U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/BLA Serial Number:	208-036 (powder-oral use) & 208-143 (suspension for oral use)
Drug Names:	EZ-HD & Readi-Cat-2
Indication(s):	EZ-HD is indicated for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenu (b) (4) Readi-Cat-2 is indicated for use in computed Tomography of the abdomen (b) (4) (b) (4)
Applicant:	Bracco Diagnostics Inc.
Date(s):	NDA Submission: EZ-HD: December 11, 2014 PDUFA Date: October 11, 2015 Readi-Cat-2: December 18, 2014 PDUFA Date: October 18, 2015
Review Priority:	Standard for both
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Keywords: Sensitivity, Specificity, Efficacy, Meta-Analysis, Random Effect Model

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1. EXECUTIVE SUMMARY

E-Z-EM Inc. was a major manufacturer of contrast agents including barium sulfate for gastrointestinal (GI) radiology for over 40 years. Bracco acquired E-Z-EM in 2008 and as a result of the acquisition Bracco has manufactured and distributed barium products since 2008. It is now the only supplier of Barium Sulfate products in the United States.

Submission of all NDAs and supplements to original NDAs for barium sulfate products using the 505(b)(2) regulatory pathway was discussed and agreed with FDA/DMIP in the context of several regulatory meetings held (17 July 2012 , 26 November 2013; 14 November 2014). Bracco submitted 505(b)(2) NDA submission for E-Z-HD barium sulfate powder for suspension (98% w/w) using the electronic common technical document (eCTD) specifications. This NDA submission is the (b) (4) NDA for E-Z-HD, powder for suspension (b) (4) The sponsor also submitted application for Readi-Cat 2/Readi-Cat 2 Smoothies.

In this submission, the sponsor is seeking approval for following indications:

E-Z-HD (powder for oral suspension) is indicated for use in adults for double-contrast radiographic examinations of the esophagus, stomach and duodenum (b) (4) .

READI-CAT® 2 (and READI-CAT® 2 SMOOTHIES): (suspension for oral use) is indicated for use in Computed Tomography of the abdomen (b) (4) .

A total of 151 publications were selected based on the abstract. 103 publications were excluded based on inclusion and exclusion criteria. 48 publications were selected for detailed review and publications were included in this submission.

The clinical and statistical teams considered 5 citations specific for currently submitted applications for review, namely E-Z-HD and 1 citation for Readi-Cat 2/Readi-Cat 2 Smoothies (esophagus, stomach, duodenum). These two barium products are being reviewed here along with some supportive publications for E-Z-HD and related products.

Quantitative data suitable for statistical analyses were limited. The analysis was limited to the reported values of several available imaging parameters such as sensitivity and specificity. The clinical and statistical reviewers found that 3 prospective and 2 retrospective studies that had information about sensitivity and specificity (key imaging parameters) for E-Z-HD product that can be used for analysis. This reviewer conducted meta-analysis to supplement the reported

sensitivity and specificity estimates reported in this report and these results are provided in Table 1.

The overall sensitivity of E-Z-HD based on 5 articles is 94.9 % with 95% confidence interval (92.0, 96.8). Likewise, the overall specificity of E-Z-HD based on 3 articles is 81.9% with 95% confidence interval (70.9, 89.4).

Table 1: Performance Characteristics for 5 studies supporting E-Z-HD

Study Type	Author/ Year	N	Sensitivity	95% Confidence Interval	Specificity	95% Confidence Interval
Prospective	Farber et al 2005	61	89.2	(74.5, 95.9)	83.3	(63.1, 93.6)
Prospective	Nawaz et al 2008	115	96.5	(89.6, 98.9)	98.4	(78.9, 99.9)
Prospective	Drudi et al 2002	39	97.4	(83.9, 99.6)	NA	NA
Meta-Analysis Prospective			94.1	(88.7, 97.1)	87.3	(71.7, 94.9)
Retrospective	Admassie et al	173	96.0	(91.8, 98.1)	NA	NA
Retrospective	Ukrisana et al	84	93.8	(82.3, 98.0)	77.8	(61.5, 88.5)
Meta-Analysis Retrospective			95.4	(91.7, 97.5)	77.8	(61.5, 88.5)
Meta-Analysis Overall			94.9	(92.0, 96.8)	81.9	(70.9, 89.4)

Conclusion: These studies individually and collectively support E-Z-HD (powder for oral suspension).

The available quantitative data in support of READI-CAT 2 (and READI-CAT 2 SMOOTHIES) was limited, but the appear to be in the right direction in support of indication for READI-CAT 2 (and READI-CAT 2 SMOOTHIES)

Supportive evidence:

The supportive evidence was mixed and only few papers had quantitative information related to diagnostic parameters. Some of these studies are summarized below.

(1) In an audit report of 131 departments conducted across the UK involving 5454 examinations in 2002, Twan et al 2005 reported that the diagnosis rate was 85.9% (4687/5454) and compared this rate with Wessex Audit 1995 where Thomas et al reported a diagnosis rate of 84.6%. Twan et al 2005 concluded that the basic process of undertaking and reporting double-contrast barium enema (DCBE) has remained relatively unchanged over the last few years (1995 to 2002).

(2) In a prospective, blinded trial at an inflammatory bowel disease clinic at an academic medical center (41 CTE examinations), Solem et al (2008) reported that the sensitivity of CE for active small-bowel Crohn's disease was similar to CTE, ileocolonoscopy, or SBFT, but specificity was lower.

(3) In a prospective, blinded study comprised of 837 asymptomatic subjects at higher than average risk for colorectal cancer who underwent CT colonography followed by same-day DCBE examinations with polyps > or =5 mm in diameter, Johnson et al (2004) reported that CT colonography and DCBE are not significantly different in full structural examinations when interpreted by a single examiner. Double-read CT colonography is significantly more sensitive than single-read DCBE.

(4) There was one pediatric study and the results were based on publication abstract only. Aggarwal et al (1995) reported that the sensitivity and specificity of DCBE was 66.66% and 100% while that of colonoscopy 74.35% and 100% respectively based on 44 children with overt rectal bleeding and underwent flexible colonoscopy and DCBE independently. The final diagnosis was made after considering all investigations.

In general these studies support the indication using barium sulfate medical imaging products.

2. INTRODUCTION

Barium sulfate, due to its high atomic number, is opaque to x-rays and therefore acts as a positive contrast agent for radiographic studies.

According to the sponsor, the Barium Sulfate medical imaging products have been used since the early 1900s as radiopaque contrast agents to opacify the GI tract following oral administration (pharynx, hypopharynx, esophagus, stomach, duodenum, and small bowel exams) or rectal administration (colon and distal segments of the small bowel). Barium Sulfate products continue to be largely used during diagnostic imaging of the GI tract with conventional X-ray and CT. The sponsor states that the safety and efficacy of barium sulfate imaging products have been well established over more than 100 years of clinical use experience.

Barium contrast products have been marketed since 1962, but they are not FDA approved.

2.1 Overview

The sponsor submitted a literature-based 505(b)(2) application and has provided a summary of clinical efficacy based on literature searches of the PubMed database that were performed to support the efficacy of Barium Sulfate during diagnostic imaging procedures. Each search was limited to articles in "humans," English language and the period 1994 to 2014 to best capture current practice and technological advances. Several study reports and many literature references were included. None of studies were performed by the sponsor and the sponsor does not have the right of reference to raw data. Reported values of available performance characteristics such as sensitivity and specificity were included. The information related to available pediatric patients was also collected and reported.

The emphasis in the submission and proposed package insert is on dosage & administration, pharmacology, non-clinical toxicology and safety. The package insert does not have clinical studies section 14.

2.1.1 Regulatory History

E-Z-EM Inc. was a major manufacturer of contrast agents including barium sulfate for gastrointestinal (GI) radiology for over 40 years. Bracco acquired E-Z-EM in 2008 and as a result of the acquisition Bracco has manufactured and distributed barium products since 2008. It is now the only supplier of Barium Sulfate products in the United States.

Submission of all NDAs and supplements to original NDAs for barium sulfate products using the 505(b)(2) regulatory pathway was discussed and agreed with FDA/DMIP in the context of several regulatory meetings held (17 July 2012 , 26 November 2013; 14 November 2014).

2.1.2 Doses

E-Z-HD barium sulfate powder for suspension

- High density barium suspension
- (b) (4)
- For use in double contrast radiographic examinations of the esophagus, stomach and duodenum, (b) (4)
- Typical dose: 65-135 ml

2.1.3 Identified Studies in the review

Bracco submitted a 505(b)(2) NDA submission for E-Z-HD barium sulfate powder for suspension (98% w/w) using the electronic common technical document (eCTD) specifications. This NDA submission is the (b) (4) NDA for (E-Z-HD, powder for suspension) (b) (4) he sponsor also submitted application for Readi-Cat 2/Readi-Cat 2 Smoothies.

2.1.4 Analysis Populations

A total of 151 publications were selected based on the abstract and further reviewed against the inclusion and exclusion criteria listed below.

Inclusion Criteria

Publications that met any of the following inclusion criteria were included in the Barium Sulfate efficacy literature summary:

- Original publication of a clinical study in human subjects with prospective or retrospective enrollment;
- Barium Sulfate was used during X-ray or CT examinations;
- Comparison was made between Barium-enhanced examinations and another reference standard;
- Sufficient information for efficacy evaluation of at least one of the Sensitivity, Specificity, Accuracy.

Exclusion Criteria

Publications that do not meet the inclusion criteria or meet the following exclusion criteria were excluded from the Barium Sulfate efficacy literature summary:

1) Study performed in non-human subjects (e.g., phantom, in vitro or animal studies);
2) Publication was not in English;
3) Barium Sulfate product utilized in the study was specified as Non-E-Z-EM/Bracco;
4) Barium Sulfate product manufactured by E-Z-EM/Bracco was not used in the study for the enhancement of the GI tract;
5) Fewer than 20 subjects dosed with Barium Sulfate were evaluated;
6) Insufficient information for efficacy results (e.g., publication was not focused on efficacy of Barium Sulfate, results were not specific to efficacy, efficacy results were not sufficiently described, etc.);
7) Publications other than study reports, such as review articles, author correspondence, editorials, letter-to-editor, case reports or conference or scientific meeting abstracts that have no or insufficient data of study population, study methodology and results or if there is a lack of completeness in the reports;
8) Duplicate publications or those that reported results of the same endpoints from the same patient population or a subset of a larger patient population that have been published elsewhere.

(b) (4)

Based on the above inclusion and exclusion criteria, a total of 103 out of the 151 publications were excluded from the Barium Sulfate efficacy literature summary as they did not meet the criteria for inclusion. Summaries of the remaining 48 publications met the criteria for inclusion.

In summary the systematic literature review yielded

- 151 citations
- 103 excluded (based on inclusion/exclusion criteria)
- 48 selected for detailed review
- 5 citations are specific for currently submitted applications for review, namely E-Z-HD and 1 citation for Readi-Cat 2/Readi-Cat 2 Smoothies (esophagus, stomach, duodenum)
- There are some supportive citations for E-Z-HD and related products

2.2 Data Sources

Safety and efficacy data included in the eCTD submission are derived from:

- Guidelines and appropriateness criteria issued by the American College of Radiology (ACR);
- Guidelines on the safety of contrast agents issued by the European Society of Urogenital Radiology (ESUR);
- Radiology textbooks;
- Published papers and review articles retrieved from the literature. It should be noted that because of the historical use and acceptance of barium sulfate products by the medical community, a few literature publications on the use of barium sulfate products in well-established imaging procedures;
- Post-marketing surveillance (PMS) database based on an estimated exposure of more (b) (4) patients worldwide, in the period comprised between January 1, 2009 to July 31, 2014.

Data elements of interest were extracted from the studies that met inclusion/exclusion criteria. Variables of interest included study author (reported by name of the first author), title of the publication, year of publication, limited information on the design of the study (prospective, retrospective or information not available), number of patients, number of readers, and dose range. Additionally, safety outcomes associated with the administration of Barium sulfate medical imaging products were also included.

The reported information and consolidated data were provided for each study separately. SAS export files of these data, excel files or data in analyzable format were not provided.

The NDA in eCTD are located at:

E-Z-HD: \\CDSESUB1\evsprod\NDA208036\208036.enx and
Readi-Cat-2 \\CDSESUB1\evsprod\NDA208143\0000

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data were not provided in analyzable format (xpt transport files, excel (xls) or in tabular form. Since the data were captured from the published articles and reports, the quality of data, was limited to the published information.

3.2 Evaluation of Efficacy

3.2.1 Study Design

- Literature-based 505(b)(2) submission.
- (b) (4)
- This submission is about E-Z-HD, Readi-Cat 2 (orange (b) (4)) and Readi-Cat 2 Smoothies (four flavors: berry, vanilla, banana, mochaccino). These two barium products are being reviewed here.
- (b) (4)

3.2.2 Objective

Indication

- Radiopaque contrast agents for use during X-ray or CT to opacify the GI tract to:
  - locate and outline normal structures,
  - distinguish between normal and abnormal anatomy

Mechanism of action:

- Increases absorption of x-rays as they pass through the GI tract, thus delineating body structures

The statistical analyses for studies currently in review (E-Z-HD, Readi-Cat 2) are presented in this report. Some supportive citations for E-Z-HD and related products are also included.

The Bracco products intended for use in radiographic examinations of the esophagus and upper GI are listed below in Table 2.

Table 2: Bracco products intended for use in radiographic examinations

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

3.2.3 Protocol Defined Methods of Analysis

In this submission, there was no protocol defined method of analysis. The information was extracted from the Barium Sulfate literature summary that met any of the following criteria:

- Original publication of a clinical study in human subjects with prospective or retrospective enrollment;
- Barium Sulfate was used during X-ray or CT examinations;
- Comparison was made between Barium-enhanced examinations and another reference standard;
- Sufficient information for efficacy evaluation of at least one of the following endpoints:
  - Sensitivity,
  - Specificity,
  - Accuracy.

The data were extracted from the publications and applicable analyses were performed. Special focus was the estimation of sensitivity and specificity wherever available.

This reviewer also performed meta-analysis to combine the results and to estimate the sensitivity and specificity for applicable studies.

3.2.4 Demographic and Baseline Characteristics

Due to the nature of data presented in the reported study publications in the analysis population, information on demographic and baseline characteristics were limited. The information is included in the individual studies if available.

3.3 Results and Conclusions

The evaluation of the following two products was submitted in the current application.

- E-Z-HD: Double contrast examination of (b) (4)
- Readi-CAT2: CT of abdomen and pelvis

The evaluation of these two products is emphasized in this review.

3.3.1 Evaluation of E-Z-HD product

- GI tract anatomy: esophagus, stomach, duodenum, small and large bowel
- Type of imaging examination: single vs double contrast; fluoroscopic vs CT; oral vs rectal administration

Inclusion Criteria (E-Z-HD)

- Use of barium sulfate during x-ray/CT
- Comparison of barium exam against reference standard
- Sufficient information for efficacy evaluation: (sensitivity/specificity/accuracy)

3.3.2 Key Articles Identified for the Quantitative Evaluation of E-Z-HD product

There were 3 prospective studies (n=215) and 2 retrospective studies (n=257). A brief description of these 5 studies is given in the following Table 3.

Table 3: Key Articles Identified for the Quantitative Evaluation of E-Z-HD product

	Author	Year	Design
Study 1	Farber et al	2005	Prospective Study, n = 61
Study 2	Nawaz et al	2008	Prospective Study, n=115
Study 3	Drudi et al	2002	Prospective Review, n = 39
Study 4	Admassie et al	1996	Retrospective Review, n = 173
Study 5	Ukrisana et al	2004	Retrospective Review, n = 84

Each of these 5 studies is described below:

3.3.3 Study 1 (E-Z-HD): Farber et al

Title: Esophageal Varices: Evaluation with Esophagography with Barium versus Endoscopic Gastroduodenoscopy in Patients with Compensated Cirrhosis – Blinded Prospective Study
Author: Evgeny Farber, MD et al
Published: online Radiology 2005; 237: 535-540

Methods: From November 2002 to May 2003, 61 consecutive ambulatory patients (34 men, 27 women, mean age 61 years, range 36-76 years) with cirrhosis met the criteria for enrollment in this prospective study. In all 61 patients, cirrhosis was diagnosed clinically or with liver biopsy. The purpose of this study was to prospectively evaluate the diagnostic value (sensitivity and specificity) of esophagography with barium versus endoscopic gastroduodenoscopy in patients with compensated cirrhosis. Blinded reading was performed by a team of 2 experienced radiologists. There was no discussion of discrepancies between readers. The truth standard was endoscopy, performed by teams of 3 experienced gastroenterologists.

All radiologic funding's for esophagram were divided into 3 grades:

- Grade 0, no esophageal varices (EV) seen
- Grade 1, very mild fold irregularity
- Grade 2, fold irregularity clearly present.

Gastroduodenoscopy endoscopy of the upper gastrointestinal tract was performed by 3 experienced gastroenterologists. The grading system (endoscopy) was as follows:
Grading System: Endoscopy

- F0, no EV detected
- F1, small straight EV
- F2, slightly enlarged tortuous EV, occupies less than 1/3 of lumen
- F3, large coil-shaped EV, occupies >1/3 of lumen

The following Table 4 describes findings at endoscopy gastroduodenoscopy diagnosed with esophagography with barium

Table 4: Findings at Endoscopy Gastroduodenoscopy Diagnosed with Esophagography with Barium

Grade Esophagography			Endoscopic Findings			
	n	%	# Grade F0	# Grade F1	# Grade F2	# Grade F3
Grade 0	24	39	20	4	0	0
Grade 1	18	29	4	10	4	0
Grade 2	19	31	0	0	13	6

The ability of esophagography with barium to depict EV according to grade assigned at endoscopic gastroduodenoscopy is given Table 5 below:

Table 5: Ability of Esophagography with Barium to Depict EV according to Grade Assigned at Endoscopic Gastroduodenoscopy

Grade of EV	TP	TN	FP	FN	Sensitivity (%) & 95% CI	Sensitivity (%) & 95% CI
Overall	33	20	4	4	89 (75.9, 96.5)	83 (64.5, 94.7)
F1	10	20	4	4	71 (44.4, 90.0)	83 (64.5, 94.5)
F2	17	20	0	0	100 (83.9, 100)	100 (86, 100)
F3	6	20	0	0	100 (60.0, 100)	100 (86, 100)

Conclusion:

The overall sensitivity and specificity (the capability of esophagography to help in the the identification of EV of all grades) was:

- Sensitivity = 89% and 95% CI - (75.9, 96.5)
- Specificity = 83% and 95% CI - (64.5, 94.7)

The data are supportive of double contrast esophagram for diagnosing EV in patients with compensated cirrhosis

3.3.4 Study 2 (E-Z-HD): Nawaz et al

Title: Role of Barium Meal Examination in Diagnosis of Peptic Ulcer
Author: Muhammad Nawaz, MD et al

Published : J Ayub Med Coll Abbottabad 2008; (20(4)

Background: Peptic ulcer is a sore in the protective lining (mucosal lining) og the gastrointestinal tract and develops when the lining is damaged. The of this descriptive validation 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 Training Hospital Peshawar from November 2000 to March 2004.

Methods: A total of 115 (80 male and 35 female, mean age -49 years and age range 27-75 years) patients with signs and symptoms of peptic ulcer disease were enrolled for this study. The diagnosis of benign/malignant peptic ulcer was made by barium meal examinations - Barium for use in UGI to diagnose peptic ulcer disease in symptomatic patients who failed to respond to an empirical trial of medical therapy. In all these patients diagnosis later was confirmed by endoscopy and or surgery (Truth Standard).

Results: There were 52 patients with duodenal cancer, 30 patients gastric ulcer, and 33 patients had normal radiological findings. In 6 out of 30 patients with gastric ulcer had radiological malignant gastric ulcer. Sensitivity and Specificity are given in Table 6 below;

Table 6: Findings at Barium Meal and Endoscopy

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

- Sensitivity = 96.5% 95% CI (90.0, 99.3%)
- Specificity = 100% 95% CI (88.4, 100%)

Conclusion: Double contrast barium UGI showed a high degree of sensitivity and specificity in diagnosing peptic ulcers

3.3.5 Study 3 (E-Z-HD) : Drudi et al

Title: Esophagogram and CT vs endoscopic and surgical specimens in the diagnosis of esophageal carcinoma.
Author: Drudi FM, et al
Published: Radiol Med. 2002 Apr;103(4):344-52.

Methods: This was a prospective study (n=39) of patients with esophageal cancer from 1993 to 2000. There were 30 males (77%) and 9 females (23%), age range 41-85 years. All patients underwent esophagogram, digestive endoscopy, and chest and abdominal CT. Truth standard was histology and surgical specimen. Barium esophagram was used in establishing location, size and morphology of esophageal carcinoma. Correlated length of tumor on esophagram with that on surgical specimen.

Results: Esophagogram identified neoplasm in **38 patients out of 39** (high detection rate), while CT identified neoplasm in all patients. Location and morphology of the neoplasm established at endoscopy were confirmed in all patients. In 13 of 22, tumor length discrepancy between esophagram and surgical specimen was < 1cm

Conclusions: Barium esophagram was adequate for visualizing esophageal lesions. Discrepancy between length of lesion on esophagram vs surgical specimen was < 1cm in 13 of 22 patients (59%).

3.3.6 Study 4 (E-Z-HD): Admassie

Title: Relative sensitivity of barium swallow examination in the diagnosis of oesophageal pathology.
Author: Admassie D.
Published: East Afr Med J. 1996 Mar;73(3):201-3

Methods: This was a retrospective study (n=173). From February 1, 1989 to August 28, 1993, 668 patients complaining of dysphagia underwent barium swallow examination; 173 of them had either histologically confirmed diagnoses and/or surgical diagnoses or oesophagoscopic diagnoses. Truth standard was histology (surgical or endoscopic diagnosis)

Results:

The purpose of this study was to compare barium swallow findings with surgical, histological, and oesophagoscopic findings. The results are given in the following Table 7:

Table 7: Disease Type versus Barium Meal/Non-barium Diagnosis

Disease Type	Barium meal diagnosis (#)	Non-barium diagnosis (#)
Malignant tumors of oesophagus	135	137
Achalasia of the cardia	21	21
Diverticula of the oesophagus	6	6
Peptic-stricture	4	5
Oesophagitis	0	4
Total	166	173

Barium swallow agreed with 166 of the 173 histologic diagnoses (96%). In conclusion, a skillful interpretation of barium swallow in patients presenting with dysphagia provides valuable information.

Conclusion: Double contrast barium esophagram is useful in diagnosing lesions in patients presenting with dysphagia

3.3.7 Study 5 (E-Z-HD): Drudi et al

Title: Evaluation of the sensitivity of the double-contrast upper gastrointestinal series in the diagnosis of gastric cancer.
Author: Ukrisana P, Wangwinyuvirat M.
Published: J Med Assoc Thai. 2004 Jan;87(1):80-6.

Methods: The purpose was to evaluate double contrast UGI for diagnosis of gastric cancer. This was a retrospective assessment of UGI exams in 84 patients with suspected gastric cancer and pathological confirmation by gastric biopsies and/or surgery (truth standard)

Results:

The results are summarized in the following Table 8:

Table 8: Double Contrast UGI Series versus Pathological Finding

Double Contrast UGI Series	Pathological Finding		
	Positive	Negative	Total
Positive	45	8	53
Negative	3	28	32
Total	48	36	84

- Sensitivity = 93.8% 95% CI (82.8, 98.7%)
- Specificity = 77% 95% CI (60.8, 89.9%)

Conclusion: Double contrast upper gastrointestinal series shows a sensitivity of 94% with 95% CI (83, 99%) and specificity of 77% with 95% CI (61, 90%) for gastric cancer.

3.3.8 Meta-Analysis Identified to Support E-Z-HD Product

This reviewer conducted meta-analysis on 5 studies that were linked to E-Z-HD product. The Random Effects Model for the Meta-Analysis was employed since it allows for heterogeneity and includes within study variance and between study variance to estimate sensitivity and specificity and their 2-sided 95% Confidence Intervals (CIs) using meta-analytical approach.

Table 9 provides meta-analytic sensitivity and specificity estimates for 5 studies (3 prospective and 2 retrospective) supporting E-Z-HD. This analysis also includes meta-analytic estimates of combined 3 prospective studies, 2 retrospective studies and overall 5 studies. The overall sensitivity of E-Z-HD based on 5 articles is 94.9% with 95% confidence interval (92.0, 96.8). Likewise, the overall specificity of E-Z-HD based on 3 articles is 81.9% with 95% confidence interval (70.9, 89.4). The results are given in the following Table 9 and pictorially represented in Figure 1 and Figure 2.

Table 9: Performance Characteristics for 5 studies supporting E-Z-HD

Study Type	Author/ Year	N	Sensitivity	95% Confidence Interval	Specificity	95% Confidence Interval
Prospective	Farber et al 2005	61	89.2	(74.5, 95.9)	83.3	(63.1, 93.6)
Prospective	Nawaz et al 2008	115	96.5	(89.6, 98.9)	98.4	(78.9, 99.9)
Prospective	Drudi et al 2002	39	97.4	(83.9, 99.6)	NA	NA
Meta-Analysis Prospective			94.1	(88.7, 97.1)	87.3	(71.7, 94.9)
Retrospective	Admassie et al	173	96.0	(91.8, 98.1)	NA	NA
Retrospective	Ukrisana et al	84	93.8	(82.3, 98.0)	77.8	(61.5, 88.5)
Meta-Analysis Retrospective			95.4	(91.7, 97.5)	77.8	(61.5, 88.5)
Meta-Analysis Overall			94.9	(92.0, 96.8)	81.9	(70.9, 89.4)

This is also graphically represented in the forest plots in figures 1 and figures 2

Figure 1: Sensitivity for 5 studies supporting E-Z-HD

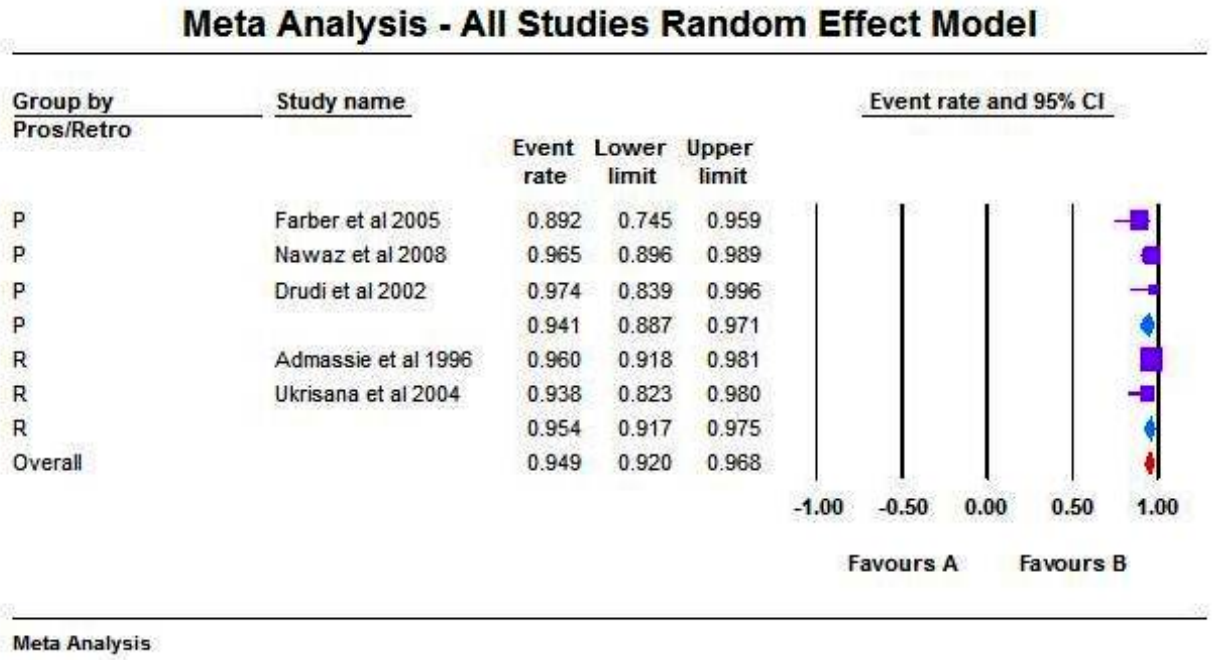
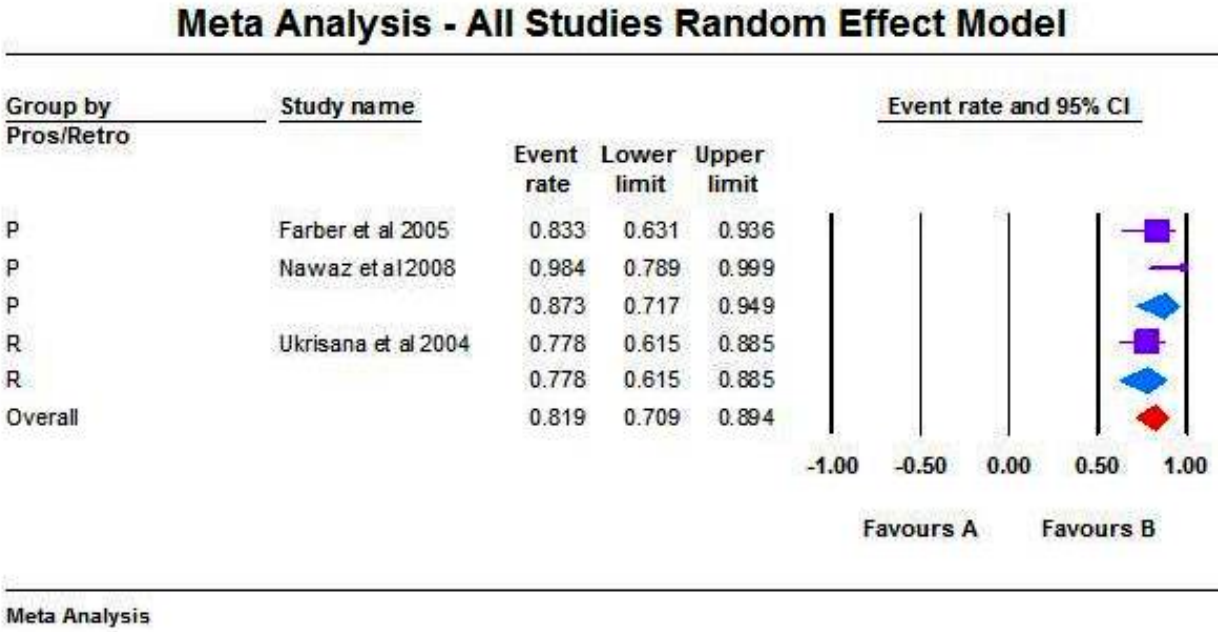


Figure 2: Specificity for 5 studies supporting E-Z-HD



3.3.9 Evaluation of Readi-CAT2 and Readi-CAT 2 Smoothies products (NDA 208134)

Readi-Cat 2 and Readi-Cat 2 Smoothie (barium sulfate oral suspension) products are a 2.0% w/v barium sulfate suspension for oral administration containing (b) (4) . Readi-Cat 2 products are white, low viscosity, flavored suspensions that are presented as a single use 450 mL fill in a (b) (4) mL natural high density polyethylene (HDPE) bottle with a white polypropylene (b) (4) cap and a (b) (4) with an aluminum heat induction seal. All Readi-Cat 2 products have a barium sulfate composition of 2 grams of barium sulfate per 100 mL of solution. Adult dose is 450 – 900 ml

The submission included the details of description and composition Readi-Cat 2 Smoothie and Barium Sulfate Suspension, etc.

Systematic literature review resulted in 151 citations, 103 citations were excluded (based on inclusion/exclusion criteria), 48 citations were selected for detailed review. Out of these 48 citations only 1 citation was specific for opacification of GI tract during abdominal and pelvic CT

Abdominal and Pelvic CT: Is positive enteric contrast still necessary? Results of a retrospective observational study by S. Kammerer, et al. *Eur Radio*l. 2014

This was a retrospective study with large number of patients (n=2008) from February 2012 to May 2013 for CT with barium vs CT with water vs CT without contrast. A comparison was made between CT with/without for various pathologies. There was no reference standard and no objective measurement of diagnostic utility

Study Design had Five groups:

- oncology (n=1359),
- inflammation (n=225),
- vascular pathology (n=235),
- trauma/surgery (n=138),
- GI pathology, i.e. bowel ischemia (n=51).

Results

- Bowel better delineated with enteric contrast.
- Studies with enteric contrast showed improvement in making a diagnosis, as well as improvement in diagnostic reliability, compared to non-contrast studies

3.4 Studies supportive of indication (b) (4)

The clinical team identified few other citations and wanted to present these data in these citations related to the current product E-Z-HD and generally for barium sulfate medical imaging products. The supportive evidence in these papers was mixed and only few papers had quantitative information related to diagnostic parameters. A brief description of these citations and related analyses are given below:

(1) In an audit report of 131 departments conducted across the UK involving 5454 examinations in 2002, Twan et al 2005 reported that the diagnosis rate was 85.9% 4687/5454) and compared this rate with Wessex Audit 1995 where Thomas et al reported a diagnosis rate of 84.6%. Twan et al 2005 concluded that the basic process of undertaking and reporting double-contrast barium enema (DCBE) has remained relatively unchanged over the last few years (1995 to 2002).

(2) In a prospective, blinded trial at an inflammatory bowel disease clinic at an academic medical center (41 CTE examinations), Solem et al (2008) reported that the sensitivity of CE for active small-bowel Crohn's disease was similar to CTE, ileocolonoscopy, or SBFT, but specificity was lower.

(3) In a prospective, blinded study comprised of 837 asymptomatic subjects at higher than average risk for colorectal cancer who underwent CT colonography followed by same-day DCBE examinations with polyps > or =5 mm in diameter Johnson et al (2004) reported that CT colonography and DCBE are not significantly different in full structural examinations when interpreted by a single examiner. Double-read CT colonography is significantly more sensitive than single-read DCBE.

(4) There was one pediatric study and the results were based on publication abstract only. Aggarwal et al (1995) reported that the sensitivity and specificity of DCBE was 66.66% and 100% while that of colonoscopy 74.35% and 100% respectively based on 44 children with overt rectal bleeding and underwent flexible colonoscopy and DCBE independently. The final diagnosis was made after considering all investigations.

In general these studies support the indication using barium sulfate medical imaging products. The details are given in Appendix II

3.5 Evaluation of Safety

Adverse reactions, such as nausea, vomiting, diarrhea and abdominal cramping, constipation, retention of barium have been reported following the administration of barium sulfate products. The reporting is infrequent and usually mild. Serious adverse reactions are rare. The clinical report has more details of safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Due to the nature of data collection based on published papers and 505(b)(2) submission, the information on race, gender, region and age was extremely limited. There are no specific instructions for Geriatric use.

4.2 Other Special/Subgroup Populations

Due to the nature of data collection based on published papers and 505(b)(2) submission, the information on special/subgroup populations was not there.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

E-Z-EM Inc. was a major manufacturer of contrast agents including barium sulfate for gastrointestinal (GI) radiology for over 40 years. Bracco acquired E-Z-EM in 2008 and as a result of the acquisition Bracco has manufactured and distributed barium products since 2008. It is now the only supplier of Barium Sulfate products in the United States.

Submission of all NDAs and supplements to original NDAs for barium sulfate products using the 505(b)(2) regulatory pathway was discussed and agreed with FDA/DMIP in the context of several regulatory meetings held (17 July 2012 , 26 November 2013; 14 November 2014). Bracco submitted 505(b)(2) NDA submission for E-Z-HD barium sulfate powder for suspension (98% w/w) using the electronic common technical document (eCTD) specifications. This NDA submission is the (b) (4) NDA for E-Z-HD, powder for suspension (b) (4) The sponsor also submitted application for Readi-Cat 2/Readi-Cat 2 Smoothies.

A total of 151 publications were selected based on the abstract. 103 publications were excluded based on inclusion and exclusion criteria. 48 publications were selected for detailed review and publications were included in this submission.

The clinical and statistical teams considered 5 citations specific for currently submitted applications for review, namely E-Z-HD and 1 citation for Readi-Cat 2/Readi-Cat 2 Smoothies (esophagus, stomach, duodenum). These two barium products are being reviewed here along with some supportive publications for E-Z-HD and related products.

Quantitative data suitable for statistical analyses were limited. The analysis was limited to the reported values of several available imaging parameters such as sensitivity and specificity. The clinical and statistical reviewers found that 3 prospective and 2 retrospective studies that had information about sensitivity and specificity (key imaging parameters) for E-Z-HD product that can be used for analysis. This reviewer conducted meta-analysis to supplement the reported sensitivity and specificity estimates reported in this report and these results are provided in Table 10.

The overall sensitivity of E-Z-HD based on 5 articles is 94.9 % with 95% confidence interval (92.0, 96.8). Likewise, the overall specificity of E-Z-HD based on 3 articles is 81.9% with 95% confidence interval (70.9, 89.4).

Table 10: Performance Characteristics for 5 studies supporting E-Z-HD

Study Type	Author/ Year	N	Sensitivity	95% Confidence Interval	Specificity	95% Confidence Interval
Prospective	Farber et al 2005	61	89.2	(74.5, 95.9)	83.3	(63.1, 93.6)
Prospective	Nawaz et al 2008	115	96.5	(89.6, 98.9)	98.4	(78.9, 99.9)
Prospective	Drudi et al 2002	39	97.4	(83.9, 99.6)	NA	NA
Meta-Analysis Prospective			94.1	(88.7, 97.1)	87.3	(71.7, 94.9)
Retrospective	Admassie et al	173	96.0	(91.8, 98.1)	NA	NA
Retrospective	Ukrisana et al	84	93.8	(82.3, 98.0)	77.8	(61.5, 88.5)
Meta-Analysis Retrospective			95.4	(91.7, 97.5)	77.8	(61.5, 88.5)
Meta-Analysis Overall			94.9	(92.0, 96.8)	81.9	(70.9, 89.4)

Conclusion: These studies individually and collectively support E-Z-HD (powder for oral suspension).

The available quantitative data in support of READI-CAT 2 (and READI-CAT 2 SMOOTHIES) are limited, but the appear to be in the right direction in support of indication for READI-CAT 2 (and READI-CAT 2 SMOOTHIES)

5.2 Conclusions and Recommendations

E-Z-HD (NDA 208036): There were 5 citations (3 prospective; 2 retrospective) that had quantitative and analyzable information. These studies provide adequate support the proposed indication.

Readi-CAT 2 (NDA 208143): The available quantitative data in support of READI-CAT 2 (and READI-CAT 2 SMOOTHIES) are limited (only 1 citation), but the appear to be in the right direction in support of indication for READI-CAT 2 (and READI-CAT 2 SMOOTHIES)

(b) (4)

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APPENDIX I - Barium Sulfate Products (Sponsor)

Barium sulfate medical imaging products are radiopaque contrast agents intended for use during X-ray or CT examinations to opacify the GI tract, (b) (4) .

Depending on the patient's clinical history and suspected clinical problem, conventional X-ray studies using barium sulfate may be performed following the oral or rectal administration of contrast and using either a single or a double-contrast technique. In the single-contrast examination, a barium sulfate suspension is administered to produce full-column opacification and distension of the segmental lumen under investigation, whereas a double-contrast examination involves the administration of a relative small volume of the barium sulfate suspension for the purpose of coating the mucosal surface of the area being studied. The so called "double-contrast" is achieved with a gas (most commonly air) which distends the lumen of the GI segment under investigation and results in a specific mucosal opacification and delineation of fine surface details.

Because of differences among the various imaging procedures and techniques using barium sulfate contrast agents there is no one single barium formulation which can totally satisfy the requirements of GI radiology.

This has led to the development of different formulations with different concentration in barium sulfate (resulting in a more opaque or less opaque agent), different viscosity (a characteristic that is related to coating and mucosal adherence performance), stability (to avoid/reduce sedimentation artifacts), and hydrophilicity. Palatabilty and flavoring are additional characteristics of barium sulfate suspensions intended for oral administration since they increase patient's acceptability of the product which may be particularly important in some patient populations (nausea-prone patients) or during CT enterography that requires oral administration of large volumes of contrast in a quite short time

(b) (4) .

Table A: Barium Sulfate Products (b) (4)

Product Names	Dose Form	Route of Administratio	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
Varibar Nectar	Suspension	Oral	Radiographic examinations of the esophagus, pharynx
Varibar Thin Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx
Varibar Honey	Suspension	Oral	Radiographic examinations of the esophagus, pharynx
Varibar Pudding	Paste	Oral	Radiographic examinations of the esophagus, pharynx
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
E-Z-Paste	Paste	Oral	Single-contrast radiographic examinations of the esophagus, pharynx, hypopharynx and for cardiac
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
Liquid Polibar Plus (E-Z-Dose)	Suspension	Rectal	Single- and double-contrast radiographic examinations of
E-Z-Disk	Tablet	Oral	Radiographic examinations of the esophagus for detection
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**	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.			

(b) (4)

APPENDIX II - Studies supportive of indication (b) (4)

The clinical team identified few other citations and wanted statistical analysis of the presented data in these citations related to the current product E-Z-HD and generally for barium sulfate medical imaging products. A brief description of these citations and related analyses are given below:

Study 1 (National Audit): Tawn et al

Authors: Tawn DJ, Squire CJ, Mohammed MA, Adam EJ.
Published: 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.
Purpose: To audit the sensitivity of double-contrast barium enema (DCBE) for colorectal carcinoma, as currently practiced in UK departments of radiology

Methodology:

Double-contrast barium enema (DCBE) is a standard technique for investigating colonic disease, and is widely used in the diagnostic of colorectal disease. 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 > or =95%; correct identification as a carcinoma > or =90%.

Results:

Across the UK, 131 departments took part in the audit, involving 5454 examinations. The overall diagnosis rate was 85.9% 4687/5454), slightly below the targets set, equivocal rate (a lesion reported, but not defined as malignant) was 6.9% (379/5454) and the demonstration rate (diagnosis rate plus equivocal rate) was 92.9% (5066/5454), the perception failure rate was 2.8% (150/5454) and the technical failure rate was 4.4%. These rates were similar to the diagnosis rate of 84.6% and the demonstration rate (diagnosis rate plus equivocal rate) of 92.7% in Wessex Audit 1995, [Thomas RD, Fairhurst JJ, Frost RA,: Wessex regional audit: barium enema in colorectal carcinoma, Clin Radiol. 1955 50:647-50]. This implies that the basic process of undertaking and reporting DCBE has remained relatively unchanged over the last decade.

Conclusion:

The basic process of undertaking and reporting DCBE has remained relatively unchanged over the last few years (1995 to 2002).

Study 2 (Small Bowel study): Solem et al

Authors: Craig A. Solem, MD et al:
Published: Small-bowel imaging in Crohn's disease: a prospective, blinded, 4-way comparison trial, Volume 68, No. 2 : 2008 Gastrointestinal Endoscopy 255-266.

Purpose:

Barium radiography has been the conventional test for diagnosis of small-bowel Crohn's disease, but ileocolonoscopy is necessary to assess for colonic and terminal ileal mucosa, and to obtain biopsy specimens. CT enterography (CTE) may detect extraluminal complications and distinguish inflammatory from fibrostenotic small-bowel Crohn's disease. The purpose of this study was to assess the sensitivity and specificity of capsule endoscopy (CE), CT enterography (CTE), ileocolonoscopy, and small-bowel follow-through (SBFT) in the diagnosis of small bowel Crohn's disease.

Methodology:

This was a prospective, blinded trial at an inflammatory bowel disease clinic at an academic medical center. Known or suspected Crohn's disease patients were enrolled. Exclusion criteria included known abdominal abscess and nonsteroidal anti-inflammatory drug (NSAID) use. Partial small-bowel obstruction (PSBO) at CTE excluded patients from subsequent CE. Patients underwent all 4 tests over a 4-day period. The main outcome measurements were sensitivity, specificity, and accuracy of each test to detect active small-bowel Crohn's disease. The criterion standard was a consensus diagnosis based upon clinical presentation and all 4 studies.

Results:

Forty-one CTE examinations were performed. Seven patients (17%) had an asymptomatic partial small-bowel obstruction (PSBO). Forty patients underwent colonoscopy, 38 had small-bowel follow-through (SBFT) studies, and 28 had CE 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 CE for detecting active small-bowel Crohn's disease was 83%, was not significantly different from CTE (83%), ileocolonoscopy (74%), or SBFT (65%). However, the specificity of CE (53%) was significantly lower than the other tests. A limitation was the use of a consensus clinical diagnosis as the criterion standard but this is how Crohn's disease is diagnosed in practice.

Conclusion:

The sensitivity of CE for active small-bowel Crohn's disease was not significantly different from CTE, ileocolonoscopy, or SBFT. However, lower specificity and the need for preceding small-bowel radiography (due to the high frequency of asymptomatic PSBO) may limit the utility of CE as a first-line test for Crohn's disease. (Gastrointest Endosc 2008;68:255-66.)

Study 3 (Colorectal Polyps): Johnson et al

Authors: Johnson et al,
Published: Comparison of the relative sensitivity of CT colonography and double-contrast barium enema (DCBE) for screen detection of colorectal polyps. Clin Gastroenterol Hepatol. 2004;2:314-21.

Purpose:

The purpose of this study was to compare the relative sensitivity and specificity of CT colonography with DCBE for detection of colorectal polyps in an asymptomatic low-prevalence population, and to assess the added value of double reading of CT colonography.

Methodology:

This prospective, blinded study comprised 837 asymptomatic subjects at higher than average risk for colorectal cancer who underwent CT colonography followed by same-day DCBE. Examinations with polyps > or =5 mm in diameter were referred to colonoscopy.

Results:

CT colonography readers detected 56% -79% of polyps > or =10 mm in diameter. In comparison, the sensitivity at DCBE varied between 39% and 56% for the 31 polyps > or =1 cm. All of the readers detected more polyps at CT colonography than DCBE, but the difference was statistically significant for only a single reader.

Relative specificity for polyps > or =10 mm on a per-patient basis ranged from 96% to 99% at CT colonography, and 99%-100% at DCBE.

Double reading of CT colonography detected significantly more polyps than DCBE (81% vs. 45% for polyps > or =1 cm, and 72% vs. 44% for polyps 5-9 mm.

Conclusion:

CT colonography and DCBE are not significantly different in full structural examinations when interpreted by a single examiner. Double-read CT colonography is significantly more sensitive than single-read DCBE.

Study 4 (Pediatric Population): Aggarwal et al

The results based on publication abstract – Article not available.

Authors: Aggarwal et al:
Published: A 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.

Purpose:

A prospective study was performed to compare the 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.

Methodology:

The final diagnosis was made after considering all investigations.

Results:

Against this gold standard, the sensitivity and specificity of DCBE was 66.66% and 100% while that of colonoscopy 74.35% and 100% respectively. When assessing polypoidal lesions of colon, diagnostic yield of enema study was 86.20% as compared to 72.41% with colonoscopy. In colitis cases, the similar figures for enema and endoscopy were 53.84% and 76.92% respectively. The observed differences were not statistically different. No significant preparation, premedication or procedure related complications were encountered.

Conclusion:

This study highlights the utility and complementary role of DCBE and colonoscopy for evaluation of children with rectal bleeding.

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