakim R, Suissa A, Yassin	The study evaluated capsule	35 patients with abdominal

K, Katz D, Fischer D. Wireless capsule video endoscopy compared to barium follow-through and computerised tomography in patients with suspected Crohn's disease—final report. Dig Liver Dis. 2004 Aug;36(8):519-22.	endoscopy with barium follow-through and entero-CT in patients with suspected Crohn's disease. 35 patients with suspected Crohn's disease underwent a barium follow-through, and if there was no contraindication (i.e. stricture), they swallowed the capsule, followed by an entero-CT. All three procedures were completed within 3 months of each other. The readers (radiologist and gastroenterologist) were blinded to each other's results. In cases of discrepancy, colonoscopy and ileoscopy were performed Barium sulfate product or dosing not specified.	pain, diarrhea and/or weight loss were included. Small bowel follow-through found abnormalities in 50% of cases. These abnormalities included wall thickening, nodularity in terminal ileum, and ulcers. Radiographic abnormalities were medically significant with regard to the patient's complaints in 9 cases, leading to a diagnostic yield of approximately 25%.
Cirillo LC, Camera L, Della Noce M, Castiglione F, Mazzacca G, Salvatore M. Accuracy of enteroclysis in Crohn's disease of the small bowel: a retrospective study. Eur Radiol. 2000;10(12):1894-8.	The aim of this study was to evaluate the accuracy of enteroclysis in the diagnosis of Crohn's disease of the small bowel in a group of consecutive patients. From January 1992 to December 1995, 165 patients with suspected Crohn's disease of the small bowel presented to the institution for enteroclysis. Most patients (78%) underwent colonoscopy and retrograde ileoscopy, which were used as standard of truth. In the remaining patients clinical follow-up was used as the standard of truth. Barium sulfate product not specified. Preselected amount	In 79 patients no radiographic abnormalities were found and 61 patients had a radiological diagnosis of Crohn's disease. In some of these patients retrograde ileoscopy (used as a form of standard of truth) was not feasible. 21 patients underwent surgery, and surgical pathology was another form of standard of truth. Overall, enteroclysis detected nearly all cases of active disease.

	of barium and methylcellulose was infused through a catheter positioned at the duodenal flexure	
Moch A, Herlinger H, Kochman ML, Levine MS, Rubesin SE, Laufer I. Enteroclysis in the evaluation of obscure gastrointestinal bleeding. AJR Am J Roentgenol. 1994 Dec;163(6):1381-4.	The diagnostic yield of enteroclysis was retrospectively evaluated for patients with obscure bleeding from the GI tract. A total of 128 patients with obscure GI bleeding were referred for enteroclysis between 1988 and 1993. The original radiologic reports were reviewed to determine the radiographic findings in these patients. The radiographic findings then were correlated with medical, surgical, and pathologic findings. Barium sulfate product or dosing not specified.	A total of 32 patients had lesions found at enteroclysis. 19 of those patients had confirmation of the radiographic diagnosis, primarily by pathologic examination of the surgical specimen. 5 other patients were found at surgery to have had FP diagnoses at enteroclysis. 8 patients ceased to bleed without pathologic corroboration, but their clinical presentation and course supported the radiographic diagnosis. Thus, 27 (21%) of the 128 patients had confirmed or highly probable lesions seen at enteroclysis as the cause of obscure GI bleeding. 17 patients (13%) had tumors involving the small bowel, and 3 (2%) had arteriovenous malformations in the jejunum. Enteroclysis is a useful for examining the small intestine in patients with obscure GI bleeding.

5.1.4 Modified Barium Swallow Studies

Study Title	**Study Design**	**Study Results**
Logemann JA, Gensler G, Robbins J, Lindbald AS, Brandt D, Hind JA, et al. A randomized study of three interventions for aspiration of thin liquids in patients with dementia or Parkinson's	The objective of the study was to identify which of 3 treatments for aspiration on thin liquids —chin-down posture, nectar-thickened liquids, or honey-thickened liquids—results in the most	Immediate elimination of aspiration on thin liquids occurred most often with honey thickened liquids, followed by nectar-thickened liquids and chin-down posture. Patients with most severe

Disease. J Speech Lang Hear Res. 2008 Feb;51(1):173-83.	successful immediate elimination of aspiration on thin liquids during the videofluorographic swallow study in patients with dementia and/or Parkinson's disease. This randomized clinical trial included 711 patients (ages 50 to 95 years) from 1998 to 2005 who aspirated on thin liquids as assessed videofluorographically. All patients received all 3 interventions in a randomly assigned order during the videofluorographic swallow study. Varibar (thin, nectar-thick, and honey-thick barium solutions) were used for the study.	dementia exhibited least effectiveness on all interventions. To identify best short-term intervention to prevent aspiration of thin liquid in patients with dementia and/or Parkinson's disease, a videofluorographic swallow assessment is useful. *Reviewer's comments: The study was designed to evaluate the effectiveness of treatments of aspiration, rather than designed to evaluate the value of barium swallow imaging test in assessing these patients with dysphagia. Nonetheless barium swallow was used to monitor aspiration as it is being treated with 3 different methods, demonstrating clinical value of barium swallow in assessing aspiration in dysphagic patients.*
Allen JE, White C, Leonard R, Belafsky PC. Comparison of esophageal screen findings on videofluoroscopy with full esophagram results. Head Neck. 2012 Feb;34(2):264-9	The aim of the study was to compare findings from the "esophageal screening" with the results of a full standard esophagram. Patients undergoing videofluoroscopic swallowing studies with an esophageal screen followed by full esophagram between January 1, 2009 and October 1, 2009 were retrospectively reviewed. Comparison of esophageal screening and full standard esophagram results were undertaken, with esophagram used as the gold standard. Esophageal screening: E-Z-	74 patients underwent esophageal screening and esophagram. With full standard esophagram used as the gold standard, esophageal screening identified 44/70 (63%) patients with esophageal disease.

	Paque (20 mL) Full esophagram: E-Z-Gas II and high-density liquid barium (E-Z-EM)	
Aviv JE. Prospective, randomized outcome study of endoscopy versus modified barium swallow in patients with dysphagia. Laryngoscope. 2000 Apr;110(4):563-74.	The purpose of this study was to provide an initial investigation of FEESST and MBS as the diagnostic test for evaluating and guiding the behavioral and dietary management of outpatients with dysphagia. Randomized, prospective cohort outcome study in a hospital based outpatient setting. 126 outpatients with dysphagia were randomly assigned to either FEESST or MBS as the diagnostic test used to guide dietary and behavioral management (postural changes, small bites and sips, throat clearing). The outcome variables were pneumonia incidence and pneumonia-free interval. The patients were enrolled for 1 year and followed for 1 year. Barium sulfate for suspension, 340 g diluted with 65 mL of water to yield 1250 mL suspension, 85% w/w, 250% w/v.	78 MBS examinations were performed in 76 patients with 14 patients developing pneumonia; 61 FEESST examinations were performed in 50 patients with 6 patients developing pneumonia. These outcomes were similar. .
Schima W, Ryan JM, Harisinghani M, Schober E, Pokieser P, Denk DM, Stacher G. Radiographic detection of achalasia: diagnostic accuracy of videofluoroscopy. Clin Radiol. 1998 May;53(5):372-5.	The purpose of this study was to retrospectively evaluate the accuracy of videofluoroscopy in the diagnosis of achalasia. Videofluoroscopic studies of the esophagus of 53 patients with manometrically revealed diagnosis of achalasia were	Non-specific oesophageal motor abnormalities were diagnosed radiographically in 18 patients (34%) and a normal motility was found in four patients (8%).

	retrospectively evaluated. The videofluoroscopic examination was performed with 1 swallow of low-density barium suspension in the erect and up to 3 swallows in the prone oblique position. Barium sulfate product not specified (10-mL bolus of low-density barium suspension).	

5.1.5 Fecal Tagging Studies

Study Title	Study Design	Study Results
Taylor SA, Slater A, Burling DN, Tam E, Greenhalgh R, Gartner L, et al. CT colonography: optimization, diagnostic performance and patient acceptability of reduced-laxative regimens using barium-based faecal tagging. Eur Radiol. 2008;18:32-42.	To establish the optimum barium based fecal tagging regimen prior to CT Colonography (CTC). 95 subjects underwent reduced-laxative (13 g senna/18 g magnesium citrate) CTC prior to same-day colonoscopy and were randomized to 1 of 4 tagging regimens using 20 ml 40%w/v barium sulfate: regimen A: 4 doses, B: 3 doses, C: 3 doses plus 220 mL 2.1% barium sulfate, or D: 3 doses plus 15 mL diatriazoate megluamine. Patient experience was assessed immediately after CTC and 1 week later. Patient responses were compared to a prior study comparing CTC to colonoscopy. 2 radiologists graded residual stool (1: none/scattered to 4: >50% circumference) and tagging efficacy for stool (1:	Preparations were good, although best for regimen D. Across all regimens, stool tagging quality was high and similar among regimens. Reduced-laxative CTC with 3 doses of 20 mL 40% barium sulfate is as effective as more complex regimens, retaining adequate diagnostic accuracy.

	untagged to 5: 100% tagged) and fluid (1: untagged, 2: layered, 3: tagged), noting the HU of tagged fluid. Study drug dosing: Tagitol V (20 mL 40% w/v barium sulfate)	

5.1.6 Pediatric Barium Enema Studies

Study Title	**Study Design**	**Study Results**
Reid JR, Buonomo C, Moreira C, Kozakevich H, Nurko SJ. The barium enema in constipation: comparison with rectal manometry and biopsy to exclude Hirschsprung's disease after the neonatal period. Pediatr Radiol. 2000 Oct;30(10):681-4.	The study asked how frequently a diagnosis of Hirschsprung's disease was made by biopsy or manometry in children who had normal BE. Age range: 4 weeks to 15 years The medical records and barium enema (BE) of 54 patients older than 28 days with constipation or difficulty passing stool who had a BE followed by manometry and/or biopsy were reviewed. Barium sulfate product or dosing not specified.	48 patients had normal enemas: 24 of those patients had biopsies, 16 had manometry, and 8 both manometry and biopsy. Of the 48, 1 had confirmed Hirschsprung's disease (one FP). 6 patients had abnormal enemas suggesting Hirschsprung's disease; however, only 5 had biopsy and manometry compatible with Hirschsprung's disease and 1 had a normal biopsy and manometry study (1 FP). Therefore, barium enema had a sensitivity and PPV of 83%, and specificity and NPV of 98% for diagnosing Hirschsprung's disease. *Reviewer's comments: The strength of the study included a solid standard of truth (biopsy), and it assessed performance characteristics (sensitivity and specificity) of pediatric barium enema in a pediatric population in which barium enema is often indicated.*
Aggarwal V, Mittal SK, Kumar N, Chowdhury V. A	A prospective study was performed to compare the	The sensitivity and specificity of DCBE were 67% and

comparative study of double contrast barium enema and colonoscopy for evaluation of rectal bleeding in children. Trop Gastroenterol. 1995 Apr-Jun;16(2):132-7.	diagnostic accuracy of high quality double contrast barium enema (DCBE) against colonoscopy in children with overt rectal bleeding. 44 children underwent flexible colonoscopy and DCBE independently. The final diagnosis was made after considering all investigations. Barium sulfate product or dosing not specified.	100%, respectively. When assessing polypoidal lesions of colon, diagnostic yield of enema study was 86%. In colitis cases, the diagnostic yield for barium enema was 54%. The study highlights the utility and complementary role of DCBE for evaluation of children with rectal bleeding.

5.1.7 Pediatric Small Bowel Studies

Study Title	**Study Design**	**Study Results**
Kurugoglu S, Korman U, Adaletli I, Selcuk D. Enteroclysis in older children and teenagers. Pediatr Radiol. 2007 May;37(5):457-66.	To report 10 years of experience and review the feasibility of enteroclysis in 83 older children and teenagers, in terms of both technique and pathological findings. Between 1996 and 2006, enteroclysis was performed using a standard technique on 83 children between 7 and 18 years of age. Morphological changes, mucosal abnormalities, luminal abnormalities, perienteric structures, the location of the disease, indirect findings regarding the bowel wall and functional information were evaluated. Barium sulfate product not specified. 150- 250 mL 70% w/v barium suspension was infused by infusion pump (flow rate: 75- 175 mL/min),	All the children tolerated the procedure without difficulty. Out of 83 patients, 63 had abnormal findings. The spectrum of diagnoses were Crohn's disease (n = 23), nonspecific enteritis (n = 10), malabsorption (n = 8), intestinal tuberculosis (n = 6), intestinal lymphoma (n = 5), Peutz- Jegher syndrome (n = 3), adhesions (n = 2), Behçet disease (n = 2), backwash ileitis due to ulcerative colitis (n = 2), common-variable immune deficiency (n = 1) and lymphangiectasis (n = 1). Enteroclysis can be performed in children over 7 years of age and when performed using a correct technique it shows high diagnostic performance without complications.

	followed by 750- 2000 mL 0.5% methylcellulose solution in water.	

5.1.8 Pediatric Modified Barium Swallow Studies

Study Title	Study Design	Study Results
Newman LA1, Keckley C, Petersen MC, Hamner A. Swallowing function and medical diagnoses in infants suspected of Dysphagia. Pediatrics. 2001;108(6), 4 pages	Objectives of this study were to determine 1) the percentage of dysphagic infants who experience laryngeal penetration, aspiration, or nasopharyngeal backflow; 2) reasons for laryngeal penetration/aspiration; 3) whether infants with laryngeal penetration/aspiration clear their airway; and 4) the relationship between swallowing disorders and medical diagnoses. 43 infants who were referred for videofluoroscopic swallowing studies in a university-affiliated pediatric medical center. Medical charts were reviewed. A 40% wt/wt (60% wt/vol) E-Z EM premixed liquid barium suspension was administered using a bottle. The videofluoroscopic swallowing studies were recorded on videotape, and each swallow was analyzed for laryngeal penetration, aspiration, nasopharyngeal backflow, cough, airway clearance, and reason for penetration/aspiration.	During Modified Barium Swallow (MBS) More than half of the infants experienced laryngeal penetration, aspiration, or nasopharyngeal backflow after multiple swallows, with 3 infants experiencing laryngeal penetration and aspiration on the first swallow. This study demonstrated that most infants suspected of dysphagia showed overt abnormalities: laryngeal penetration, aspiration, and/or nasopharyngeal backflow on the videofluoroscopic barium swallowing study. Most of these infants did not demonstrate abnormalities in the first few swallows but displayed deterioration in swallowing function as they continued to feed.

5.2 Review Strategy

Reviews of the published literature have been performed to support the efficacy of barium sulfate during diagnostic procedures of the gastrointestinal tract. The objective of the review was not to establish diagnostic performance characteristics for a specific radiologic procedure for specific structural or functional abnormality. Instead the evidence of diagnostic use was considered supportive of the proposed indication of structure delineation.

(b) (4)

The criteria for publication quality included prospective design, adequate numbers (20 or above), well defined patient population, pre-specified primary efficacy outcome, reference standard for diagnosis, data analysis plan, information regarding reading methodology, and minimization of bias in read and patient selection, accounting for all patients entered in the study

The reviewer first identified studies prospective in design, designed to evaluate performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of the efficacy of the barium sulfate, conducted in intended patient population, and using histopathology and/or endoscopy/surgery as the standard of truth.

Because most of the publications provided in the submission did not give details on the specific barium products used in the studies, the reviewer next conducted literature searches to identify studies that specifically used the applicant's barium products

Quality of studies
The quality of the studies was divided into three categories: primary, supportive and evaluable for safety. The reviewer relied on the primary publications for the assessment of efficacy and safety. The remaining publications were evaluated for safety. Given the long history of use of barium, adequate and well controlled studies are not available in the literature and are not feasible or required for this submission. Therefore the 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.

6 Review of Efficacy

6.1 Esophagram and Upper Gastrointestinal Series

Barium sulfate is indicated for (b) (4) double contrast examination of the upper gastrointestinal tract.

(b) (4)

Double contrast exams involve distention of the GI segment under evaluation, usually utilizing Sodium bicarbonate effervescent granules, which produce carbon dioxide on contact with water, combined with uniform coating of the mucosa by relatively high-density barium. This gives a "relief map" of the mucosal surface, as well as bowel distention, allowing demonstration of the mucosal surface and bowel margins. Use of (b) (4) w/v barium sulfate suspension is recommended.

Clinical Conditions for which Esophagram may be diagnostic

An esophagram is useful to assess mucosal or submucosal structural defects, foreign body, and suspected or known motility disorders. Imaging can show features suggestive of the following entities: esophagitis, strictures, varices, suspected esophageal perforation, neoplasms, esophageal obstruction.

Signs and symptoms for which UGI is commonly performed include symptomatic or suspected gastro-esophageal reflux, abdominal pain, epigastric distress or discomfort, dyspepsia, nausea, vomiting, signs and symptoms of upper GI bleeding, anemia and weight loss.

An upper gastrointestinal examination may be helpful for patients with suspected or known gastritis or duodenitis, peptic ulcer disease, hiatal hernia, varices, suspected perforation, neoplasms, gastric outlet obstruction, pre-operative anatomical evaluation, such as prior to bariatric surgery, postoperative assessment, and gastric or duodenal masses.

The Bracco products (b) (4) in radiographic examinations of the upper gastrointestinal tract are listed below:

Product Names	Type of Examination and Target Segment of GI
E-Z-HD	For use in double-contrast radiographic examinations of the esophagus, stomach and duodenum
E-Z-Paque	For use in single-contrast radiographic examinations of the esophagus, stomach, duodenum and small bowel
Liquid E-Z-Paque	Single-contrast radiographic examinations of the stomach
Liquid Polibar Plus	For use in radiographic examinations of the GI tract. Oral: Esophagus (undiluted for double-contrast) and cardiac series, stomach (single- and double-contrast) and small bowel series.
E-Z-Paste	For use in single-contrast radiographic examinations of the esophagus, pharynx, hypopharynx and for cardiac series
E-Z-Disk	Radiographic examinations of the esophagus for detection of esophageal strictures

Literature Review of Esophagography and Upper Gastrointestinal Series in Adult Patients

Sixteen publications on the efficacy of barium sulfate study in the esophagus and upper gastrointestinal tract were submitted for review. The reviewer focused on studies prospective in design, designed to evaluate performance characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of the efficacy of the barium sulfate, and using endoscopy as the standard of truth.

The reviewer identifies the following two publications as providing literature evidence to support the efficacy of barium sulfate in double-contrast study of the esophagus and upper gastrointestinal tract.

Nawaz M, Jehanzaib M, Khan K, Zari M. Role of barium meal examination in diagnosis of peptic ulcer. J Ayub Med Coll Abbottabad. 2008 Oct-Dec;20(4):59-61.

The objectives of this study were to determine the validity of Barium Meal examination in the diagnosis of peptic ulcer disease in comparison to the gold standard, i.e., endoscopic evaluation in peptic ulcer disease. The study was conducted at Radiology Department Khyber Teaching Hospital Peshawar in Pakistan from November 2000 to March 2004. A total of 115 patients with signs and symptoms of peptic ulcer disease were selected for this study. All enrolled study subjects underwent barium meal examinations of the esophagus and upper gastrointestinal tract and later endoscopy and/or surgery. In all these patients the diagnosis was later on confirmed by endoscopy and/or surgery. Of the 115 patients, 80 were male and 35 were female patients. Their ages ranged from 27–75 years with mean age of 49 years.

Fifty-two patients had duodenal ulcer, 30 patients gastric ulcer (24 benign, 6 malignant gastric ulcer), and 33 patients had normal radiological findings. Endoscopy/surgery was used as the standard of truth.

	Endoscopy		
Barium Meal	+	-	**Total**
+	82	0	82
-	3	30	33
Total	85	30	115

The sensitivity of Barium meal in diagnoses of peptic ulcer disease is 96.5%, specificity 100%,

Farber E, Fischer D, Eliakim R, Beck-Razi N, Engel A, Veitsman E, et al. Esophageal varices: evaluation with esophagography with barium versus endoscopic gastroduodenoscopy in patients with compensated cirrhosis—blinded prospective study. Radiology. 2005 Nov;237(2):535-40.

Study design: single center prospective study

Study objective: The objective of the study was to prospectively evaluate the accuracy of esophagography with barium in diagnosis of esophageal varices (EV) in patients with compensated cirrhosis

Study population: 61 patients with cirrhosis (34 men, 27 women; mean age, 61 years; range, 36–76 years) received a diagnosis clinically or with liver biopsy.

Study drug dosing: From November 2002 to May 2003, 61 patients were administered 50– 100 mL of high-density barium sulfate, 60% wt/vol (E-Z HD) at a single center.

Reviewer's comments: Bracco believes that the above published barium strength was inadvertently misstated. In the publication, the barium strength for the E-Z-HD (powder for suspension) was stated as 60 % w/v, and the barium strength for E-Z-Paste (paste formulation) was stated as 98% w/v. Bracco believes that the correctly stated barium strengths for these formulations should be E-Z-HD (98% w/w), and E-Z-Paste (60% w/w). The reviewer agrees with this assessment.

Study endpoints: Barium esophagography was performed within 3 weeks of endoscopic gastroduodenoscopy, and EV were assigned grades as follows: 0, no EV were seen; 1, EV manifested as very mild irregularities of the folds; and 2, the irregularity of the folds (EV) was clearly present.
They were also assigned grades for shape and size:

- grade F0, no EV detected;
- grade F1, small straight EV;
- grade F2, slightly enlarged tortuous EV occupying less than one-third of esophageal lumen;
- grade F3, large coil-shaped EV that occupied more than one-third of esophageal lumen.

Study standard of truth: endoscopic gastroduodenoscopy

Study results: All large EV (grades F2 and F3) were diagnosed at esophagography. The overall sensitivity of esophagography was 89%, the overall specificity was 83%. Sensitivity appeared to be numerically lower with small EV (grade F1).

Reviewer's comments: the study prospectively evaluated the performance characteristics of E-Z-HD in barium esophagram for the diagnosis of esophageal varices. The study used a solid standard of truth. Another strength of the study is that it specifically used E-Z-HD, Bracco's proposed product for a double-contrast barium study of the upper gastro-intestinal tract. Weakness of the study included being single center study with relatively small number of patients.

<u>Other Supportive Study</u>
The following study provides important information on the specific barium sulfate product used in the publication by Farber et al above.

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.

In the study , 119 patients were administered high-density barium sulphate (E-Z.HD 250% wt/vol). The study assessed performance of E-Z-HD high-density, low-viscosity formulation (with barium sulfate sourced from [redacted] (b) (4) for double contrast visualization of esophageal varices.

Reviewer's comments: This is a single center pilot study assessing the methodology of using barium sulfate in detecting esophageal varices. This publication describes the study methodology, whereas the publication by Faber et al discussed above reports the results of the study in using barium sulfate to detect esophageal varies. This publication provides details of the specific barium sulfate product (EZ-HD) that was used in the study by Farber et al. The FDA Chemistry, Manufacturing, and Control (CMC) review team used this publication to establish a CMC 'bridge' to assess the barium sulfate product data

[redacted] (b) (4)

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

6.5 Opacification of the Gastrointestinal Tract in Computed Tomography (CT) of the Abdomen/Pelvis

Oral contrast agents are commonly administered to patients undergoing a CT exam of the abdomen, with the aim of marking and distending the bowel lumen for detection/exclusion of mural thickening and mural masses. Those used are almost always positive contrast agents, such as 1% to 2% barium suspensions and 2% to 3% solutions of iodinated water-soluble agents. At the low concentrations used, the barium sulfate product does not coat the mucosa, but simply fills the bowel lumen. Positive lumen opacification of the GI tract is routinely used in CT of the abdomen and pelvis in patients with no localizing signs and symptoms, in oncology patients, and in patients with non-traumatic abdominal pain.

While both water-soluble iodinated contrast and low-concentration barium sulfate preparations enabled adequate CT imaging, iodine-containing water-soluble contrast agents could dilute in the GI tract before reaching the ileum; also, iodine contrast agents are systemically adsorbed and excreted via the kidney, with associated osmotic effects, whereas, barium sulfate is insoluble and inert, is not diluted in the GI tract, is not systemically adsorbed and does not produce either peristaltic or osmotic effects.

Barium sulfate suspensions for use in CT were originally developed as a concentrate for dilution prior to use (an example of such products was EZ-CAT). Further development in the formulation resulted in low-concentration, ready-to-use (not requiring dilution prior to use) product (Readi-Cat 2) with a formulation that would maintain barium particles in suspension after ingestion in order to produce homogeneous opacification of the bowel lumen.

Bracco Barium Sulfate products for use in CT imaging include:

Product Names	Type of Examination and Target Segment of GI
Readi-CAT 2	For use in CT examinations of the abdomen
Readi-CAT 2 Smoothies	For use in CT examinations of the abdomen
	(b) (4)

In the original NDA submission for E-Z-HD, (b) (4), submitted on December 11, 2014, no clinical studies were included for Readi-Cat 2 (b) (4). In response to FDA information requests, Bracco submitted an amendment to the NDA on July 29, 2015. Four clinical studies from the literature were submitted in the amendment to support clinical utility of dilute barium sulfate (b) (4) for the opacification of the gastrointestinal tract during CT of the abdomen and pelvis.

All four submitted studies used E-Z-Cat Dry. No submitted study used Readi-Cat2. The reviewer independently conducted a literature search, and did not identify additional clinical studies on the use of Readi-Cat2 in CT.

Reviewer's comments: E-Z-Cat Dry is a barium sulfate powder for reconstitution into barium sulfate suspension to be used in clinical examinations. In all four submitted clinical studies, E-Z Cat Dry was reconstituted into low concentration (range 1%-1.7% w/v) barium sulfate suspension. This is close to 2% w/v barium concentration in the proposed ready-to-use barium sulfate suspension product Readi-Cat 2, and the reviewers considers all four publications submitted for review in support of (b) (4) *Readi-Cat 2.*

Out of the four submitted studies, the reviewer focused on the following two studies that evaluated the efficacy of low-concentration barium sulfate in the opacification of the gastrointestinal tract in abdominal/pelvic CT. The other two studies did not evaluate the efficacy of barium sulfate in CT imaging.

Nyman U, Dinnetz G, Andersson I. E-Z-CAT An oral contrast medium for use in computed tomography of the abdomen. Acta Radiologica Diagnosis 25 (1984) Fasc. 2

Study design: prospective, randomized, comparative trial

Study population: 100 consecutive patients referred for CT of the abdomen

Study drug dosing: E-Z-CAT (prepared for use to 1.7% w/v barium sulfate); Gastrografin (prepared for use to 2.2% w/v, diatrizoate).

- Group 1: 400mL of preparation(s) (EZ-CAT/Gastrografin) 30 min prior to CT
- Group 2: 500 mL of preparation(s) (EZ-CAT/Gastrografin) 1 hour prior to CT
- Additional 100mL of preparation(s) taken immediately prior to CT (all patients)

Study endpoints: image quality and imaging artifacts

- Filling of the stomach and intestines (good, poor, none)
- Presence of imaging artifacts (none), artifacts not affecting diagnostic information (weak), and artifacts impairing diagnostic information (marked);
- Signs of sedimentation of the contrast agent and possible coating of the gastrointestinal mucosae.

Study results: Gastrografin and E-Z-CAT have similar attenuation in the stomach (the median value was about 200 HU), degree of filling of various gastrointestinal sections, or as regards the occurrence of imaging artifacts. Neither of the contrast media displayed tendency to undergo sedimentation.

Doyle GJ, O'donnell SC, Mcdonald JR, Murthy LNS, Keir MJ, Wright AR. Evaluation of "Gastromiro" for bowel opacification during computed tomography: comparison with diatrizoate and barium sulphate. The British Journal of Radiology,1993, 66, 681-684

Study design: prospective, blinded comparison trial

Study patient population: 150 consecutive patients referred for abdominal/pelvic CT scans were randomized into three groups. Each group received a different type of contrast-medium

Study drug dosing: the three contrast-medium used in this comparison study were Gastromicro, Urografin, and E-Z Cat. Study drug dosing is shown in the following table.

Table 4: Study Drug Dosing Among Three Study Cohorts

	Group A (n = 52)	Group B (n = 48)	Group C (n = 50)
Contrast	Gastromiro	Urografin	E-Z CAT
Iodine content	300 mg ml^{-1}	370 mg ml^{-1}	N/A
Solution strength	3%	2.4%	1.4%
Volume (abdominal CT)	400 ml	400 ml	400 ml
Volume (abdo/pelvic CT)	700 ml	700 ml	700 ml

Image evaluation: CT scans were independently assessed by two radiologists who were unaware of the type of contrast medium used. Images were evaluated for quality of opacification in eight regions, namely: stomach, duodenum, jejunum, ileum, ascending-, transverse and descending colon and rectum.

Study endpoints: Each bowel region was given a score of 0 or 1 for opacification as follows:

- 0-no opacification or poor opacification
- 1-good opacification

The average score of the two CT image readers were used in comparison in the eight gastrointestinal segments and among the three contrast-media in comparison.

Study results: Opacification quality in the seven of the eight gastrointestinal tract segments was similar between EZ-CAT and other two contrast media.

Reviewer's comments: the above two studies demonstrate the efficacy of dilute barium sulfate in the opacification of the gastrointestinal tract in CT imaging of the abdomen and pelvis. Dilute barium sulfate is as efficacious as Gastrografin, which is approved for a similar indication.

Gastrografin is approved "as an adjunct to contrast enhancement in computed tomography of the torso (body imaging); the preparation is indicated, in conjunction with intravenous administration of a radiopaque contrast agent, when unenhanced imaging may not provide sufficient definition in distinguishing normal loops of bowel from adjacent organs or areas of suspected pathology."

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

6.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Double-contrast barium exams (DCBEs) involve distension of the GI segment under evaluation combined with uniform barium coating of the mucosa and allow demonstration of both mucosal surface and bowel margins. This type of procedure requires air or other gases to produce distension and a high density, low viscosity barium sulfate preparation to flow over and coat the mucosa. Use of 210% to 250% w/v barium sulfate suspensions is recommended by the ACR for use in double-contrast examinations of the esophagus and upper GI tract. A similar recommendation can be found in textbooks and published papers. Gaseous distension of the esophagus and stomach is obtained with the use of effervescent agents which produce carbon dioxide on contact with water. E-Z-HD (barium sulfate 250% w/v) was developed and first marketed in 1980.

E-Z-HD is a barium sulfate powder for oral suspension. E-Z-HD is supplied as a unit dose in a single use plastic bottle containing 340 g of barium sulfate powder for oral suspension. It needs reconstitution using 65 mL of water to yield approximately 140 mL of a (b) (4) % w/v oral suspension (2.3 (b) (4) grams barium sulfate per mL). The proposed barium dosing is "The typical adult dose can range from 65 – 135 mL of reconstituted product". It is based on *Module 1, Levine Radiology 1988, Skucas Textbook of Gastrointestinal Radiology, Chapter 1, 2008,* and dosing varies depending on the patients' clinical condition.

Most of the submitted publications do not include information on the specific barium product, nor concentration or mass dose or volume of administration. Only the following publications include limited information on specific barium product, mass dose or volume of administration.

Publication	Barium product	Barium dosing
Value of barium swallow studies in predicting the response to rabeprazole in elderly patients with laryngopharyngeal reflux disease and nonerosive reflux disease in particular. Kimura et al. Ann Otol Rhinol Laryngol. 2010	Not specified	10 mL of 130% w/v barium sulfate
Clinical utility of endoscopy and barium swallow X-ray in the diagnosis of sliding hiatal hernia in morbidly obese patients: a study before and after gastric bypass. Fornari et al. Obes Surg. 2010	Not specified	200 mL of diluted barium
Preoperative diagnosis of gastric tumors by three-dimensional multi-detector row CT and double contrast barium meal study: correlation with surgical and histologic results. Chen et al. J Formos Med Assoc. 2007	E-Z-HD	200-250 mL
Evaluation of the sensitivity of the double-contrast upper gastrointestinal series in the diagnosis of gastric cancer. Ukrisana et al. J Med Assoc Thai. 2004	Not specified (Highdensity barium suspension and effervescent powder).	Not specified
Esophagogram and CT vs endoscopic and surgical specimens in the diagnosis of esophageal carcinoma. Drudi et al. Radiol Med. 2002	Not specified (high-density barium suspension for double contrast esophagram; low density barium suspension for single-contrast esophagram)	Not specified
Bread and barium. Diagnostic value in patients with suspected primary esophageal motility disorders. Nellemann et al. Acta Radiol. 2000	Not specified	• 10 mL barium suspension (0.4 g/mL barium sulfate); 2 wet swallows • barium paste (0.7 g/mL

		barium sulfate) mixed with bread and liver pate'; 6 g • 180 mL of barium suspension (0.4 g/mL barium sulfate) through a straw, twice.
Motility disorders of the esophagus: diagnosis with barium-rice administration. Schwickert et al. Eur J Radiol. 1995	Not specified	high-density barium sulfate suspension; high density barium sulfate suspension mixed with boiled rice

Reviewer's comments: The submitted publications do not provide adequate information in barium dosing. Only one study from the publications listed E-Z-HD as the barium product used in the study. The barium dose varies widely in these published studies, ranging 10-250 mL in the volume of barium administration. Bracco therefore proposes barium dosing based on an authoritative radiology textbook. The reviewer finds this approach and the proposed barium dosing acceptable.

Since radiographic opacification is dependent on the total amount of barium in the path of X-ray beams, the density of the barium sulfate preparation is generally inversely related to the lumen size of the GI segment under investigation. (b) (4) [redacted].

7 Review of Safety

Safety Summary

The safety of Barium Sulfate products has been well established during more than 100 years of clinical use. Since this time, barium sulfate has become a standard contrast for GI studies, and the frequency of complications is very low, considering the vast number of procedures performed.

Barium sulfate has no pharmacological effects. It is poorly soluble in water, and demonstrates negligible absorption from the GI tract following either oral or rectal administration. It is excreted, unchanged, in the feces at a rate dependent upon route of administration, as well as the patient's peristalsis and GI motility. Orally administered barium is excreted generally within 24 hour, and rectally administered barium is eliminated upon evacuation of the enema. Urinary excretion is minimal, in the range of 0.02-0.09 x 10 to the -6th power.

Adverse events such as nausea, vomiting, abdominal cramping or discomfort, constipation and colonic retention of barium are rare, and almost always mild. Severe events, which can uncommonly occur, include mediastinitis or peritonitis in cases of perforation of the GI tract, respiratory distress and pneumonia in cases of aspiration, and venous intravasation in cases of trauma or misplacement of the enema tip, as a consequence of complications related to the imaging *procedure* using barium sulfate as an imaging contrast. Anaphylactoid reactions to Barium Sulfate products are very uncommon, usually mild, and in most cases related to additives to the barium preparations.

7.1 Methods

The safety evaluation mainly relied on safety assessments from the radiology professional society guidelines, textbooks, and peer-reviewed literature, as well as Bracco's own product safety database for the time period of January 1, 2009 to July 31, 2014.

A review of the published literature was performed to identify case reports/series that describe adverse events associated with the use of Barium Sulfate products. Braccos's pharmacovigilance database includes all papers focusing on safety information, which were published between January 1, 2003 and July 31, 2014.

7.2 Adequacy of Safety Assessments

Barium Sulfate has been in use as a contrast medium since the early 1900s. E-Z-EM proprietary products are authorized globally in a number of formulations for oral and rectal administration in 40 countries worldwide over the past 40 years.

The clinical safety profile of Barium Sulfate products is supported by Bracco's product safety data based on an estimated exposure of more than (b) (4) patients worldwide in the period 2009 - 2014.

7.3 Major Safety Results

7.3.1 Safety Results from Bracco Post-Marketing Surveillance Data (PMS)

Bracco acquired E-Z-EM in April 2008. During the market use period of Barium Sulfate products for which sales data are available to Bracco (i.e., from January 1, 2009 to the NDA submission's data cut-off of July 31, 2014), an estimated (b) (4) adult and pediatric patients were exposed to Barium Sulfate products.

During the market use period of Barium Sulfate products for which exposure to the products has been captured (from January 1, 2009 to July 31, 2014; estimated (b) (4) exposed patients), a total of 308 cases (RR (b) (4)%) have been spontaneously reported which were not considered to be "unrelated" to the administration of Barium Sulfate products by both Reporter and the Sponsor assessments. Among the 308 cases, a total of 50 were classified as serious (RR< (b) (4)%) and 258 as non-serious (RR (b) (4)%). The majority of adverse reactions were reported at a single occurrence. The more frequently reported serious adverse reactions (>4 patients) during this time period were aspiration (n=14), barium impaction (n=4), and dyspnea (n=4).

During the market use period of Barium Sulfate products for which exposure to the products had not been captured (i.e., from July 1, 1997 to December 31, 2008), a total of 370 cases have been spontaneously reported, all of which were considered to be of some association to the administration of Barium Sulfate products by both Reporter and the Sponsor assessments. Among the 370 cases, 70 were classified as serious and 300 as non-serious. The serious adverse reactions most often reported (>4 patients) during this period were: aspiration (n=10); urticaria (n=7); large intestine obstruction (n=6); dyspnea (n=5); and rectal perforation, vomiting, and pneumonia aspiration (n=4, each). There is no significant difference between the 2 reporting periods.

7.3.2 Safety Findings from Literature

Bracco also submitted review of the published literature on case reports/series that describe adverse events (a collective name for equivalent terms used in the publications such as adverse reactions, complications, side effects, and adverse effects) associated with the use of Barium Sulfate products that have not been identified within the above reported Radiology professional society guidelines.

Blakeborough, A, Sheridan, M.B. and Chapman, A.H. (1997). Complications of Barium Enema Examinations: A Survey of UK Consultant Radiologists 1992-1994. Clinical Radiology 52, 142-148.

This is a retrospective study of complications of barium enema examinations performed during the three year period 1992-1994. 1470 questionnaires were sent, to all Consultant Radiologists in the UK, regarding complications from barium enema examinations performed. 815 (55.4%) were returned, of which 3 were not completed, and 56 (6.9%) of the Consultants had not performed barium enemas from 1992-1994. Complications were reported by 77 of the remaining 756 Consultants (10.2%), for a total of 82 complications, including 13 deaths, from a total of 738,216 examinations. Thus, the complication rate is 1 in 9003 enemas, and a death every 56,786 enemas.

There were 30 cases of perforation, resulting in 3 deaths: overall mortality 10%; 13 intraperitoneal perforations (2 deaths) and 17 extraperitoneal perforations (1 death).

There were 8 reported cases of barium impaction, which generally resolved without further complication, with the exception of a case of sigmoid volvulus requiring surgical intervention. Two cases of vaginal catheter placement caused complications, persistent hemorrhage in one requiring hysterectomy, the other developing extraperitoneal extravasation presumably from vaginal rupture, with death occurring 3 weeks later. One case of venous intravasation occurred without sequelae, an allergic reaction promptly recognized and treated, and 2 cases of septicemia, one associated with diverticulitis, without sequelae, and the other with colovesical fistula due to underlying carcinoma, treated surgically.

Serious complications of barium enema occurred in the 3-year period 1992 to 1994 were retrospectively assessed through a postal survey of all consultant radiologists in UK (n=1470). Complications were reported by 77 of the 756 consultants who returned a valid questionnaire. Eighty-two (82) complications were reported from a total of 738,216 examinations (complication rate of 1 in 9003 or 0.0111%), as summarized in the Table below. In 13 cases, the complication resulted in a fatal outcome (overall mortality rate of 1 in 56,786 or 0.0018%).

The number and types of complications are summarized in the following table:

Table 8: Reported Complications from Barium Enema Examinations

Type of Complication	No. of Adverse Events	No. of Deaths
Intraperitoneal perforation	13	2
Extraperitoneal perforation	17	1
Barium impaction in the colon	8	0
Vaginal placement of rectal catheter leading to a complication	2	1
Venous intravasation of barium	1	0
Allergic reaction (requiring treatment)	1	0
Septicaemia	2	0
Cardiac arrhythmia	16	9
Other		
Vasovagal attack	15	0
Rectal bleeding	3	0
CVA	1	0
Miscellaneous	3	0
TOTAL	**82**	**13**

Vora, P. and Chapman A. Complications from Radiographer-performed Double Contrast Barium Enemas. Clinical Radiology (2004) 59, 364-368.

This retrospective study involved questionnaires sent to 741 radiographers who had attended the Leeds Barium Enema Course for Radiographers prior to 2001. 407 were returned, for a 54.9 % response. Twenty three radiographers no longer performed barium enemas, leaving 384 completed questionnaires for evaluation. 59 radiographers reported a total of 89 complications as shown in the Table 9. These resulted in 5 deaths from a total of 348,433 examinations, giving a mortality of 1 in 69,687.

Complications included 24 bowel perforations, resulting in 2 deaths: mortality of 8%. Both followed intraperitoneal perforations. Underlying pathology was present in 5 of the 13 intraperitoneal perforations, three malignant tumors and 2 cases of inflammatory bowel disease. 4 of the 11 extra-peritoneal perforations had underlying pathology, 2 diverticular abscesses, and 2 rectal tumors. Of the 39 arrhythmias, 33 had an injection of Buscopan (hyoscine-n-butylbromide, Boehringer Ingelheim, IN, USA), commonly used to minimize bowel motion during barium enemas. There were two deaths from the six reported myocardial infarctions. There were twelve allergic reactions, most mild, with no deaths. One of the vasovagal attacks was severe, necessitating overnight hospitalization, and the CVA resulted in death of the 73 year old patient.

A retrospective survey was conducted among radiographers performing double contrast barium enemas (DCBE). The questionnaire was designed to ascertain the number, type, and outcome of complications that have been encountered by the radiographers when performing barium enema. Among the 384 radiographers who completed the questionnaire, 59 reported a total of 89 complications from 348,433 exams performed.

Table 9: Reported Complications from Over 348,000 Examinations (*Vora and Chapman, 2004*)

Type of Complication	No. of Adverse Events	No. of Deaths	Frequency
Perforationa	24	2	1 in 14,500
Intraperitoneal	11	0	1 in 31,500
Extraperitoneal	13	2	1 in 27,000
Cardiac complications	45	2	1 in 8000
Myocardial infarction	6	2	1 in 58,000
Arrhythmia	39	0	1 in 8900
Barium impaction	2	0	1 in 175,000
Vaginal placement of tube	2	0	1 in 175,000
Allergic reaction	12	0	1 in 29,000
Cerebrovascular accident	1	1	1 in 348,000
Vasovagal	3	0	1 in 115,000
TOTAL	89	**5**	1 in 4000

7.3.3 Safety Results from Practice Guidelines

The safety profile of barium sulfate medical imaging products has been described in the Manual on Contrast Media issued by the American College of Radiology (ACR) and the guidelines on contrast agents of the European Society of Urogenital Radiology (ESUR) as well as in ACR Practice Parameters for performance of imaging procedures with barium sulfate**.**

ACR Manual on Contrast Media

In the chapter dedicated to GI contrast media, adverse reactions to oral and rectal Barium Sulfate products are reported as being almost always mild. The most common reactions include nausea, vomiting, and abdominal cramping or discomfort during and/or after the examination, and are most likely due to a physiologic response resulting from distention of a viscus. Vasovagal reactions can also be encountered, after the colon is distended during a double contrast barium enema.

Anaphylactoid reactions to Barium Sulfate products are very uncommon and usually mild; most common reactions include transient rashes, urticaria, itching, and mild bronchospasm. Moderate and severe anaphylactoid reactions are reported to occur in 1 in 2.5 million exposures, with manifestations including more extensive dermal responses, respiratory symptoms, and vascular events, such as hypotensive episodes. Reference is made to isolated reports of life-threatening reactions from double contrast colon examinations, especially those performed with injection of glucagon, and to a potential association between a history of asthma and anaphylactoid reaction to barium, although no conclusive evidence of cause and effect is available.

The cause of allergic-like reactions during barium studies remains unknown, although different candidates for allergens have been explored. Barium sulfate is generally considered insoluble, although miniscule amounts can dissociate, resulting in availability of free barium ions that can dissolve into solution and potentially be absorbed from the GI tract. However, those tiny amounts of absorbed barium during a GI examination would be an unlikely allergen.

Additives and preservatives are commonly used in commercial Barium Sulfate preparations to reduce flocculation, improve product stability and patient acceptance, increase coating properties. Although these additives and preservatives are used in a variety of food products and appear in the FDA list of products generally regarded as safe (GRAS), they may represent a potential source for anaphylactoid reactions during GI exams.

Leakage of barium into the mediastinum or the peritoneal cavity and aspiration in the bronchial tree are reported as complications from the use of barium. Barium leakage is the most serious complication which, depending on the site of spill, may result in mediastinitis or peritonitis and may carry high mortality if the escape of barium occurs in the colon where the bacterial count is highest (in this case, the mortality is likely primarily related to leakage of stool). Aspiration of barium sulfate may cause inflammation and other symptoms, particularly in patients with underlying lung disease in whom the damaged bronchial epithelium delays the normal elimination of barium. Furthermore, high volume aspiration can lead to acute respiratory distress or pneumonia.

Contrast Media: safety issues and ESUR guidelines

Barium Sulfate products are described as being generally safe and associated with uncommon adverse events. These include abdominal pain, constipation and rarely the development of baroliths (barium fecoliths). Baroliths are usually asymptomatic, but may be associated with abdominal pain, appendicitis, bowel obstruction, or perforation. Toxic dilatation of the colon may be aggravated by barium enema with increased risk of colonic perforation.

Perforation into the peritoneal cavity is a rare complication of barium enema which may be triggered by procedural actions or may result from hydrostatic pressure and is reported to be associated with 47% to 58% mortality. Risk of perforation during barium enema is higher in children, debilitated patients and patients with weakened bowel walls by inflammatory or neoplastic diseases. Extraperitoneal perforation and barium leakage into the mediastinum may also occur with development of delayed endotoxic shock.

Intravenous barium intravasation after barium enema has been reported and may be associated with mortality of up to 55%. Pulmonary embolism, disseminated intravascular coagulation, septicemia and severe hypotension have been reported following barium intravasation. Most cases have been attributed to trauma from the enema tip or retention balloon or misplacement of the tip into the vagina; intestinal obstruction or thinning and diminished lumen elasticity may be predisposing factors.

Aspiration of barium sulfate into bronchi following its oral administration can cause respiratory failure, especially in patients with poor respiratory function and general conditions, and fatal pneumonia. Bronchoscopy has been recommended after barium aspiration to remove barium from the bronchial tree; antibiotic prophylaxis is also important to reduce the risk of lung infection.

Hypersensitivity reactions to Barium Sulfate products are extremely rare, as it would be expected for a compound that is almost insoluble, is not metabolized and is excreted unchanged from the body. However, very small amounts of barium ions can be absorbed from the GI tract and a number of additives are present in commercial barium sulfate suspensions that might induce an immune response. Isolated cases of barium encephalopathy have been attributed to absorption of barium. A patient with history of a severe reaction to barium sulfate should not receive barium products again.

7.4 Safety Findings in the Pediatric Population

Although the clinical indications and techniques for examining the GI tract in children are often different from those in adults, the safety profile of Barium Sulfate preparations is similar in pediatric patients and adults with adverse events being rare and mild in most cases. These include nausea, vomiting, abdominal cramping or discomfort, constipation, and colonic retention of barium.

Similar to what was reported in adults, severe events may occur in association with barium sulfate procedures in pediatric patients, including perforation of the GI tract, leakage of barium into the mediastinum or the peritoneal cavity and aspiration in the bronchial tree.

Aspirated barium sulfate in small amounts is generally well tolerated and readily cleared from the tracheobronchial tree by coughing and the action of cilia lining bronchial walls. However, aspiration in a larger quantity could be fatal and may cause pneumonitis, peribronchial granulomatosis or fibrosis.

Barium sulfate impaction of the colon is uncommon in children. When encountered, there are usually predisposing conditions such as intestinal motility disorders, Hirschsprung’s disease, or partial obstruction. Barium sulfate may cause obstruction of the small bowel in patients with cystic fibrosis.

Since the barium suspensions used for barium enemas consist mainly of water, retention of large amounts of such suspensions in neonates and infants with intestinal motility disorders may result in water absorption and fluid overload. Reported cases also suggest that children with Hirschsprung's disease are particularly susceptible to this complication, and care should be taken to avoid administering large volumes of barium suspension in these cases.

In the Bracco PMS database, the adverse reactions reported were among those most commonly reported in clinical use in adults and included abdominal pain, diarrhea, aspiration, barium impaction, intestinal obstruction, and allergy-like reactions.

8 Pediatric Research Equity Act (PREA) Requirements

Bracco Survey - Barium Sulfate Pediatric Usage Data

Bracco conducted two surveys among current users and medical experts of barium sulfate products in pediatric patients in order to assess how these products are used. One survey was the 'General Barium Survey", and the other was the "Barium Swallow Survey". The results of these two surveys were submitted as an amendment to the NDA on September 14, 2015, entitled "Barium Survey – Pediatric Usage Data (Barium Sulfate)", along with Pediatric Development Plans for EZ-HD and Readi-Cat 2 and Readi-Cat 2 smoothie products.

The target population for the "General Barium Survey" was 2,159 Bracco customers who were identified from the Bracco sales contact list and were either radiologists or CT/radiology technicians or CT/Radiology managers. The response rate to the survey was low at 20%, with responses received from 429 recipients, either online or via phone call.

Respondents first were asked to indicate whether they routinely use barium sulfate products in children in their practices and if they were familiar with details of protocols applied during examinations with barium at their practices. A negative answer to one of the two questions would terminate the survey. These qualifying questions allowed Bracco to include only those respondents who could provide detailed information on the use of barium sulfate products in pediatric patients.

Of the 429 respondents to the "General Barium Survey", 197 answered "yes" to qualifying questions (100 online, and 97 via phone call). The other 232 survey respondents (95 online, 137 via phone call) were disqualified because of unfamiliarity with the use of barium sulfate products in pediatric population.

Modified barium swallow (an imaging technique which uses videofluoroscopy after oral administration of barium to assess abnormalities of the oral and pharyngeal phases of swallowing) is usually performed by speech language pathologists. Bracco's "Barium Swallow Survey" on the modified barium swallow (MBS) was distributed to 3,778 speech pathologists.

The "Barium Swallow Survey" was sent to 3,778 Speech Language Pathologists. Response rate was very low at 1.3%, with responses received from 51 of them. Among the 51 respondents to the "Barium Swallow Survey" questionnaire, 35 reported use of barium sulfate in pediatric patients.

Each of two surveys covered all pediatric age groups: up to 1 month (Group I), 1 mo – 2 years (Group II), 2-12 years (Group III), >12 years (Group IV).

Table 10: Distribution of Bracco Barium Sulfate Pediatric Use Surveys

Survey Approach	Number of Contacts/ Phone interviews	Number of valid respondents[b]	Number of respondents not using Barium[c]	Number of respondents with Barium use[d]
General Barium Survey				
Online	2,159	195	95	100
Phone	680[a]	234	137	97
Total	2,159	429	232	197
Barium Swallow Survey				
Online	3,778	51	16	35
Overall Survey				
Total online and phone	5,937	480	248	232

[a] Subset of 2,159 customers not responding to the online "*General Barium Survey*" and were contacted by phone.
[b] A valid respondent is a customer who started the survey and provided responses.
[c] Respondents who answered "NO" to one of the 2 qualifying questions.
[d] Respondents who answered "Yes" to both of the 2 qualifying questions.

8.1 Esophagus and Upper Gastrointestinal Studies

In the NDA submission, Bracco [redacted] (b) (4) did not submit pediatric studies/publications for the esophagus and upper gastrointestinal tract. In the Pediatric Development Plan for E-Z-HD submitted as an amendment to the NDA on September 14, 2015, Bracco [redacted] (b) (4) did not submit pediatric studies/publications for the esophagus and upper gastrointestinal tract.

Among the 197 respondents to the "General Barium Survey" (online or phone survey) who were considered barium users, 174 provided information about use of barium sulfate products in pediatric patients for the assessment of the esophagus and upper GI tract under fluoroscopy. One hundred and twenty-eight (128) of the 174 (74%) respondents indicated that barium is used in their practice for fluoroscopic exams of the esophagus and upper GI tract in children (see table below).

Table 11: Barium Studies of Esophagus and Upper GI Examinations in Pediatric Patients

| Product Name | Total number of users* | Age Group | | |

It is clear from the survey results presented in the table above that E-Z-HD is currently used in fluoroscopic exams of the esophagus and upper gastrointestinal tract across all pediatric age groups. (b) (4) *In addition to EZ-HD, other barium sulfate products, such as EZ-Paque, liquid EZ-Paque, Liquid Polibar Plus, EZ-Paste, and EZ-Disk, are also currently used in fluoroscopic exams of the esophagus and upper gastrointestinal tract in all pediatric age groups.*

Although Bracco did not submit clinical studies or publications for use of barium sulfate products in the pediatric population, Bracco submitted publications that supported the use of E-Z-HD in fluoroscopic exams of the esophagus and upper GI tract in the adult population, and the reviewer considers the efficacy and safety of barium sulfate products in the adult population to be readily extrapolated to all pediatric age groups. The reviewer recommends approval of E-Z-HD for use in fluoroscopic exams of the esophagus and upper gastrointestinal tract in all pediatric populations.

On October 21, 2015, that Pediatric Research Committee (PeRC) discussed Pediatric Research and Equity Act (PREA) requirements of E-Z-HD. Because this is a new NDA of a marketed unapproved product, the Division of Medical Imaging Products (DMIP) determined there is no reason to waive this product in pediatric patients as it has been widely used for many years in both adults and pediatric patients. The Division proposed labeling to cover all age groups based on the sponsor submitting literature, safety data and a pediatric use survey to support labeling of this product in pediatric population. The PeRC agreed with the Division's comments to label the product for use in all pediatric age groups based on literature and safety data and not to waive pediatric patients. (b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

8.4 Opacification of the Gastrointestinal Tract in Computed Tomography (CT) of the Abdomen/Pelvis

In the NDA 208143 submission for Readi-CAT2 and Readi-CAT2 Smoothies, Bracco (b) (4) did not submit pediatric studies/publications for the proposed indication of opacification of the gastrointestinal tract in CT of the abdomen and pelvis.

Bracco later conducted a pediatric use survey of barium sulfate products. Among the 197 respondents to the "*General Barium Survey*" (online or phone survey) who were considered barium users, 142 provided information about use of barium sulfate products in pediatric patients for CT examinations of the abdomen and pelvis. Seventy-five (75) of the 142 (53%) respondents indicated that barium is used in their practice during CT exams in children. Among respondents who do not use barium for CT of the abdomen and pelvis in pediatric patients, 28 provided information about alternative diagnostic procedures; almost all of them indicated that water

soluble contrast agents are used and some of them reported that barium is used in patients with known allergy to iodinated agents.

The survey showed that the most commonly used barium sulfate products in pediatric CT of the abdomen and pelvis were Readi-CAT2 Smoothies and Readi-CAT2, especially in patients 2 years and above. The survey results are summarized in Table 14.

Information about the dose was provided by some of the respondents who indicated that 450mL of the barium suspension is usually administered to patients of 2-12 years of age and 450-900mL of the barium suspension is administered to patients > 12 years.

Table 14: Survey Results of Barium Sulfate Products in Computed Tomography (CT) of the Abdomen and Pelvis in Pediatric Patients

Product Name	**Total number of users***	**Age Group**			
		Group I up to 1 mo.	**Group II** < 2 yrs	**Group III** 2-12 yrs	**Group IV** > 12 yrs
Readi-CAT 2:					
Online	4	1	1	2	4
Phone	27	19	20	22	22
Total	31	20	21	24	26
Readi-CAT 2 Smoothies:					
Online	13	1	3	10	13
Phone	28	17	17	20	22
Total	41	18	20	30	35
EZ-CAT Dry:					
Online	2	0	1	1	1
Phone	0	0	0	0	0
Total	2	0	1	1	1

Data obtained from the "*Online – General Barium Survey*" and the "*Phone – General Barium Survey*".
*Total number of respondents who reported use of the barium product, across all age groups.

In the Pediatric Development Plan for Readi-CAT2 and Readi-CAT2 Smoothies submitted as an amendment to the NDA on September 14, 2015, Bracco requested full pediatric assessment for Readi-CAT2 and Readi-CAT2 Smoothies.

Reviewer's comments: It is clear from the survey results in the table above that Readi-CAT2 and Readi-CAT2 Smoothies are currently used in clinical practice in CT of the abdomen and pelvis in all pediatric age groups.

Although Bracco did not submit clinical studies or publications for use of barium sulfate products in the pediatric population, Bracco submitted publications (b) (4) (b) (4) *EZ-CAT Dry in CT of the abdomen and pelvis in the adult population.*

(b) (4) *In the submitted clinical studies, E-Z Cat Dry was reconstituted into low concentration (range 1%-1.7% w/v) barium sulfate suspension. This is close to 2% w/v barium concentration in the proposed ready-to-use barium sulfate suspension product Readi-Cat 2 and Readi-CAT2 Smoothies.*

The reviewer therefore considers EZ-CAT Dry a similar barium sulfate product to Readi-CAT2 and Readi-CAT2 Smoothies, and the efficacy and safety of barium sulfate products in the adult population to be readily extrapolated to all pediatric age groups. The reviewer recommends approval of Readi-CAT2 and ReadiCAT2 Smoothies for use in CT of the abdomen and pelvis in all pediatric populations.

On October 21, 2015, the Pediatric Research Committee (PeRC) discussed Pediatric Research and Equity Act (PREA) requirements of Readi-CAT2 and Readi-CAT2 Smoothies. This is a newly submitted NDA for a marketed unapproved drug. The applicant requested full pediatric assessment for all pediatric age groups based on published literature to support labeling in all pediatric age groups. The Division of Medical Imaging Products (DMIP) clarified that this NDA cross-references the E-Z-HD NDA for clinical data. The PeRC agreed with the Division's comments to label the Readi-CAT2 for use in all pediatric age groups based on literature, safety data, and pediatric use survey.

8.5 Modified Barium Swallow (MBS) Examination

One publication was submitted in the NDA to support the clinical use of barium sulfate in Modified Barium Swallow (MBS) examinations:

Newman LA1, Keckley C, Petersen MC, Hamner A. Swallowing function and medical diagnoses in infants suspected of Dysphagia. Pediatrics. 2001;108(6), 4 pages

Study objective: Objectives of this study were to determine 1) the percentage of dysphagic infants who experience laryngeal penetration, aspiration, or nasopharyngeal backflow; 2) reasons for laryngeal penetration/aspiration; 3) whether infants with laryngeal penetration/aspiration clear their airway; and 4) the relationship between swallowing disorders and medical diagnoses.

Study population: 43 infants (1 week to 11.5 months) with dysphagia were referred for videofluoroscopic swallowing studies.

Study design: Liquid barium suspension was administered using a bottle. The videofluoroscopic swallowing studies were recorded on videotape, and each swallow was analyzed for laryngeal

penetration, aspiration, nasopharyngeal backflow, cough, airway clearance, and reason for penetration/aspiration.

Study drug dosing: A 40% wt/wt (60% wt/vol) E-Z EM premixed liquid barium suspension was administered using a bottle.

Study Results: More than half of the infants experienced laryngeal penetration, aspiration, or nasopharyngeal backflow; and the first occurrence of these events was after multiple swallows. Only 3 infants experienced laryngeal penetration and aspiration on the first swallow. Premature infants experienced significantly more nasopharyngeal backflow. Material in the pyriform sinuses before pharyngeal swallowing was associated with penetration/aspiration.

Reviewer's comments: The study was not designed to assess the performance characteristics of barium sulfate in Modified Barium Swallow (MBS) studies. However, the ability of the examiner to observe laryngeal penetration, aspiration, or nasopharyngeal backflow demonstrates the clinical usefulness of barium sulfate in the MBS study in pediatric population.

In addition to submitting the above publication, Bracco also conducted a "*Barium Swallow Survey*" to assess the use of barium sulfate in MBS in pediatric population. A total of 203 respondents provided information about use of barium sulfate products in pediatric patients for MBS. One hundred and fourteen (114) of the 203 (56%) respondents indicated that barium is used in their practice for MBS in children. In general, all Varibar products are used in children during MBS (Table 15).

Information about the dose was provided by some of the respondents who indicated that doses between 10-30 mL are used in patients < 1month and doses between 30 and 60 mL are used in all other age groups.

Table 15: Survey Results of Barium Sulfate Products in Modified Barium Swallow (MBS) Studies in Pediatric Patients

Product Name	Total number of users*	Age Group			
		Group I up to 1 mo.	**Group II** < 2 yrs	**Group III** 2-12 yrs	**Group IV** > 12 yrs
Varibar Thin Liquid					
Online General Barium	20	14	16	18	17
Phone General Barium	27	19	20	20	20
Barium Swallow	14	12	14	14	13
Total	61	45	50	52	50
Varibar Nectar:					
Online General Barium	16	9	12	14	15
Phone General Barium	15	10	11	11	11
Barium Swallow	12	9	11	11	12
Total	43	28	34	36	38
Varibar Thin Honey:					
Online General Barium	12	6	9	10	11
Phone General Barium	16	10	11	11	11
Barium Swallow	6	2	6	6	6
Total	34	18	26	27	28
Varibar Honey:					
Online General Barium	9	5	6	6	7
Phone General Barium	15	10	10	11	10
Barium Swallow	5	1	5	4	4
Total	29	16	21	21	21
Varibar Pudding:					
Online General Barium	14	4	8	11	14
Phone General Barium	13	9	9	9	9
Barium Swallow	11	2	9	11	11
Total	38	15	26	31	34

Data obtained from the "*Online – General Barium Survey*", the "*Phone – General Barium Survey*", and the "*Barium Swallow Survey*".
*Total number of respondents who reported use of the barium product, across all age groups.

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

/s/

BRENDA Q YE
11/16/2015

LIBERO L MARZELLA
11/17/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:208143 **Applicant:Bracco** **Stamp Date: December 18, 2014**

Drug Name: Ready Cat-2 **NDA/BLA Type:505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	XX			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	XC			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3691123

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Pivotal Study #2 Indication:				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	Not applicable.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3691123

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reference ID: 3691123

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Harris E. Orzach, M.D.	January 21, 2015
Reviewing Medical Officer	Date
Libero Marzella, M.D.	January 22, 2014
Clinical Team Leader	Date

Reference ID: 3691123

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

/s/

HARRIS E ORZACH
01/22/2015

LIBERO L MARZELLA
01/22/2015