These results would not support the proposition that simethicone coated cellulose is the active ingredient in SonoRx.

The endpoint most relevant to the indication for delineation of anatomy was the question of the nature of the additional information for those patients whose post dose scan provided additional information over the pre dose scan. A true worst case analysis would have included the entire intent to treat population and imputed no improved delineation of abdominal anatomy to those patients whose scans were not read or those for whom no additional information was obtained. The sponsor has not performed such a worst case analysis but has rather re-presented the previous analysis from the previous submission the only difference is that the placebo patients are now included in the efficacy analysis. The sponsor's analysis is presented below for SonoRx for all endpoints and for placebo for improved delineation of anatomy. In addition, the reviewer has performed a simple "worst case analysis by dividing the number of scans, for each reader, with improved delineation of abdominal anatomy, by the total number of patients who ingested any dose of SonoRx

TABLE 10 NATURE OF ADDITIONAL INFORMATION IN SonoRx POST DOSE IMAGES 42,440-3B

		Blinded Readers			
SonoRx	Investigators N=66*	Reader#1 N=55*	Reader#2 N=33*	Reader#3 N=61*	Reader#4 N=52*
Improved delineation of abdominal anatomy	57/66 86%	55/55 100%	30/33 91%	56/61 92%	52/52 100%
Improved delineation of abdominal anatomy (worst case analysis calculated by reviewer)**	57/94 61%	55/94 59%	30/94 32%	56/94 60%	52/94 55%
Improved confidence in exclusion of pathology	39/66 59%	37/55 67%	10/33 30%	45/61 74%	24/52 46%
Improved delineation of pathology	32/66 48%	9/55 16%	5/33 15%	17/61 27%	7/52 13%
Improved evaluation of extent of disease pathology seen	17/66 26%	7/55 13%	2/33 6%	12/61 20%	2/52 4%
er	4/66 6 %	2/55 4%	0/33 0%	1/61 2%	0/52 0%
Placebo	N=14	N=19	N=11	N=12	N=17
Improved delineation of abdominal anatomy	12/14 86%	19/19 100%	10/11 91%	11/12 92%	17/17 100%

*N = number of patients with additional information according to each individual reader

** The reviewer has performed a simple worst case analysis by dividing the number of patients with additional information by the total number of patients (94) who received any dose of SonoRx

***Reviewer's Comment**: In this study, in the sponsor's per protocol analysis, the percentage of scans with improved delineation of abdominal anatomy ranged from 100% to 86%.In the reviewer's worst case analysis the range was 61% to 32%. Only for reader #2 did the percentage fall below 50%. In contrast, in the intent to treat analysis, the percentage of images with improved delineation of pathology, the range was 48% to 13%, and if the investigators were excluded, 27% to 13%. 42,440-3B thus provides stronger evidence for improved delineation of abdominal anatomy than does 42,440-3A. The probable reason is that a much smaller proportion of the scans required worst case ascribed data because of exclusion This study does not provide evidence for improved delineation of pathology. However, comparing the first and last lines of table 10 there appears to be no advantage of SonoRx over placebo in providing improved delineation of abdominal anatomy*

42,440-7

42,440-7 is a phase 3 supporting study in which SonoRx was compared to water. As in tables 5 and 9, the effect of gas shadowing artifact is reduced to a 3 point scale. The readers were asked to rate images of individual anatomic structures for gas shadowing artifact. The p values are for SonoRx images less obscured than water images for the sponsor's worst case analysis. There were no cases in which water images were less obscured than SonoRx images that were statistically significant. SonoRx images were statistically significantly less obscured than water images for two readers for the stomach, gastric wall and pylorus and for one reader for the duodenum pancreatic tail and pancreatic duct. The question of whether individual anatomical structures are obscured by gas shadowing artifact is relevant to both the claims of "reduces gas shadowing artifact" and of "facilitates visualization of anatomy in the upper abdomen

Table 11 Impact of Gas Shadowing Artifact SonoRx Less Obscured Than. Water 42,440-7					
Area	investigators	Reader #1	Reader #2	Reader #3	Reader #4
Stomach	p = 0.0070	p = 0.0161	NS	NS	NS
Gastric Wall	p = 0.0351	p = 0.0201	NS	NS	p = 0.0266
Pylorus	NS	p = 0.0266	NS	p = 0.0433	
Duodenum	p = 0.0107	NS	NS	NS	NS
Pancreas Head	NS	NS	NS	NS	NS
Pancreas Body	NS	NS	NS	NS	NS
Pancreas Tail	p = 0.0001	NS	NS	NS	NS
Pancreas Duct	p = 0.0490	NS	NS	NS	NS

Safety

The sponsor has provided an integrated summary of safety including an analysis of all of the adverse events from all Phase 1, 2 and 3 clinical trials .A total of 385 subjects received any dose of SonoRx and 138 patients received any dose of the control agent one of the control agents. Included are 24 healthy normal subjects who received both SonoRx and water in a Phase 1 crossover study and 51 patients who received both SonoRx and water in the supporting Phase 3 crossover study. In the Phase 3 pivotal studies the control agent was not water but rather SonoRx without 4 of the ingredients. ingredients

84/385 (17.7%) of the patients who received SonoRx experienced 127 adverse events and 16/138 (11.6%) of the patients who received control agent experienced 20 adverse events. For the SonoRx patients, the system most commonly effected was the digestive system (45 subjects, 11.7%) and digestive complaints included diarrhea (6%), nausea (3%) abdominal pain (2%) and vomiting (2%) In contrast, only 6.5% of subjects who received control agent experienced GI adverse events.

There were 8 serious adverse events reported in 4/385 (1.0 %) SonoRx subjects and 2 adverse in 2/138 (1.4%) of the subjects who received control agent.There were no deaths.

Sponsor's Conclusion:

"The data presented in this document fully support the conclusion in the ISE and the ISS that SonoRx is a safe and efficacious ultrasound contrast agent for use in patients with a wide variety of abdominal pathology. The efficacy results presented herein, demonstrate that SonoRx reduces the impact of gas shadowing as well as providing additional information in post dose images. The safety data from the combined phase 1,2 and 3 studies demonstrate that SonoRx is safe and well tolerated"

***Reviewer's comment**: note that the sponsor's conclusion states that SonoRx "**reduces** the impact of gas shadowing" whereas proposed indication states that SonoRx. "rapidly absorbs and disperses gas in the stomach and the bowel thereby **eliminating** shadowing artifacts"*

Reviewer's Conclusions:
The sponsor's resubmission contains both an "intent to treat" analysis in which "worst case" data is imputed for those subjects who ingested any dose of SonoRx but whose images were not read, and an integrated safety analysis in which all adverse events form all clinical studies were tabulated and analyzed together.

Safety:
Both cellulose and simethicone are not pharmaceutically active, are not absorbed from the bowel and are excreted unchanged in the feces. Cellulose is a component I n over the counter preparations for constipation and simethicone is a component in over the counter flatulence medications. Both are considered to be safe in humans at doses proposed for SonoRx.

17% of patients who received SonoRx experienced adverse events which were mostly mild in severity and short in duration. There was a slight excess of GI complaints (diarrhea, nausea, abdominal pain, vomiting), in the SonoRx group compared to the control agent group (11.7% vs. 6.5%) and this is what might be expected from a bulk agent that is not absorbed but remains in the bowel lumen. There were 1% serious adverse events in the SonoRx Group vs 1.4% in the control agent group and there were no deaths. In conclusion, SonoRx raises no serious safety concerns that would effect approvability.

Efficacy.
There were serious deficiencies in the design and implementation of the Phase 3 pivotal studies. These Deficiencies identified in the NA letter include;

1) There was no adequate and consistent "standard of truth" for the final "true" diagnosis
2) The determination of whether diagnoses "matched" were not made by independent blinded reviewers
3) The evaluations of specificity were based on an insufficient number of subjects
4) The analyses were not did not include data from the entire group of subjects who were randomized to receive SonoRx or the entire group of subjects who actually received SonoRx. (*Reviewer's comment: Data was not available for subjects whose images were not read because: the images were found to be "technically inadequate by either a technical reviewer or by the individual reader, the subject' video images could not be located, the sponsor intentionally performed a "per protocol analysis" only for all outcome variables other than the primary outcome variable).*
5) An integrated safety analysis of all adverse events from all clinical studies was not performed

Conclusions Concerning Specific Claims:

Detection, Delineation or Exclusion of Pathology

In this reviewer's opinion, deficiencies 1, 2 and 3 are fundamental flaws that can not be remedied by reanalysis of existing data. They make it impossible for the data obtained from these studies to support a claim for detection, exclusion or delineation of pathology.

Reduction of Gas Shadowing Artifact

42,440-3A

The data from the worst case intent to treat analysis from study 42,440-3A is contained in table 5. The data for the investigators and for reader #2 show a statistically significant difference with pre dose images more obscured than post dose images, while the data for readers 3 and 4 show a statistically significant differences with post dose images more obscured than post dose images. For reader 1, the difference is not statistically significant. The results of this analysis are contradictory, but the results for readers 3 and 4 might be discounted because of the relatively large number of images that were not read for which worst case data had to be imputed

42,440-3B

The data from the worst case intent to treat analysis from study 42,440-3B is contained in table 9. There is a statistically significant difference in favor of pre dose images more obscured than post dose images for the investigators and readers1, 3 and4. The difference for reader 2 was not statistically significant. This data does support the claim that SonoRx reduces gas shadowing artifact

42,440-7

The data from the worst case intent to treat analysis from study 42,440-7 is contained in table 11. Readers compared the effect of gas shadowing artifact on the visualization of individual anatomic structures for both SonoRx and water. The difference between the number of water images more obscured than SonoRx and SonoRx images more obscured than water, was statistically significant in favor of SonoRx for the Stomach (investigators, reader1), the gastric wall (investigators, reader 1,.reader 4)the pylorus (reader1, reader 3) and the duodenum, pancreatic head and pancreatic tail (investigators only) In all other cases the differences were not statistically significant. There were no cases where a statistically significant difference in favor of water.

Delineation of Anatomy

42,440-3A

The data from study 42,440-3A is contained in table 6 The sponsor did not present a worst case analysis but rather represented the data analysis from the original submission. This reviewer performed a simple worst case analysis without a statistical analysis. In tae reviewer's analysis. the percentage of the total number of patients who ingested SonoRx who had images with improved delineation of anatomy was 49%, 24%, 77%, 43% and 16 % for the investigators and readers 1, 2, 3, and 4 respectively.

42,440-3B

The data from study 42,440-3B is contained in table 6 The sponsor did not present a worst case analysis but rather represented the data analysis from the original submission. This reviewer performed a simple worst case analysis without a statistical analysis. In the reviewer's analysis the percentage of the total number of patients who ingested SonoRx who had images with improved delineation of anatomy was 61%, 59%, 32%, 60% and 55 % for the investigators and readers 1, 2, 3, and 4 respectively.

Final Conclusions

Safety: In this reviewer's opinion there are no major safety issues that would make this submission non-approvable.

Efficacy: :In this reviewer's opinion for the worst case analysis:
The data from study 42,440-3A does not support the claim "decreases gas shadowing artifact"
The data from study 42,440-3B supports the claim "decreases gas shadowing artifact"
The data from study 42,440-7 supports the claim "decreases gas shadowing artifact"

The data from study 42,440-3A supports the claim "improves delineation of anatomy in the upper abdomen"
The data from study 42,440-3B supports the claim "improves delineation of anatomy in the upper abdomen"
The data from study 42,440-7 supports the claim "improves delineation of anatomy in the upper abdomen"

The "worst case" data in support of both claims is weak but this is may be due to poor study design and implementation and the relatively large number of subjects for which "worst case " data had to be imputed, rather than lack of efficacy of the product.

Recommendation:

If the chemistry issues have been satisfactorily resolved, the NDA should be approvable with the limited indication:

"SonoRx is an ultrasound contrast agent that reduces gas shadowing artifact and facilitates the visualization of anatomy in the upper abdomen"

/S/ 7/22/98

I agree with Dr Yaes reasoning + the conclusion he has drawn. If there are no other chemistry or other reviewing disciplines issues SonoRx approval with the suggested limited indication is reasonable

/S/
7/22/98

SEP 30 1997

DEPUTY DIRECTOR'S MEMORANDUM TO THE FILE

NDA: 20-773
Drug: Simethicone coated cellulose
Proposed Trade Name: SonoRx®
Dosage Form: Suspension
Route of Administration: Oral
Strength: 7.5 mg/dl
Proposed Dose: 400 ml (minimum)
Proposed Use: Imaging agent for diagnostic ultrasound
Classification: Standard
Applicant: Bracco Diagnostics Inc.
Date Received: 30 September 1996
Review Completed: 30 September 1997
Related Reviews:

Chemistry: D. Place (9/17/97)
Microbiology: P. Stinvage (1/13/97, 6/23/97)
Pharmacology/Toxicology: N. Sadrieh (7/17/97)
Clinical Pharmacology and Biopharmaceutics: D. Udo (8/05/97)
Clinical: R. Yaes (9/12/97)
Statistics: M. Al-Osh (7/18/97)
Environmental assessment: N. Sanger (11/26/96, 9/11/97)

BACKGROUND:

As stated by Bracco Diagnostics, "SonoRx is an orally administered ultrasound contrast agent that is intended for use in the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen, including the gastrointestinal tract and the retroperitoneum." The applicant asserts that the product "creates an acoustic window by adsorbing and dispersing gas, thereby improving through transmission of the ultrasound beam and providing improved delineation of underlying structures." Thus, as stated by the applicant, SonoRx is intended to limit the "artifacts arising from gas in the stomach and adjacent bowel which prevent visualization of the deeper lying organs of interest."[1] In technical terms, the acoustic impedance mismatch that arises at interfaces of gastrointestinal air with the bowel wall or bowel contents causes most of the ultrasound beam to be reflected or scattered, inhibiting visualization of deeper structures. Adsorption and dispersion of the gastrointestinal gas will therefore decrease this acoustical barrier to the ultrasound waves.

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[1] From volume 1, page 2-11.

SonoRx is formulated as an orange-flavored aqueous suspension. Its active ingredient, according to the applicant, is cellulose coated with 0.25% simethicone.. The cellulose is in a crystalline form (manufactured from wood). According to the applicant, the acoustical properties of SonoRx have been optimized by the use of simethicone-coated cellulose that has a median fiber length of approximately 22 microns.

The two principal starting materials for the manufacture of the drug substance are cellulose powder, NF and simethicone (antifoam A), medical grade. Cellulose is an unbranched polysaccharide with glucose in β-(1,4) linkage. Man lacks the enzyme, cellulase, that hydrolyzes cellulose to the disaccharide cellobiose. Simethicone, a mixture of dimethicones and silicon dioxide, is used medically as an antiflatulant. It is also used as an antifoaming agent prior to gastroscopy (to improve visualization) and prior to radiography of the intestines to decrease gas shadows. According to the applicant, the role of cellulose is to create uniform echogenicity with the bowel lumen, whereas simethicone is intended to reduce the surface tension of the gas bubbles and cause them to coalesce.[2]

The major issues that have been identified in the review of SonoRx fall primarily within the Chemistry, Manufacturing and Controls section and the Clinical/Statistical section of the application. Accordingly, these sections will be summarized in some detail in this review. This review also contains a summary of the overall safety database.

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[2] From volume 16, page 8-25.

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CHEMISTRY, MANUFACTURING AND CONTROLS, AND ESTABLISHMENT EVALUATION REQUEST (EER)

The Drug Product has the following composition:[3]

Component	Amount per ml	Amount per 400 ml*
Simethicone coated cellulose	7.5 mg	g
Xanthan gum, NF	mg	g
Simethicone, USP	mg	mg
Sodium Lauryl Sulfate, NF	mg	mg
Citric Acid, USP	mg	mg
Fructose, USP	mg	g
Orange Oil	mg	mg
FD&C Yellow No. 6	mg	mg
Sodium Benzoate, NF	mg	mg
Purified Water, USP		

* Minimum dose proposed by the applicant

Reviewer's comments: The amount of simethicone in a 400 ml dose is 80 mg, which is similar to doses used clinically for antiflatulence or for the enhancement of visualization during gastroscopy or radiography ("off-label" usage). Hence, this "free" simethicone (as opposed to the simethicone-coated cellulose) in the drug product may contribute significantly to the safety and efficacy of SonoRx.

Outstanding issues with Chemistry and Manufacturing include the following:

1. Significant CGMP deficiencies were noted in the Establishment Inspection Report (EIR) for the manufacturing site of the drug product. The manufacturing site is Westwood Squibb Pharmaceutical; 100 Forest Avenue; Buffalo, NY 14213. The facility was inspected from June 10 - July 7, 1997. As summarized in the Chemistry review and the memorandum in response to the EER from the Division of Manufacturing and Product Quality (DMPQ), deficiencies included manufacturing errors, omissions, and lack of available data. The Office of Compliance has classified the Westwood site as

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[3] Adapted from volume 1, page 2-16.

"Unacceptable" for manufacture of the SonoRx drug product. The FDA Buffalo District Office, DMPQ, and reviewing chemist concur that approval of SonoRx should be withheld until these deficiencies are corrected. The deficiencies include the following:

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[4] Continental White Cap, Spec. No. MC-1600-2S

[5] Continental White Cap, Spec. No. SX-CP-1600-1

2. The reviewing chemist identified additional critical deficiencies that include the following:[6]

Reviewer's comments: The drug product has several major CMC deficiencies, including, but not limited to, problems with the container/closure system inadequate documentation or acquisition of stability data, manufacturing errors, and lubricant or grease in samples of the drug product that have been recently manufactured. Ideally, caps for SonoRx should be acquired that do not have Less optimally (if this is not possible), validated screening and confirmatory tests should be developed that are able to detect pinholes accurately, reproducibly, and with sensitivity. Cap liners with pinholes could then be identified and not used in the packaging of

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[6] See pages 2-3 of the chemistry review for a summary of both the critical and non-critical deficiencies.

SonoRx. Once the problems with manufacturing and with the container/closure system have been resolved, stability testing using validated caps and an appropriate sampling protocol should be performed on at least two batches of the drug product. For a revised application to be considered by the Agency, a minimum of six months of stability testing (both room-temperature and accelerated testing) should be completed prior to the resubmission.

ENVIRONMENTAL ASSESSMENT:

Final Recommendation (9/11/97): FONSI

MICROBIOLOGY

SonoRx is intended for oral administration, and the drug product is not required to be sterile. The product, however, does comply with specifications on microbial limits:

Microbial count:
1. Less than 100 microorganisms/gram
2. Freedom from;
   a. All gram-negative bacilli
   b. Coagulase-positive, gram-positive cocci
3. No fungi (yeast or mold) present.

Issues identified in the microbiology review have been resolved. The drug product appears to have microbial integrity.

PHARMACOLOGY AND TOXICOLOGY

Neither preclinical pharmacokinetic nor pharmacology studies were performed with SonoRx. Pharmacokinetic studies in animals were not performed for the stated reason that the pharmacokinetics of the starting materials for SonoRx (cellulose and simethicone) are published and well established. Pharmacology studies were not performed in animals for the stated reasons that a) cellulose is not digested and is excreted in the feces, and; b) simethicone is physiologically inert and does not appear to be absorbed from the gastrointestinal tract or interfere with the absorption of nutrients. In addition, simethicone is excreted unchanged in the feces after oral administration.

The evaluation of the nonclinical toxicology of SonoRx included the following (all studies were performed in compliance with Good Laboratory Practice [GLP] regulations and used the formulation of SonoRx intended for marketing):

a) Acute toxicity (single dose oral studies in mice and rats [up to 40 ml/kg]);
b) Repeat-dose toxicity (28-day repeat oral dose studies in rats [up to 40 ml/kg/day] and dogs [up to 20 ml/kg/day]);
c) Reproductive toxicology studies (Segment I, II, and III in rats, and Segment II in rabbits);

d) Genotoxicity studies (Salmonella-Escherichia coli/mammalian microsome reverse mutation assay, chromosomal aberration assay in Chinese Hamster Ovary [CHO] cells with and without metabolic activation, the CHO/HGPRT forward mutation assay, and the in vivo mammalian micronucleus assay), and;

e) Studies of the effects of single intraperitoneal injections (mice and rats).

The carcinogenic potential of SonoRx was not evaluated.

The results of these studies were generally unremarkable, with the exception of the studies of the effects of single intraperitoneal injections. As summarized in the Pharmacology Review (pages 30-31), single intraperitoneal (IP) injections caused significant inflammatory responses in the animals:

a. In mice that received single IP injections of SonoRx (10. 20, or 40 ml/kg), increases were noted over time in the incidence of enlarged livers (with pale and/or raised areas with interlobular adhesions), and to a lesser extent in the incidence of enlarged spleens (with raised areas and adhesions in the abdominal cavity). Histopathology showed dose-dependent and treatment-related changes including capsular granulomatous inflammation of the liver, spleen and small intestine. Phagocytosis of a "non-polarizing material" (presumably cellulose) by Kupffer cells was also observed. Therefore a single IP injection of SonoRx as low as 10 ml/kg (approximately half the maximum human dose) caused some degree of inflammation and proliferation of connective tissue (i.e., adhesion) within the peritoneal cavity of the mouse, and this effect persisted for at least 14 days after dosage with SonoRx, and was not shown to be reversible.

b. In rats, the administration of SonoRx at 5, 10, and 20 ml/kg by single IP injection produced capsular granulomatous inflammation of the spleen, liver and kidneys, and an accumulation of non-polarizing amorphous material, presumably cellulose, in the red pulp of the spleen and glomerulus of the kidney. The inflammatory response persisted for 90 days after administration of SonoRx, and was not shown to be reversible. No significant resolution of the inflammatory response was noted up to three months after administration of a single dose of the test agent. The lowest dose (5 ml/kg) at which this effect was seen is one-fourth of the maximum dose evaluated in humans (1000 ml/50 kg = 20 ml/kg).

Reviewer's comments: In conclusion, SonoRx should not be administered to individuals with suspected or potential bowel perforation. It should not be administered to individuals at risk of aspiration. If approved, the package insert should cite the results of the animal studies that found granulomatous inflammation after intraperitoneal administration. See the pharmacology/toxicology review for additional labeling recommendations.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The pharmacokinetic profiles of a single dose of SonoRx (400 ml) and of a comparative test agent[7] were evaluated in two randomized, double-blind studies One study was performed in 10 healthy subjects (Protocol 42,440-6), and the other study was performed in 18 patients (15 evaluable) with impaired bowel motility or impaired bowel mucosa (Protocol 42,440-05):[8]

- Protocol #42,440-6: *A Phase I Safety and Pharmacokinetic Evaluation of SonoRx in Healthy Normal Subjects*

- Protocol #42,440-5: *A Phase I Safety and Pharmacokinetic Evaluation of SonoRx in Subjects with Impaired Bowel Motility or Impaired Bowel Mucosa*

In each study, three subjects were to be randomized to the comparative test agent and the remainder to SonoRx. Five days prior to drug administration (Day 1), each subject was placed on a special, low fiber diet containing a maximum of 10 g of dietary fiber per serving. On the 6th day of the study (Day 1) the subjects received either 400 ml SonoRx or the comparative test agent. At six hours after administration of the test agent, each subject ingested a carmine red fecal marker as an aid to determining when feces containing SonoRx or placebo is eliminated. For pharmacokinetic analysis, serial specimens were obtained of blood (Day -5 to Day +3), urine (Day -5 to +48 hours), and feces (Day -5 to +72 hours). Blood and urine samples were analyzed for silicon (a surrogate marker for simethicone). Fecal samples were analyzed for cellulose.

In the large majority of samples of blood and urine, silicon was not detected, thereby limiting any conclusions that can be drawn from the studies. Furthermore, in some subjects, silicon was detected in blood and urine prior to test-agent administration (SonoRx or the comparative test agent) at levels that were comparable to levels detected after drug administration. As concluded by the biopharmaceutical review, silicon levels were not considered a reliable indicator of absorption of the simethicone component of SonoRx. Furthermore, the individual subject blood and urinary excretion profiles of silicon were not adequate for a pharmacokinetic evaluation of silicon. Evaluation of the fecal samples for cellulose indicated that the cellulose in SonoRx passes through the gastrointestinal tract and is eliminated in the feces. In the majority of

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[7] The comparative test agent was SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.

[8] In Study 42,440-05, The twelve evaluable patients who received SonoRx had gastrointestinal disorders that included Crohn's disease (n=5), chronic constipation (n=2), diabetes (n=1), ulcerative colitis/constipation (n=1),, duodenal ulcer (n=1), ulcerative colitis (n=1), and irritable bowel syndrome (n=1). The three evaluable patients who received placebo had gastrointestinal disorders that included esophagitis/gastritis/diabetes (n=1), diverticulitis (n=1), and peptic ulcer disease/chronic constipation (n=1).

subjects, SonoRx was eliminated within 48 hours, as was indicated by the excretion of the carmine fecal marker.

No studies were performed to evaluate the metabolism or plasma protein binding of SonoRx. Possible food effects, gender differences, drug-drug interactions, or the pharmacokinetics in pediatric patients were not evaluated.

Reviewer's comments; The application is considered approvable from the perspective of the Office of Clinical Pharmacology and Biopharmaceutics. See the clinical pharmacology and biopharmaceutics review for additional labeling recommendations.

CLINICAL AND STATISTICAL REVIEWS

OVERVIEW:

In addition to the two clinical pharmacokinetic studies summarized immediately above, six studies have been performed in the clinical development plan of SonoRx. These included two phase-1 pilot efficacy studies, a phase-2 dose selection study, two phase-3 trials that are considered "pivotal" by the applicant, and a phase-3 supportive study. This overview will focus on the three phase-3 studies, but for completeness listings of all the studies and of any comparative test agents are provided below:

Phase-1

- Protocol #42,440-1: *A Phase I Clinical Investigation of the Safety and Efficacy of SonoRx in Normal Healthy Volunteers*

- Protocol #42,440-4: *A Phase I Clinical Investigation of the Safety and Efficacy of SonoRx versus Water in Normal Volunteers*

Phase-2

- Protocol #42,440-2: *A Phase II Clinical Evaluation of the Safety and Efficacy of SonoRx in Patients Highly Suspected of having Abdominal Pathology*

Phase-3

- Protocol #42,440-3A: *A Phase III Clinical Evaluation of the Safety and Efficacy of SonoRx in Patients Highly Suspected of having Abdominal Pathology.* This study was of a parallel design. Key aspect of the design are discussed in detail below.

- Protocol #42,440-3B: *A Phase III Clinical Evaluation of the Safety and Efficacy of SonoRx in Patients Highly Suspected of having Abdominal Pathology.* This study was of

a parallel design and was conducted under the same protocol as study #42,440-3A. Key aspect of the design are discussed in detail below.

- Protocol #42,440-7: *A Phase III Evaluation of the Safety and Efficacy of SonoRx versus Water in Patients Highly Suspected of having Abdominal Pathology.* This study was of a randomized crossover design, with 1-4 days between the dose of SonoRx and the dose of water. Other aspects of the trial such as dose, drug administration, and imaging were similar to those of Studies #42,440-3A and #44,440-3B.

Two of these phase-3 trials were designated in the submission as adequate and well-controlled studies that demonstrate efficacy (**Studies 42,440-3A and 42,440-3B**). In this review, these studies will hereafter referred to as "**Study 3A**" and "**Study 3B**"). These studies were conducted under an identical protocol. The third phase-3 trial was designated as a supportive study (Study 42,440-7). Detailed descriptions of these studies may be found in the clinical and statistical reviews. Essential features of these trials will be summarized later in this review.

Comparison with other test agents: As summarized in the table below, several comparative test agents were used in clinical trials of SonoRx. The following table summarizes these:

Phase of Development	Protocol #	Comparative test agent
1	42,440-1	SonoRx minus simethicone-coated cellulose
1	42,440-4	Tap water
1	42,440-5	SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.
1	42,440-6	SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.
2	42,440-2	None
3	42,440-3A	SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.
3	42,440-3B	SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.
3	42,440-7	Degassed water, or if not available, tap water that was left undisturbed for at least 30 minutes prior to administration

PRINCIPAL EFFICACY STUDIES:

Description of Studies 3A and 3B:

As stated in the protocols, the objectives of these studies was as follows:

The objective of this study is to evaluate the safety and efficacy of SonoRx as an ultrasound contrast agent in patients highly suspected of having abdominal pathology. Specifically the goals are:

- *To expand the initial safety profile established in Phase I and II.*
- *To determine the efficacy of SonoRx in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in a broad spectrum of patients undergoing abdominal ultrasound.*

These studies were randomized, multicenter, parallel studies in which patients, at least 18 years of age or older, who were highly suspected of having abdominal pathology[9] were randomly allocated to receive either an oral dose of either SonoRx (400 ml within 15 minutes) or of a comparative test agent (400 ml within 15 minutes) in an allocation ratio of 10:3.[10] Administration of the test-agent was double blind and occurred after the patient fasted for at least four hours. Static and video ultrasonic images were obtained of the abdomen, both immediately prior to administration of the test agent and within 10 minutes afterward.[11] Both pre-dose and post-dose images were to be performed by the same sonographer using the same ultrasound unit and imaging parameters (including the transducer). As stated in the protocol, the primary endpoint of the study was *the ability of the post-dose imaging results to provide additional*

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9 All patients were required to have undergone, or be scheduled to undergo, evaluation with a comparative diagnostic modality that included (but was not limited to) computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine imaging, standard abdominal x-ray, endoscopy, laparoscopy, biopsy, and/or surgery.

10 The comparative test agent was SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.

11 For both pre-dose and post-dose images, the patient was to be imaged in the supine, left posterior oblique and right posterior oblique views. If necessary, the patient could also be imaged while erect. The following seventeen anatomic structures were to be imaged: stomach, gastric wall, pylorus, duodenum, liver, gallbladder, common bile duct, pancreatic head, pancreatic body, pancreatic tail, pancreatic duct, left kidney, left renal artery, splenic vein, superior mesenteric artery, abdominal aorta, para-aortic lymph nodes.

information over the pre-dose images.[12] It is important to note that despite the presence of a control arm (i.e., the arm with the comparative test-agent), the primary efficacy comparison is not made with respect to this arm. Rather, the applicant states that the presence of this arm is for purposes of evaluating safety. The primary efficacy evaluation is a comparison of the images obtained after SonoRx administration, with those obtained before SonoRx administration.

Although not explicitly defined as secondary endpoints in the protocol and not ranked for their relative importance, the following information was also sought on the case report forms:

- a description of the nature of the additional information provided by the post-dose images compared to the pre-dose images (i.e., assuming the blinded reader felt that the post-dose images provided additional information over the pre-dose images): possibilities among which the blinded reader could choose included I) improved delineation of abdominal anatomy, ii) improved delineation of pathology, iii) improved confidence in exclusion of pathology, iv) improved evaluation of extent of disease or pathology, and v) other. Each possibility was scored on a binomial (yes/no) scale;

- the ability of the post-dose images, compared to the pre-dose images, to delineate the anatomy and to exclude or detect pathology in each of the seventeen abdominal areas (as scored on a five-point ordinal scale),[13] and;

- the impact of overall gas shadowing on the post-dose images, compared to the pre-dose images (as scored on a five-point ordinal scale).[14]

Sample size calculations required that the 95% confidence intervals be within 10% of the observed percentages of interest (i.e., the rate for which images obtained after SonoRx administration provided additional information over those obtained prior to SonoRx administration). By assuming the real rate is greater than 75%, the applicant concluded that a minimum of 75 patients would be required in the SonoRx arm to result in appropriate confidence

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[12] Mechanistically, for the investigators and the blinded readers this was assessed by their answers to the following question: *Overall did the post-dose images provide additional information over the pre-dose images?* (for the investigators, this was question 13 on the case report form (CRF), for the blinded readers it was question 3). This primary endpoint was evaluated on a binomial scale (yes/no).

[13] The scale used for scoring was a five-point ordinal scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent). See page 73 of the clinical review for greater detail of how these terms were defined.

[14] The scale used for scoring was a five-point ordinal scale (0=completely obscured, 1=markedly obscured, 2=moderately obscured, 3=mildly obscured, 4=not obscured).

intervals.[15] Notably, in the applicant's actual (post-hoc) analysis of the primary endpoint, the applicant assumed the real rate is greater than 1% (rather than 75%).

Images were evaluated in a paired fashion[16] by the unblinded investigator. Images were also evaluated by blinded readers for each study, (but only if they were found to be "technically adequate" by a prior evaluation by another radiologist who acted as a technical reviewer). These blinded readers were unaware of the patients clinical history, clinical findings, or to the identity of the test agent. The blinded readers performed both an "Individual Image Evaluation" and a "Comparison Image Evaluation."[17]

It's important to note, however, that for the sponsor's evaluation of the efficacy endpoints of principal interest (primary and major secondary endpoints listed above), the blinded readings were performed in a **paired** fashion. Specifically, for purposes of evaluating efficacy the post-dose images were evaluated in a paired fashion: with the pre-dose images present, and with a copy of the pre-dose scores present (i.e., post-dose scores were recorded on the same "Comparison Image Evaluation" page of the case report form as the pre-dose scores). As this is an important point, a copy of the Blinded Readers' Case Report Forms is attached as Appendix 1 of this review. If the above comments are not readily understood, perusal of this Case Report Form should make the above comments clear.

Two other major discrepancies occurred in the blinded reading of the images. These were summarized succinctly on pages 5-8 of the statistical review:

- First, the blinded reading was performed twice. Specifically, four blinded readers participated in the blinded readings. Blinded readers #1 and #2 only received only the static ultrasound images. According to the applicant, the results of these readings were not consistent with those of the Phase-2 study. The applicant thus decided to perform an additional blinded reading. Blinded readers #3 and #4 received both the static and the video ultrasound images;

- Second, blinded readers #3 and #4 did not receive all of the images to evaluate. These readers only received images of patients that qualified as being "per protocol." (In addition, as noted above, these readers also only received ultrasound images that had been deemed "technically adequate" by the technical reviewer).

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15 See page 8 of the statistical review for more detail.

16 In a paired reading, both pre-dose and post-dose images are simultaneously available to the reader.

17 The four blinded readers were different for Study 3A and Study 3B. The studies used the same technical reviewer.

RESULTS FROM STUDIES 3A AND 3B:

Disposition of subjects

The table below, adapted from the statistical review, summarizes the disposition of the subjects entered in Studies 3A and 3B. The term "intent-to-treat population" in this table uses the applicant's definition: "patients who received any volume of either SonoRx or the control agent, and had images of acceptable technical quality." Thus, subjects with images of "unacceptable" technical quality were not included in the applicant's intent-to-treat population. As described in more detail on page 9 of the statistical review, the applicant's "intent-to-treat" population also includes imputed "worst-case" values for patients not evaluated by blinded readers 3 and 4 (i.e., Because of an error, these two blinded readers only received images from the per-protocol group of patients). Thus, for these readers, "worst-case" values were imputed for 12 subjects in Study 3A for 4 subjects in Study 3B (whose images had erroneously not been sent to the blinded readers). The FDA statistical analyses also used this definition. A more detailed table (i.e., "Table 2") may be found on page 11 of the FDA statistical review.

Disposition of Subjects in Study 3A and Study 3B

	Study 3A		Study 3B	
	SonoRx	Comparator	SonoRx	Comparator
Patients enrolled	95	24	95	28
Patients dosed	93	24	94	28
"Intent-to-treat" population*				
Blinded Readers 1 and 2	85	24	84	24
Blinded Readers 3 and 4	76	24	85	24
Per-protocol population				
Blinded Readers 1 and 2	73	19	80/78**	22
Blinded Readers 3 and 4	64	17	81	21

* As defined by the applicant (see text)

** Second number for blinded reviewer #2

Principal efficacy results as presented by the applicant:

The applicant used the "intent-to-treat" population only for analysis of the primary endpoint (i.e., "the ability of the post-dose imaging results to provide additional information over the pre-dose images"). All other analyses performed by the applicant used the per-protocol population. A summary of the applicant's analysis of the primary endpoint is summarized in the two tables below.[18] A more detailed analysis may be found on page 15 of the statistical review. The applicant's analyses of the effects of SonoRx on gas-shadowing artifacts may be found on pages 19-22 of this review. The applicant's analyses of several secondary endpoints, including the delineation of anatomy, are included in Appendix 2.[19]

Applicant's Analysis of Primary Efficacy Results
(Ability of the post-dose images to provide additional information over the pre-dose images)
"Intent-to-treat" Population

	Study 3A		Study 3B	
Reader	% of subjects with additional information	95% CI	% of subjects with additional information	95% CI
Investigators	58	(48.0, 68.1)	76	(66.8, 84.2)
Blinded Reader 1	41	(30.7, 51.6)	69	(59.2, 78.9)
Blinded Reader 2	99	(96.5, 100.0)	43	(32.3, 53.4)
Blinded Reader 3	55	(44.1, 66.4)	72	(62.2, 81.3)
Blinded Reader 4	20	(10.8, 28.7)	61	(50.8, 71.5)

[18] Adapted from "Reviewer's Table 3" on page 15 of the statistical review.

[19] Reproduced from Attachments I and II of the statistical review (pages 42-48).

p Values for Applicant's Analysis of Primary Efficacy Results
Testing versus 50% and Testing versus 1%*
(Ability of the post-dose images to provide additional information over the pre-dose images)
"Intent-to-treat" Population

	Study 3A		Study 3B	
Reader	Testing vs 50%	Testing vs. 1%	Testing vs 50%	Testing vs. 1%
Investigators	0.1462	0.0001	0.0001	0.0001
Blinded Reader 1	0.1284	0.0001	0.0006	0.0001
Blinded Reader 2	0.0001	0.0001	0.2299	0.0001
Blinded Reader 3	0.4422	0.0001	0.0001	0.0001
Blinded Reader 4	(0.0001)**	0.0001	0.050	0.0001

* Note that sample size calculations assumed a real rate of 75%.
** Significantly *less* than 50%

Gas Shadowing-Artifacts: The sponsor's per-protocol analyses of the effects of SonoRx on gas shadowing are shown on the next two pages (pages 19 and 20). As can be seen, in Study 3A three of the four blinded readers found significantly less shadowing artifacts on images obtained after SonoRx administration compared to images obtained before SonoRx administration. In Study 3B, all four of the blinded readers found significantly less shadowing artifacts on images obtained after SonoRx administration compared to images obtained before SonoRx administration.

However, the "vehicle" control agent also appears to improve gas shadowing somewhat (see the tables on pages 21 and 22). Note that the number of subjects who received vehicle was less than the number of subjects who received SonoRx.

Other Secondary Endpoints: In The sponsor's per-protocol analyses of the diagnostic performance characteristics of SonoRx (i.e., its "sensitivity" and "specificity") for these protocols may be found on pages 89 and 120 of the medical review. They are also summarized on page 19 of the statistical review. A commentary on these results will be included in the "Assessment" section near the end of this review.

Applicant's Analysis of Effects of SonoRx on Gas-Shadowing Artifact in Study 42,440-3A as Assessed by Blinded Readers in Per-Protocol Analysis[20]								
	Reader 1 (n=73)		Reader 2 (n=73)		Reader 3 (n=64)		Reader 4 (n=64)	
	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)
Completely Obscured	0 (0)	0 (0)	0 (0)	0 (0)	3 (5)	2 (3)	0 (0)	0 (0)
Markedly obscured	7 (10)	4 (6)	1 (1)	0 (0)	15 (23)	15 (23)	3 (5)	3 (5)
Moderately obscured	19 (26)	19 (26)	18 (25)	3 (4)	29 (45)	20 (31)	10 (16)	14 (22)
Mildly Obscured	38 (52)	32 (44)	52 (71)	60 (82)	14 (22)	17 (27)	50 (78)	46 (72)
Not Obscured	9 (12)	18 (25)	2 (3)	10 (14)	3 (5)	10 (16)	1 (2)	1 (2)
p value*	0.0142		<0.0001		0.0008		0.4316	

better ↓

* Statistical significance between pre-dose and pose-dose, based on all ratings, as assessed by the Wilcoxon signed rank test

73 73

[20] Adapted from Table AF; volume 24, page 8-91

Applicant's Analysis of Effects of SonoRx on Gas-Shadowing Artifact in Study 42,440-3B as Assessed by Blinded Readers in Per-Protocol Analysis[21]								
	Reader 1 (n=80)		Reader 2 (n=78)		Reader 3 (n=81)		Reader 4 (n=81)	
	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)
Completely Obscured	0 (0)	0 (0)	9 (11)	4 (5)	9 (11)	2 (2)	0 (0)	0 (0)
Markedly obscured	25 (31)	6 (7)	18 (23)	20 (26)	22 (27)	7 (9)	7 (9)	2 (2)
Moderately obscured	32 (40)	23 (29)	32 (41)	32 (41)	26 (32)	20 (25)	30 (37)	13 (16)
Mildly Obscured	22 (28)	45 (56)	17 (22)	19 (24)	16 (20)	26 (32)	39 (48)	49 (61)
Not Obscured	1 (1)	6 (8)	2 (3)	3 (4)	8 (10)	26 (32)	5 (6)	17 (21)
p value*	<0.0001		0.0260		<0.0001		<0.0001	

* Statistical significance between pre-dose and pose-dose, based on all ratings, as assessed by the Wilcoxon signed rank test

[21] Adapted from Table AG; volume 29, page 8-89

Applicant's Analysis of Effects of "Vehicle"[22] on Gas-Shadowing Artifact in Study 42,440-3A as Assessed by Blinded Readers in Per-Protocol Analysis[23]								
	Reader 1 (n=73)		Reader 2 (n=73)		Reader 3 (n=64)		Reader 4 (n=64)	
	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)
Completely Obscured	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Markedly obscured	0 (0)	0 (0)	0 (0)	0 (0)	3 (18)	3 (18)	0 (0)	0 (0)
Moderately obscured	6 (32)	3 (16)	3 (16)	0 (0)	8 (47)	5 (29)	4 (24)	4 (24)
Mildly Obscured	10 (53)	11 (58)	16 (84)	15 (79)	5 (29)	7 (41)	13 (76)	13 (76)
Not Obscured	3 (16)	5 (26)	0 (0)	4 (21)	1 (6)	2 (12)	0 (0)	0 (0)
p value*	not calculated		not calculated		not calculated		not calculated	

* Statistical significance between pre-dose and pose-dose, based on all ratings, as assessed by the Wilcoxon signed rank test

22 "Vehicle" = SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.

23 Adapted from Tables A.6, B.6, C.6, and D.6; volumes 24 and 25

Applicant's Analysis of Effects of "Vehicle"[24] on Gas-Shadowing Artifact in Study 42,440-3B as Assessed by Blinded Readers in Per-Protocol Analysis[25]								
	Reader 1 (n=80)		Reader 2 (n=78)		Reader 3 (n=81)		Reader 4 (n=81)	
	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)	Pre-dose n (%)	Post-dose n (%)
Completely Obscured	0 (0)	0 (0)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Markedly obscured	5 (23)	2 (9)	5 (23)	5 (23)	8 (38)	2 (10)	4 (19)	1 (5)
Moderately obscured	9 (41)	3(14)	9 (41)	5 (23)	5 (24)	4 (19)	6 (29)	1 (5)
Mildly Obscured	8 (36)	15 (68)	6 (27)	11 (50)	5 (24)	7 (33)	10 (48)	16 (76)
Not Obscured	0 (0)	2 (9)	1 (4.5)	1 (4.5)	3 (14)	8 (38)	1 (5)	3 (14)
p value*	not calculated		not calculated		not calculated		not calculated	

* Statistical significance between pre-dose and pose-dose, based on all ratings, as assessed by the Wilcoxon signed rank test

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24 "Vehicle" = SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate.

25 Adapted from Tables A.6, B.6, C.6, and D.6; volumes 29 and 30

Principal efficacy results as evaluated by the FDA statistician:

The FDA statistician re-analyzed the primary and secondary endpoints using different assumptions and statistical tests. A commentary on these results will be included in the "Assessment" section near the end of this review.

In the analysis of the primary endpoint (i.e., whether the images obtained after SonoRx administration provide more information than those obtained before SonoRx administration), the FDA statistician used the same "intent-to-treat" population as the applicant (making the same assumptions about missing data as the applicant), but tested a different hypothesis:

H_0: the percentage of patients for whom post-dose images provide additional information over the pre-dose images (Ps) is equal to the percentage of patients for whom pre-dose images provide additional information over the post-dose images (Pr). If the null hypothesis was rejected, 95% confidence intervals were calculated around the difference of Ps-Pr. McNemar's test was used to calculate p values. The following two tables summarize the results of this analysis:[26]

FDA Statistician's Analysis of Primary Efficacy Results
(Comparison of Additional Information Provided
for Post-dose over Pre-dose and for Pre-Dose over Post Dose)
"Intent-to-treat" Population

	Study 3A			Study 3B		
Reader	Ps	Pr	95% CI of d=Ps-Pr	Ps	Pr	95% CI of d=Ps-Pr
Investigators	58	6	(41, 62)	71	2	(59, 78)
Blinded Reader 1	35	6	(20, 40)	70	0	(59, 80)
Blinded Reader 2	85	0	(75, 92)	43	10	(23, 44)
Blinded Reader 3	54	20	(24, 46)	72	7	(54, 75)
Blinded Reader 4	20	16	(1, 11)	61	5	(45, 67)

Post > Pre Pre > Post

[26] Adapted from pages 30-32 of the statistical review.

p values for FDA Statistician's Analysis of Primary Efficacy Results
(Comparison of Additional Information Provided
for Post-dose over Pre-dose and for Pre-Dose over Post Dose)
"Intent-to-treat" Population

	Study 3A	Study 3B
Reader	p value Ps=Pr	p value Ps=Pr
Investigators	<0.0001	<0.0001
Blinded Reader 1	<0.0001	<0.0001
Blinded Reader 2	<0.0001	<0.0001
Blinded Reader 3	<0.0007	<0.0001
Blinded Reader 4	0.7011	<0.0001

The FDA statistical analyses of the delineation of anatomy (a secondary endpoint) are reproduced on pages 25 and 26. In this analysis, the question was whether there was an improvement in the categorical score as a result of receiving SonoRx. The analysis was performed only for Blinded Readers 3 and 4. The population analyzed is the same as in the prior so-called "intent-to-treat" analysis of the primary endpoint, with the exception that individuals with missing data were not assigned the "worst-case" but instead were assigned a "neutral case." A simplified scoring system was used: subjects were assigned a score of "1" if the post-dose score was greater than the pre-dose score, "0" if the post-dose score equaled the pre-dose score, and "-1" if the post-dose score was less than the pre-dose score. The magnitude of the gain (i.e., a difference from a score of zero) and its 95% confidence intervals were then computed.[27] A commentary on these results will be included in the "Assessment" section near the end of this review.

[27] See pages 32-33 of the statistical review for a more detailed discussion of the methodology.

Reviewer's Analysis

Analysis of Pre-dose and Post-dose image Scores for Certain Anatomical Areas

(Secondary Endpoint, Pivotal Study 42,440-3A, ITT Population *)

	Blinded Reader # 3				Blinded Reader # 4			
Anatomical Area	Ns/N (Ps) [1]	Nr/N (Pr) [2]	p-value Ps = Pr [3]	d = Ps - Pr [4] (95% C.I.)	Ns/N (Ps)[1]	Nr/N (Pr) [2]	p-value Ps = Pr [3]	d = Ps - Pr [4] (95% C.I.)
Stomach	47/ 76	1/ 76	<0.0001	0.61 (0.49, 0.72)	41 / 76	6/ 76	<0.0001	0.46 (0.35, 0.58)
Gastric Wall	46/ 76	1 / 76	<0.0001	0.59 (0.57, 0.70)	37/ 76	6/ 76	<0.0101	0.41 (0.30, 0.53)
Pylorus	44/ 76	1 / 76	<0.0001	0.57 (0.45, 0.68)	30/ 76	10/ 76	<0.0001	0.26 (0.17, 0.38)
Duodenum	43/ 76	0 / 76	<0.0001	0.57 (0.45, 0.68)	28/ 76	8/ 76	0.0003	0.26 (0.17, 0.38)
Pancreatic Head	11/ 76	2 / 76	0.0066	0.12 (0.06, 0.21)	25/ 76	10/ 76	0.0106	0.20 (0.11, 0.30)
Pancreatic Body	8/ 76	1/ 76	0.0273	0.09 (0.04, 0.18)	16/ 76	9/ 76	0.0883	0.09 (0.04, 0.18)
Pancreatic Tail	28/ 76	2/ 76	<0.0001	0.34 (0.24, 0.46	19/ 76	18/ 76	0.7016	-0.01 (.00, 0.07)
Pancreatic Duct	3/ 76	0/ 76	0.2500	0.04 (0.01, 0.11)	21/ 76	13/ 76	0.9128	0.11 (0.05, 0.20)
S. Mes. Artery	3/ 76	1/ 76	0.5000	0.03 (0.00, 0.09)	18/ 76	15/ 76	0.9153	0.04 (0.01, 0.11)
Para- Lymph Nodes	2/ 76	0/ 76	0.5000	0.03 (0.00, 0.09)	1/ 76	2/ 76	1.000	-0.01 (0.00, -0.07).

* patients with missing data (about 4 patients) assumed to have no improvement (i.e, the pre-dose equal the post-dose score).

[1] Ns is the number of patients for whom post-dose image score is higher than pre-dose image score and N is the total number of patients analyzed, Ps is the corresponding percentage.

[2] Nr is the number of patients for whom pre-dose image is higher than post-dose image score and N is the total number of patients analyzed, Pr is the corresponding percentage

[3] the p-value is for testing the hypothesis in (i) concerning p_{ij}

[4] the improvement score discussed before used for these computations

Reviewer's Analysis

Analysis of Pre-dose and Post-dose image Scores for Certain Anatomical Areas

(Secondary Endpoint, Pivotal Study 42,440-3B, ITT Population *)

	Blinded Reader # 3				Blinded Reader # 4			
Anatomical Area	Ns/N (Ps) [1]	Nr/N (Pr) [2]	p-value Ps = Pr [3]	d = Ps - Pr [4] (95% C.I.)	Ns/N (Ps) [1]	Nr/N (Pr)[2]	p-value Ps = Pr [3]	d = Ps - Pr [4] (95% C.I.)
Stomach	65/ 85	1/ 85	<0.0001	0.75 (0.65, 0.84)	60/ 85	0/ 85	<0.0001	0.71 (0.60, 0.80)
Gastric Wall	62/ 85	1 / 85	<0.0001	0.72 (0.61, 0.81)	65/ 85	1 / 85	<0.0101	0.75 (0.65, 0.84)
Pylorus	51/ 85	2 / 85	<0.0001	0.58 (0.46, 0.68)	54/ 85	0 / 85	<0.0001	0.64 (0.52, 0.74)
Duodenum	45/ 85	1/ 85	<0.0001	0.52 (0.41, 0.63)	42/ 85	0/ 85	<0.0001	0.49 (0.38, 0.60)
Pancreatic Head	44/ 85	1 / 85	<0.0001	0.51 (0.40, 0.62)	16/ 85	0 / 85	<0.0001	0.19 (0.11, 0.29)
Pancreatic Body	37/ 85	1/ 85	<0.0001	0.42 (0.32, 0.54)	11/ 85	0/ 85	0.0010	0.13 (0.07, 0.22)
Pancreatic Tail	43/ 85	0 / 85	<0.0001	0.51 (0.40, 0.62	24/ 85	0 / 85	<0.0001	0.28 (.19, 0.39)
Pancreatic Duct	36/ 85	0/ 85	<0.0001	0.42 (0.32, 0.54)	6/ 85	0/ 85	0.0313	0.07 (0.03, 0.15)
S. Mes. Artery	28/ 85	0 / 85	<0.0001	0.33 (0.23, 0.44)	0/ 85	0 / 85	n/a [3]	0.00 (0.00, 0.04)
Para- Lymph Nodes	28/ 85	1/ 85	<0.0001	0.32 (0.22, 0.43)	1/ 85	0/ 85	1.000	0.01 (0.00, 0.07).

* patients with missing data (about 4 patients) assumed to have no improvement (i.e, the pre-dose equal the post-dose score).

[1] Ns is the number of patients for whom post-dose image score is higher than pre-dose image score and N is the total number of patients analyzed, Ps is the corresponding percentage.

[2] Nr is the number of patients for whom pre-dose image is higher than post-dose image score and N is the total number of patients analyzed, Pr is the corresponding percentage

[3] No discordant to calculate p-values

[3] the p-value is for testing the hypothesis in (i) concerning p_{ij}

[4] the improvement score discussed before used for these computations

EFFICACY RESULTS FROM SUPPORTIVE STUDY #42,440-7:

As indicated above (in the listing of the titles of the phase-3 studies), this was a randomized, crossover study in which the effects of 400 ml of SonoRx and 400 ml of water were compared. Patients were randomly allocated to the sequence in which they received the test agents. Between one and four days were allowed to elapse between the dose of SonoRx and the dose of water. In contrast to Studies 3A and 3B, the primary endpoint was whether images obtained after SonoRx provided more information than images obtained after water. The blinded readers obtained both static and video images of the subjects. However, only the images obtained *after* administration of each test agent (SonoRx or water) were reviewed. Other aspects of the trial such as dose, drug administration, and imaging were similar to those of the phase-3 Studies 3A and 3B.

To assess the effects of SonoRx and water on gas shadowing, the blinded readers were instructed to place the films of each test agent side by side, and compare the films for the impact of gas shadowing artifacts. Seven anatomical areas were evaluated: stomach, gastric wall, pylorus, duodenum, pancreatic head, pancreatic body, and pancreatic tail. Each anatomical area was graded on a four-point ordinal scale (0=completely obscured, 1=markedly obscured, 2=moderately obscured, 3=mildly obscured).[28]

Primary endpoint: The principal results of this study may be found on pages 21-25 of the statistical review. In brief, the planned analysis of the primary endpoint (i.e., whether post-dose images provide more information than pre-dose images) using the binomial test demonstrated the results were not statistically significant (i.e., the effects of SonoRx cannot be distinguished from those of water). The applicant, however, also performed several post-hoc analyses of statistical significance, which included the "equal split test" and the "sign test." Although in some cases the results became statistically significant after application of these post-hoc tests, the tests have substantial limitations. These limitations are clearly articulated in the statistical review on pages 21-25.

Other secondary endpoints: The sponsor's detailed per-protocol analyses of the effects of SonoRx on gas shadowing may be found on in Appendix 3.[29] These are also summarized on page 61 of the medical review. In short, gas shadowing was significantly ($p \leq 0.05$) less for SonoRx than water for the following anatomical areas:

Blinded Reader 1: Stomach (p=0.0011), gastric wall (p=0.0044), pylorus (p=0.0231), duodenum (p=0.0342), pancreatic body (p=0.0367), and pancreatic tail (p=0.0437);

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[28] From Item #15 of the Blinded Readers' case report form; volume 35, page 8-63.

[29] From volume 16, pages 8-305 to 8-312.

Blinded Reader 2:	When the effects of SonoRx and water were compared, the effects were not significantly different for any anatomic area;
Blinded Reader 3:	Stomach (p=0.0065), gastric wall (p=0.0352), pylorus (p=0.009), duodenum (0.0067), pancreatic head (0.0396), and pancreatic body (p=0.0372);
Blinded Reader 4:	Stomach (p=0.0049), gastric wall (p=0.0040), duodenum (p=0.0134), pancreatic tail (0.0307).

The sponsor's per-protocol analyses of the delineation of anatomy may be found on pages 58-60 of the medical review. For many of the comparisons of the effects of SonoRx and water, a statistically significant difference was not found. In addition, the sponsor's per-protocol analyses of the diagnostic performance characteristics of SonoRx (i.e., its "sensitivity" and "specificity") may be found on page 25 of the statistical review and on pages 62 and 63 of the medical review. A commentary on these results will be included in the "Assessment" section near the end of this review.

Reviewer's comments: In brief, this study generally failed to show that SonoRx provides more diagnostic information upon ultrasound imaging when its effects are compared to those of equal volumes of water. Similarly, in Study 3A and Study 3B, the effects of SonoRx on the primary endpoint were not shown to be significantly different than the comparative agent (the comparative agent was SonoRx minus the following ingredients: simethicone-coated cellulose, xanthan gum, simethicone, and sodium lauryl sulfate).[30] The study, however, provides some supportive evidence that SonoRx decreases gas-shadowing artifacts in specific anatomical areas in the upper abdomen. Nonetheless, the effects of SonoRx alone on this parameter were not assessed in this study, because images obtained after SonoRx administration were not compared to images obtained before SonoRx administration.

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30 See page 36 of the statistical review.

SAFETY

The applicant did not provide an overall summary of the safety experience of all subjects exposed to SonoRx. Rather, the Integrated Summary of Safety discussed the safety by describing the experience of subjects who received SonoRx in each phase of clinical development (i.e., phases 1, 2, and 3). This review constitutes the Division's integrated review of safety.

Extent of exposure:

A total of 386 subjects were exposed to SonoRx in the eight clinical trials that were conducted with the agent. One subject in study #42,440-2 received only 10 ml of SonoRx (instead of the assigned amount of 400 ml) and then withdrew consent. This subject was excluded from the safety analysis, bringing the number of subjects to 385 that were included in the overall evaluation of safety. Of these 385 subjects, 36 were healthy volunteers enrolled in three phase-1 studies (#42,440-1 [n=5], #42,440-4 [n=24], and #42,440-6 [n=7]), 12 were patients with impaired bowel function enrolled in a phase-1 pharmacokinetic study (#42,440-5), and the remaining 337 were patients highly suspected of having abdominal pathology who were enrolled in the phase-2 and phase-3 studies (#42,440-2 [n=99], #42,440-3A [n=93], #42,440-3B [n=94], and #42,440-7 [n=51]). Stated differently, in the phase-2 dose-ranging study 99 subjects were exposed to SonoRx. In the two principal phase-3 studies, 187 subjects were exposed to SonoRx; and in the supportive phase-3 study, 51 subjects were exposed to SonoRx.

Doses of SonoRx evaluated in the development program ranged from 200 ml to 1000 ml, with the majority of subjects assigned to receive 400 ml. The table below summarizes the doses of SonoRx received for the 337 subjects who received the drug in the phase-2 and phase-3 studies:

Subjects (n) who Received Doses of SonoRx in Phase-2 and Phase-3 Trials[31]

Dose SonoRx (ml)	0-200	201-400	401-600	601-800	801-1000	>1000	Total
Patients (n)	29	253	24	19	10	3	337

Demographics: An overall demographic profile of the subjects exposed to SonoRx was not provided. However, considering the 337 subjects who were exposed to SonoRx in the phase-2 and phase-3 studies, the mean age was 55-56 years (range: 21-86 years). Of these subjects, 149 (44%) were women and 188 (66%) were men. Considering race and ethnicity, 265 (79%) were classified as white and 72 (21%) as non-white. The 337 subjects had a mean weight of 75-76 kg (range: 27-160 kg) and a mean height of 170 cm (range: 130-203 cm). The mean body surface area was 1.86 m^2 (range: 1.19-2.80 m^2).

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[31] Modified from Table H, volume 17, page 8-23

Deaths or Withdrawals because of Adverse Events: No subject died during the clinical trials, and no subject withdrew because of an adverse event.

Serious Adverse Events: Eight serious adverse events were reported for four subjects who received SonoRx. With the exception of one of these adverse events (chest pain of unknown relationship to study agent), all were classified by the investigator as "not related" to administration of the study agent. These serious adverse events are summarized in the table below:

Serious Adverse Events in Phase II and III Studies
All Subjects who Received SonoRx
(Studies #42,440-2, #42,440-3A, #42,440-3B, and #42,440-7)[32]

Patient (Study)	Age (sex)	Adverse Event Costart Term	Drug Relation	Clinically Significant	Outcome
608 (-2)	63 (M)	Epistaxis	Not related	Yes	Recovered
316 (-3B)	42 (M)	Pain Chest	Unknown	Yes	Recovered
1305 (-3B)	59 (F)	Pain Chest	Not related	Yes	Recovered
		Pneumothorax	Not related	Yes	Recovered
713 (-7)	38 (F)	Pain Pelvic	Not related	Yes	Recovered
		Pain Abdo	Not related	Yes	Present-being treated
		Hematoma	Not related	Yes	Present-no treatment
		Pain Back	Not related	Yes	Present-being treated

Narratives for these subjects follow:[33]

Patient 608 (63 year-old male, 200 ml SonoRx [Study 42,440-2]) experienced one serious adverse event (epistaxis which started at 10 hours post-administration and lasted for 8 days. The patient was admitted to the hospital and the epistaxis resolved after surgical intervention. The Investigator reported this event as not related to SonoRx and noted that it was a pre-existing condition. The Sponsor agrees that the adverse event was unrelated to SonoRx as it was a pre-existing condition.

Patient 316 (42 year-old male, 400 ml SonoRx [Study 42,440-3B]) experienced one serious adverse event (chest pressure; COSTART term: chest pain) which started approximately 9 hours

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32 Adapted from Table S, volume 17, page 8-38

33 Taken verbatim from volume 17, pages 8-39 to 8-40

post-dose and lasted 4 hours. Prior to this adverse event, he experienced nausea, vomiting and cold feeling approximately 3, 5, and 6.5 hours post-dose (COSTART terms: nausea, vomiting, and chills, respectively). The patient's chest pain was relieved by nitroglycerin (2.5 mg x 2). The Investigator considered all events to be clinical (sic) significant however all events resolved without residual effects. The Investigator noted that the nausea and vomiting were probably related to post-dose medication (Creon 10 mg, Prozac 20 mg, and Dilaudid 2 mg). The Investigator also noted that the "patient started three new medications after contrast prior to the adverse events. Medications were taken on an empty stomach. These medications can cause vomiting, nausea and chest pain." The chills and chest pressure were considered by the Investigator to be of unknown relationship to study agent, however, he noted that he thought these events were "a consequence of vomiting and reflux or secondary to pancreatitis." The Sponsor agrees with this assessment and further noted that the patient had a history of myocardial infarction relating to alcohol and cigarette abuse.

Patient 1305 (59 year-old female, 400 ml SonoRx [Study 42,440-3B]) experienced two serious adverse events (chest pain, pneumothorax), both of which were considered to be not related to SonoRx and clinically significant. The Investigator noted that this patient "developed pneumothorax as a complication of central line placement requiring chest tube for approximately 24 hours." The event resolved; the chest tube was removed. The Sponsor agrees with this assessment.

Patient 713 (38 year-old female, 395 ml SonoRx second administration [Study 42,440-7]), who had a preliminary diagnosis of pancreatitis, experienced four serious adverse events: pelvic pain, abdominal pain, hematoma (retroperitoneal), and back pain. It was noted that these adverse events were considered serious because they prolonged the patient's hospitalization. All of these events were considered by the Investigator to be clinically significant; however, none was considered to be related to SonoRx. Approximately 18 hours after receiving water in the first period (approximately 4 hours prior to SonoRx administration), the patient reported pain in the right groin (COSTART term: pelvic pain) of moderate intensity. At that time, the Investigator considered the event to be non-serious. The pelvic pain persisted into the second period of the study at which time it was considered to be a serious adverse event. The patient also reported abdominal pain and back pain, both of which were considered to be serious adverse events, at approximately 6 and 21 hours after the administration of SonoRx. computed tomography 24 hours post-SonoRx revealed an abnormal right psoas muscle representative of hematoma or infection (retroperitoneal bleed). The patient received IV antibiotics (vancomycin, gentamicin, and Flagyl) for the infection started on the day of the SonoRx administration. The Sponsor agrees with these assessments and notes that the data supports (sic) a pre-existing condition.

Reviewer's comments: None of these serious adverse events are clearly related to SonoRx administration.

Adverse Events and Other Safety Evaluations

An integrated summary of adverse events was not provided. Instead, adverse events were summarized by the phase of the investigation (i.e., phase 1, 2, or 3) and by the characteristics of the study population (e.g., healthy volunteers vs. patients highly suspected of having abdominal pathology).

PHASE-1 STUDIES

Healthy Volunteers: Overall, 36 healthy volunteers were exposed to SonoRx in three phase-1 studies (#42,440-1 [n=5], #42,440-4 [n=24], and #42,440-6 [n=7]). Three of these 36 subjects (8.3%) experienced a total of three adverse events. These included diarrhea (n=2, 5.6%) and pharyngitis (n=1, 2.8%). these adverse events are also summarized on page 19 of the clinical review.

By comparison, 30 healthy volunteers received a control agent or water. Two of these subjects who ingested the control agent (SonoRx without the simethicone-coated cellulose) experienced a total of four adverse events. These included dyspepsia (n=1, 3.3%), dizziness (n=2, 6.7%), and epididymitis (n=1, 3.3%). These events are also summarized on page 10 of the clinical review.

No clinically significant findings were noted for other safety parameters which included physical examinations, electrocardiograms, vital signs, and clinical laboratory evaluations (i.e., hematology, serum chemistry, and urinalysis).

Reviewer's comments: These studies are consistent with the conclusion that the most common adverse events after SonoRx administration are related to the gastrointestinal system.

Subjects with impaired bowel motility or impaired bowel mucosa (study #42,440-5): For a description of this study, see the section on Clinical Pharmacology and Biopharmaceutics. Twelve subjects with impaired bowel function received SonoRx (400 ml) in this study, and three subjects received the control agent (SonoRx without simethicone-coated cellulose, simethicone, xanthan gum, or sodium lauryl sulfate).

Seven of the 12 patients exposed to SonoRx (58%) experienced 16 adverse events. Five of these 16 adverse events involved the digestive system. The adverse events included headache (n=2, 16.7%), rhinitis (n=2, 16.7%), asthenia (n=1, 8.3%). back pain (n=1, 8.3%), neck pain (n=1, 8.3%), dyspepsia (n=1, 8.3%), eructation (n=1, 8.3%), flatulence (n=1, 8.3%), nausea (n=1, 8.3%), vomiting (n=1, 8.3%), somnolence (n=1, 8.3%), sinusitis (n=1, 8.3%), eye disorder (n=1, 8.3%), and ear pain (n=1, 8.3%).

By comparison, 1 of the three subjects who received the control agent experienced an adverse event. This one patient experienced dyspepsia (n=1, 33.3%).

No clinically significant findings were noted for other safety parameters which included physical examinations, electrocardiograms, vital signs, and clinical laboratory evaluations (i.e., hematology, serum chemistry, and urinalysis).

Reviewer's comments: These studies are consistent with the conclusion that the most common adverse events after SonoRx administration are related to the gastrointestinal system. Although the numbers are small, the results suggest that individuals with impaired bowel motility or impaired bowel mucosa may be more likely than others to experience adverse events after SonoRx administration.

PHASE-2 AND PHASE-3 STUDIES:

In the four Phase-2 and phase-3 studies (#42,440-2 [n=99], #42,440-3A [n=93], #42,440-3B [n=94], and #42,440-7 [n=51]), 58 of the 337 subjects (17%) who received SonoRx experienced 88 adverse events, whereas 13 of the 105 subjects (12%) who received the control agent or water experienced 15 adverse events. The most commonly reported adverse events (with a prevalence greater than 0.5%) among subjects who were exposed to SonoRx were diarrhea (5.6%), nausea (3.6%), abdominal pain (2.4%), vomiting (2.1%), headache (1.5%), eructation (0.9%), back pain (0.9%), chest pain (0.9%), chills (0.6%), and rash (0.,6%). Other adverse events that occurred with a frequency of 0.3% included fever, malaise, pain, pelvic pain, bradycardia, hematoma, hypertension, pallor, palpitations, tachycardia, dry mouth, dyspepsia, dysphagia, flatulence, melena, ecchymosis, lymphadenopathy, hypoglycemia hypertonia, epistaxis, pharyngitis, pneumothorax, ear pain, and dysuria.

See Table Q in Appendix 4 for a summary of adverse events in the phase-2 and phase-3 studies. See Table T and Table U in Appendix 4 for a summary of adverse events in only the phase-2 dose-ranging study (also see pages 31-35 of the clinical review). Finally, see Table V in Appendix 4 for a summary of all adverse events in the three Phase-3 studies (A discussion of the adverse events noted in the phase-3 trials may be found in the clinical review: for Study 3A see pages 78-83; for Study 3B see pages 108-114; for study 42,440-7 see pages 51-56).

Reviewer's comments: These studies are consistent with the conclusion that the most common adverse events after SonoRx administration are related to the gastrointestinal system. Adverse events were not clearly related to dose in the phase-2 dose-ranging study (#42,440-2).

Subgroup analyses: The adverse events noted in the phase-3 trials were evaluated for possible relationships to sex (male/female), age (18-40 years, 41-65 years, >65 years), race (white, non-white), body surface area (<1.6 m^2, 1.6-2.0 m^2, >2.0 m^2) and preliminary diagnosis (pancreatic mass vs. non-pancreatic mass, and gastrointestinal pathology vs. non-gastrointestinal pathology). Specific adverse events were noted by the applicant in the summary tables only if they exhibited

"doubling"[34] in one group as compared to another. This convention has also been followed in this review.

The overall rate of adverse events was higher for women than men (women: 31 adverse events among 109 women = 28.4%; men: 16 adverse events among 129 men = 12.4%). When specific adverse events were evaluated, women were more likely than men to experience diarrhea (9.2% vs. 3.9%), nausea (6.4% vs. 2.3%), abdominal pain (4.6% vs. 1.6%), and headache (3.7% vs. 0.8%) after SonoRx administration.

The overall rate of adverse events was similar for white subjects and non-white subjects. However, when specific adverse events were evaluated, white subjects were more likely than non-white subjects to experience diarrhea or headache after SonoRx administration. In contrast, non-white subjects were more likely to experience vomiting than white subjects.

The overall rate of adverse events for subjects of different ages did not follow a consistent trend (i.e., the rate of adverse events neither consistently increased nor decreased with age). However, when specific adverse events were evaluated, younger subjects were more likely than older subjects to experience nausea after SonoRx administration.

The overall rate of adverse events increased as body size decreased (body surface area [BSA] > 2.0 m^2: 9 adverse events among 69 subjects = 13.0%; BSA 1.6-2.0 m^2: 27 adverse events among 131 subjects = 20.6%; BSA <1.6 m^2: 11 adverse events among 38 subjects = 28.9%). Compared to subjects with a large body surface area, smaller subjects were more likely to experience abdominal pain (0%, 3.1%, and 7.9%, respectively, for the three categories of BSA) and vomiting (0%, 2.3%, and 7.9%, respectively).

The overall rate of adverse events was higher for subjects with a pancreatic mass (13 adverse events among 46 subjects = 28.3%) than for subjects without a mass (34 adverse events among 192 subjects = 17.7%). When specific adverse events were evaluated, subjects with a pancreatic mass were more likely than subjects without a pancreatic mass to experience chills (4.3% vs. 0%), nausea (8.7% vs. 3.1%), and vomiting (4.3% vs. 2.1%).

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[34] To be presented, specific adverse events had to meet the applicant's "doubling" criteria: a) if the lowest incidence was at least 2%, then the incidence of the adverse event in the highest category had to be at least twice the lowest incidence; b) if the lowest incidence was less than 2%, then the incidence of the adverse event in the highest category had to be at least 2% greater than the incidence of the lowest incidence *and* the number of reports in the highest incidence category had to be more than one, and; c) in cases when more than two categories were created (e.g., age, body size), the incidence of the adverse event was to show a consistent increasing or decreasing trend with respect to that categories.

The overall rate of adverse events was similar for patients with a preliminary diagnosis of gastrointestinal pathology than those without such a diagnosis. No specific adverse events exhibited "doubling" in their incidence between diagnostic subgroups (i.e., gastrointestinal pathology versus non-gastrointestinal pathology).

Reviewer's comments on subgroup analyses: The analyses performed by the applicant were limited to the phase-3 studies. These analyses should be repeated using the entire database of subjects who were exposed to SonoRx. Nonetheless, the most notable findings in these analyses are that adverse events are more common in women than in men, in smaller individuals than larger individuals, and in subjects with a pancreatic mass than in those without a mass. These may be related to one another (e.g., women tend to be of smaller body sizes than men, patients with a pancreatic mass may have lost weight and may therefore be of smaller body size than those without a pancreatic mass). However, the specific adverse events that were identified as "doubling" were not always identical across groups (sex, body size, and presence or absence of a pancreatic mass), suggesting that this might not be the explanation. Because SonoRx is administered as a fairly large volume, it's quite plausible that smaller individuals tolerate SonoRx less well than larger individuals.

ASPIRATION:

The applicant reviewed the adverse events in the clinical trials for SonoRx and concluded that no subject aspirated SonoRx during clinical trials. The applicant also performed a literature search of the toxicology of inhalation/aspiration of simethicone and cellulose. No published data were found for simethicone. The only literature available for cellulose was for the safety of airborne cellulose by the American Conference of Governmental and Industrial Hygienists (ACGIH). The applicant states that "if an aspiration were to occur during administration of SonoRx, aspirated the (sic) volume would probably be at most 3 to 5 ml, containing 22.5 to 37.5 mg of cellulose. Since the cellulose is in an aqueous suspension, it would likely only reach the tracheal region of the lung and would be cleared by ciliary action."[35]

Reviewer's Comments: The applicant's argument is not persuasive because data are not available for simethicone or simethicone-coated cellulose. The ACGIH data are of uncertain relevance because the cellulose in SonoRx is in a suspension and is not airborne. The applicant's assumptions made about the volume of aspiration and clearance by ciliary mechanisms are conservative and have not been validated. As summarized above in the Pharmacology/Toxicology section, intraperitoneal injections of simethicone-coated cellulose in mice and rats produced an inflammatory response of abdominal organs, particularly of the liver and spleen, which was not shown to be reversible. Accordingly, individuals at risk for possible aspiration should not be administered SonoRx.

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[35] From volume 17, page 8-334

OVERALL ASSESSMENT

The application is approvable from the perspectives of microbiology, pharmacology and toxicology, and biopharmaceutics and clinical pharmacology. The final recommendation from the environmental assessment was a designation of "FONSI." From the clinical/statistical perspective the application is approvable, but for an indication that is more narrow than that sought by the applicant (see below). However, the application does not provide adequate pre-clinical or clinical evidence that the activity of the SonoRx is solely due to simethicone-coated cellulose.

As summarized earlier, significant deficiencies remain in the Chemistry, Manufacturing, and Controls portion of the application (see pages 4-7). Until these are resolved, the application is non-approvable. These issues will not be discussed further.

ACTIVITY OF SONORX:

The application does not provide adequate pre-clinical or clinical evidence that the activity of the SonoRx is solely due to simethicone-coated cellulose. Although phantom studies suggest that the acoustic properties of simethicone-coated cellulose are optimized with a median fiber lengths of approximately 22 microns, the simethicone-coated cellulose may not be the only, or even the most important, factor that determines the activity of the drug product. The unbound simethicone and the vehicle of the product (water) may also contribute substantially to the drug's activity.

a) In order to claim that simethicone-coated cellulose is the "active ingredient" of SonoRx, additional preclinical and clinical studies should be conducted to establish the relative contributions of the simethicone-coated cellulose, free simethicone, and water to the overall clinical activity of the drug.

b) References in the package insert that state or imply that simethicone-coated cellulose is the "active ingredient" should be modified to indicate that the unbound simethicone and the vehicle of the product (water) may also contribute substantially to the drug's activity.

CLINICAL AND STATISTICAL OVERVIEW:

Considering the Clinical/Statistical portions of the application, the applicant seeks the following indication:

The application did not provide sufficient evidence that SonoRx is approvable for this broad indication. However, it is approvable for a more narrow indication. From the clinical/statistical perspective, the application supports the use of SonoRx to decrease gas

shadowing during ultrasound examination of the upper abdomen.[36] The application marginally demonstrates SonoRx's efficacy in delineating abdominal anatomy.

The data do not sufficiently demonstrate that the SonoRx-enhanced images facilitate the detection of pathology, exclusion of pathology, or the evaluation of the extent of pathology. Not only were the data less consistent for these claims, but these claims are also problematic because the two principal phase-3 efficacy trials (Studies #42,440-3A and #42,440-3B) did not require that investigators rigorously verify the type, presence, location, or extent of pathology. The studies lacked adequate standards of truth by which the interpretation of pathologic findings could be validated, and the studies did not ensure that these standards were applied consistently. Likewise, for the impact of SonoRx on patient management or therapy, the assessments made by the blinded readers lacked confirmation that the decisions were clinically appropriate.

EFFICACY:

Gas Shadowing: As summarized on pages 18-22, the two principal phase-3 clinical trials (Studies #42,440-3A and #42,440-3B) provided evidence that SonoRx helps to decrease gas artifacts. An item on the Blinded Readers' case report form asked for an evaluation of the degree to which gas obscures the image before SonoRx administration compared to after SonoRx administration (Item #2 of the Blinded Reader Comparison Image Evaluation). In a per-protocol analysis in Study 3A, three of the four blinded readers found significantly less shadowing artifacts on images obtained after SonoRx administration compared to images obtained before SonoRx administration. In a per-protocol analysis in Study 3B, all four of the blinded readers found significantly less shadowing artifacts on images obtained after SonoRx administration compared to images obtained before SonoRx administration. Unfortunately, these assessments by the blinded readers were not performed in an optimal way. Optimally, in order to decrease potential bias, the images should have been assessed in a non-paired, randomized reading. The scores assigned to the post-dose and pre-dose images could then be compared to evaluate drug effect. In this circumstance, however, the images were evaluated in a paired fashion. These analyses should be repeated using a true intent-to-treat population (e.g., a "worst-case" analysis). Stated differently, the intent-to-treat analyses should not exclude subjects with "technically inadequate" images. Finally, it should be noted that the "vehicle" control in these studies also appears to decrease gas-shadowing.

As summarized on pages 27-28, the supportive phase-3 study (Study #42,440-7) also provided evidence that SonoRx decreases gas shadowing in specific anatomic areas of the upper abdomen. To assess the effects of SonoRx and water on gas shadowing, the blinded readers were instructed to place the films of each test agent side by side, and compare the films for the impact of gas shadowing artifacts (Item #15 of the Image Evaluation). Seven anatomical areas were evaluated:

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[36] This specific language is not necessarily intended to be the final wording that appears in the package insert, assuming the chemistry issues are resolved.

stomach, gastric wall, pylorus, duodenum, pancreatic head, pancreatic body, and pancreatic tail. In a per-protocol analysis, three of the four blinded readers found that gas shadowing was significantly ($p \leq 0.05$) less for SonoRx than water for at least four of these anatomic areas. However, one of the blinded readers did not find that gas shadowing was significantly less for SonoRx than water for any of the anatomic areas. As above, these analyses should be repeated using a true intent-to-treat population (e.g., a "worst-case" analysis). It also should be noted that the effects of SonoRx alone on gas shadowing were not assessed in this study, because images obtained after SonoRx administration were not compared to images obtained before SonoRx administration (i.e., images obtained after administration of SonoRx were compared only to those images obtained after administration of water). Finally, as above, the SonoRx images and water images optimally should have been assessed in a non-paired, randomized reading. However, if the blinded readers were truly unable to distinguish between water and SonoRx on the images, this is less of an issue for this supportive study than it is for Studies 3A and 3B.

Delineation of anatomy: One of the stated goals in the two principal phase-3 clinical trials (Studies #42,440-3A and #42,440-3B) was "to determine the efficacy of SonoRx in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in a broad spectrum of patients undergoing abdominal ultrasound." This goal actually has three subcomponents: a) to delineate abdominal anatomy; b) to detect pathology, and; c) to exclude pathology.

Four items on the blinded readers' case report form were related to these subgoals:

a) Item 2 on the Individual Image Evaluation requested the following: "Based on the ultrasound images, list any patient diagnoses/pathology identified and estimate your confidence in each." This item was intended to capture data about the ability of SonoRx to detect pathology.

   Reviewer's comments: The responses to this item are of limited use from the perspective of establishing efficacy of SonoRx. Diagnoses were not routinely confirmed in a consistent or stringent way, and the type, presence, location, or extent of pathology were not reliably validated. In the absence of consistent and exacting validation of diagnoses and pathology, the estimates of confidence cannot be confirmed. Hence, the responses to this item are not considered further in this review.

b) Item 3 on the Individual Image Evaluation asked the question: "Based on the ultrasound images, what is your confidence that the patient has no other diagnoses/pathological process?" This item captures data about the ability of SonoRx to exclude pathology.

   Reviewer's comments: As immediately above, the responses to this item are of limited use from the perspective of establishing efficacy of SonoRx. Diagnoses were not routinely confirmed in a consistent or stringent way, and pathology (i.e., its type, presence, location, or extent) was not reliably validated. In the absence of consistent and

exacting validation of diagnoses and pathology, the estimates of confidence cannot be confirmed. Hence, the responses to this item are not considered further in this review.

c) Item 1 on the Comparison Image Evaluation requested the following information on seventeen abdominal structures: "Complete the following table on delineation of abdominal anatomy comparing the post-dose images to the pre-dose images using the following scale:

0 = none	Non-diagnostic image; cannot identify area of interest, cannot exclude nor detect pathology
1 = poor	Marginally diagnostic image; limited delineation; low confidence level in excluding or detecting pathology
2 = fair	Diagnostic image; fair delineation, fair level of confidence in excluding or detecting pathology
3 = good	Diagnostic image; good delineation, good level of confidence in excluding or detecting pathology
4 = excellent	Diagnostic image; excellent delineation, high level of confidence in excluding or detecting pathology

Reviewer's comments: Although the preface to this item implies that its primary purpose is to capture data on the delineation of anatomy, this item is ambiguous because of the wording describing each score. That wording implies that the purpose is broader and is not only to capture data about the ability of SonoRx to delineate anatomy, but also to assess whether SonoRx can detect and exclude pathology. The relative contribution of each of these (i.e., anatomical delineation, detection of pathology, and exclusion of pathology) to the blinded readers' scores for a particular anatomic area cannot be determined, because each response was captured in a single score. In effect, the scores given by the blinded readers were composite scores. Thus, this item provides only inadequate confounded data about anatomical delineation. Finally, as above, the type, presence, location, or extent of pathology were not reliably validated. Hence, the responses to this item are not considered further in this review.

d) Item 3a on the blinded readers' Comparison Image Evaluation was to be answered only if the reader responded "yes" to the question: "Overall did the post-dose images provide additional information over the pre-dose images?"

"If "yes" what was the nature of the additional information provided? a) improved delineation of abdominal anatomy; b) improved delineation of pathology; c) improved confidence in exclusion of pathology; d) improved evaluation of extent of disease or pathology, or; e) other (specify)."

Reviewer's comments: This item captures data about the ability of SonoRx to delineate anatomy, to detect pathology, and to exclude pathology. The relative contribution of each of these to the blinded readers' scores for a particular anatomic area can be determined from this item, because each question was asked separately. Hence, these data provide the strongest direct support that SonoRx has use in delineation of anatomy. However, an affirmative response to this item does not provide an assessment of the range of improvement, the type of technical features on the image (e.g., sharpness of margins, contour, homogeneity) that were improved, or the location of the improved features. Thus, responses to this item are potentially useful, but incomplete.

Results from clinical trials: In the sponsor's analysis of data from the per protocol populations of Studies #42,440-3A and #42,4430-3B the blinded readers were asked to specify the nature of the additional information that was provided after SonoRx administration. The blinded readers most consistently specified "improved delineation of abdominal anatomy" (See Appendix 2). These analyses should be repeated using an intent-to treat population. Other possibilities (e.g., improved confidence in exclusion of pathology, improved delineation of pathology, or improved evaluation of extent of disease or pathology) were specified less consistently. In any case, as noted above, these items are problematic because the two trials did not require that investigators rigorously verify the type, presence, location, or extent of pathology.

Technical quality of images: The technical quality of the images was not used as an endpoint in any of the phase-3 studies. In Studies 3A and 3B, images were evaluated for their technical quality by a "technical reviewer" and by the blinded readers (see page 15 of this review for details). The technical quality of the images was then used to decide whether further blinded evaluation of the images should occur. For example, in Studies 3A and 3B, the first item of the blinded readers' Individual Image Evaluation asked whether the images were of "acceptable" technical quality for evaluation. If not, the readers were instructed to state why and to proceed no further. In the supportive phase-3 study (#42,440-7), the blinded readers were given similar instruction when first evaluating the SonoRx or water images.

However, since SonoRx appears to decrease gas-shadows, then it may be possible to use the comparative technical qualities of the pre-SonoRx and post-SonoRx images as an efficacy endpoint. That is, more post-SonoRx images may be of acceptable technical quality than pre-SonoRx images. Conversely, if the situation is reversed (i.e., more pre-SonoRx images are of acceptable technical quality than post-SonoRx images), then this information should be included in the product labeling as well. Thus, for all images that were judged to be technically inadequate and were not forwarded to the blinded readers, the applicant should provide the number that were technically inadequate before SonoRx administration, after SonoRx administration, or both. Similar information should be provided for the images that the blinded readers found to be technically inadequate.

Performance Characteristics (sensitivity and specificity): The two principal phase-3 trials clinical trials (Studies #42,440-3A and #42,440-3B) were not adequately designed to evaluate the diagnostic performance characteristics (e.g., "sensitivity" and "specificity") of SonoRx:

a) The studies lacked adequate "standards of truth" by which the interpretation of the SonoRx images could be validated, and the studies did not ensure that these standards were applied consistently. Instead, for purposes of analysis, the diagnostic assessments performed by the investigator were utilized de facto as standards of truth. Hence, across subjects, neither the adequacy of the standard of truth for a particular condition nor its consistent application was ensured.

   Adequate standards of truth are essential because they permit scientifically valid and accurate characterization of the performance characteristics of a diagnostic product. Also, in the clinical settings in which SonoRx is likely to be used, adequate standards of truth are critical because of the potentially life-altering implications of both correct (i.e., accurate) and incorrect (i.e., inaccurate) diagnostic information.

b) The procedures used to identify diagnostic "matches" or "mismatches" were not adequate to minimize the effects of possible biases on the values obtained for sensitivity and specificity. Specifically, independent blinded reviewers were not used to determine whether the diagnoses made from the SonoRx images and the diagnoses made from other modalities constituted a match or not.

c) The values of sensitivity obtained by the blinded image evaluations in Studies #42,440-3A and #42,440-3B were not consistent between the two studies. In the comparison of the images obtained after SonoRx administration to those obtained before SonoRx administration, the values for sensitivity showed a slight increase in Study 42,440-3B, whereas they either decreased or did not change in Study 42,440-3A.

d) The values of specificity obtained by the blinded image evaluation in Studies #42,440-3A and #42,440-3B were based on the evaluation of images from an insufficient number of subjects (i.e., 9 patients and 10 patients, respectively) to draw reliable conclusions.

e) The analyses used to determine sensitivity and specificity were incomplete. Sensitivity and specificity were calculated only with data from the "per protocol" subset of subjects, and not with data from other sets of interest (e.g., intent-to-treat analysis) and not with data imputed to test whether the calculated values are robust (e.g., "worst-case" analysis).

Increased information: The primary endpoint in the two principal phase-3 clinical trials (Studies #42,440-3A and #42,440-3B) was "the ability of the post-dose imaging results to provide additional information over the pre-dose images." The question in the blinded readers' and investigators' case report forms that directly corresponded to this primary endpoint was

"Overall did the post-dose images provide additional information over the pre-dose images?"[37] The responses to this question did not yield adequate data upon which to base an indication for SonoRx.

a) The question asks the reader of the image to provide a subjective opinion rather than to provide the objective data upon which his or her answer to the question is based.

b) The question was not formulated adequately. A negative answer is ambiguous and may mean that the two images provided similar information or may mean that the pre-dose image provided more information than the post-dose image.

c) The blinded readings were not performed in a way that minimizes potential bias. Therefore, the possible impact of bias on the results cannot be assessed. Specifically, images were evaluated in a paired fashion, in which both the pre-dose and the post-dose images were simultaneously available to the readers, and the readers were asked to make a comparative judgement. An unpaired reading in which the informational content of each image was evaluated on an absolute (i.e., non-comparative) scale was not performed.

d) Analyses were compared to response rates that were defined post-hoc (i.e., response rates of 1% and 50%), instead of the rate anticipated in the protocol (i.e., a response rate of 75%).

When the 50% response rate was used in the "intent-to-treat" analysis for the blinded readers, the results were neither statistically significant consistently across readers within a study nor were they statistically significant consistently across the two studies. In Study #42,440-3A, for example, the results for Blinded Readers #1 and #3 were not statistically significant (p=0.1284 and 0.4422, respectively). In Study #42,440-3B, the results for Blinded Reader #2 was not statistically significant (p=0.2299), and the result for Blinded Reader #4 was marginally significant (p=0.05).

Although the results of the "intent-to-treat" analysis of the blinded image evaluation, compared to a 1% response rate, were statistically significant, the clinical significance of superiority over this low rate is questionable.

e) The analyses used to evaluate the response rate for the primary endpoint were incomplete. A substantial number of subjects were excluded from these analyses, including the so-called "intent-to-treat" analyses. For example, of the 95 subjects enrolled in the SonoRx arm of Studies #42,440-3A and #42,440-3B, a total of 93 subjects actually received

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[37] This was item 3 of the Comparison Image Evaluation for the blinded readers, and item 13 of the Image Evaluation for the investigators.

SonoRx in Study #42,440-3A and 94 subjects actually received SonoRx in Study #42,440-3B. Yet the "intent-to-treat" population in Study #42,440-3A included only 85 subjects for Blinded Readers 1 and 2, and 76 subjects for Blinded Readers 3 and 4. Similarly, in Study #42,440-3B, the "intent-to-treat" analysis included only 84 subjects for Blinded Readers 1 and 2, and 85 subjects for Blinded Readers 3 and 4.

Similarly, although some analyses of the response rate were performed with "worst-case" data imputed to test whether the results were robust, these analyses never included data from either the entire group of subjects randomized to receive SonoRx or from the entire group of subjects that actually received SonoRx.

f) The results of the "intent-to-treat" analysis of the blinded image evaluation were highly variable. The lower limits of the confidence interval ranged from about 11% to 97% in Study 42,440-3A (Blinded Readers #4 and #2, respectively) and from about 32% to 62% in Study 42,440-3B (Blinded Readers #2 and #3, respectively). Similarly, in the per-protocol analysis, values of the Kappa statistic for agreement between the blinded readers were not far from what is expected under chance agreement alone.

SAFETY:

As noted in the safety review (see pages 29-35), a true integrated summary of adverse events was not provided. Instead, adverse events were summarized by the phase of the investigation (i.e., phase 1, 2, or 3) and by the characteristics of the study population (e.g., healthy volunteers vs. patients highly suspected of having abdominal pathology). Exposure, by dose, across the entire database was difficult to assess from the application.

Most of the adverse events associated with the use of SonoRx involved the gastrointestinal tract (e.g., diarrhea, nausea, vomiting, abdominal pain). Based on the preclinical studies that found granulomatous inflammation of abdominal organs after intraperitoneal administration, the risks of intraperitoneal leakage or aspiration of the product may be substantial. The potential risks of SonoRx after intraperitoneal leakage (e.g., in patients with bowel perforation) or after aspiration should be emphasized in the labeling. Otherwise, the pre-clinical and clinical safety profiles appear to be unremarkable.

In the safety subgroup analyses of the phase-3 clinical trials, the most notable findings were that adverse events are more common in women than in men, in smaller individuals than larger individuals, and in subjects with a pancreatic mass than in those without a mass (see page 35). These may be related to one another (e.g., women tend to be of smaller body sizes than men). Because SonoRx is administered as a fairly large volume, it's quite plausible that smaller individuals tolerate SonoRx less well than larger individuals. These analyses should be repeated using the entire database of subjects who were exposed to SonoRx.

The following items should be included in any resubmission of this application:

a) Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. In addition to the format used in the applicant's initial submission, this should include analyses and composite summary tables of all subjects who received SonoRx in any clinical trial (i.e., pooled data for the entire NDA database, not just for the phase 2 & 3 trials). These tables should reflect all demographic data and adverse events by subgroups, including by body size and dose ingested.

b). Retabulation of the exposure data by dose of SonoRx received. As above, this should include analyses and composite summary tables of all subjects who received SonoRx in any clinical trial (i.e., pooled data for the entire NDA database, not just for the phase 2 & 3 trials).

c) Full characterization of adverse events related to the gastrointestinal system (e.g., diarrhea, nausea, vomiting) with regards to their duration, onset, severity, seriousness, etc. An analysis should be provided of these adverse events by the dose ingested and by body size.

d) Characterization of any episodes of aspiration or possible aspiration. An analysis should be provided of these adverse events by the dose ingested and by body size.

ADDITIONAL STUDIES:

Other studies that the applicant may wish to discuss with the Division include clinical studies in the pediatric population and preclinical aspiration studies.

LABELING AND MARKETING:

In anticipation that this product may eventually be approved, the pharmacologist and biopharmaceutics reviewer made specific labeling recommendations in their reviews. The clinical and statistical reviewer have also made revisions to the draft labeling submitted by the applicant. Additional labeling comments follow:

a) Unless evidence is presented to the contrary, references in the package insert that state or imply that simethicone-coated cellulose is the "active ingredient" should be modified to indicate that the unbound simethicone and the vehicle of the product (water and other ingredients) may also contribute substantially to the drug's activity.

b) Given the information currently available, the Indication will likely primarily focus on the effects of SonoRx on gas-shadowing. It must be limited to the upper abdomen.

c) The focus of the Clinical Trials section of the labeling should be on the effects of SonoRx on gas-shadowing artifacts in the upper abdomen (e.g., data from the two principal phase-3 studies and the supportive phase-3 study). Limited information about anatomical delineation may potentially be included in the labeling (e.g., the response to Item #3a on the Comparison Image Evaluation from studies 42,440-3A and 42,440-3B). If appropriate, the effects of SonoRx (either favorable or unfavorable) on the technical adequacy of images may be included in the labeling. Efficacy comparisons to water and "vehicle" may potentially be included in this section of the labeling.

d) The description of the clinical trials should include the imaging parameters that were used in the phase-3 studies.

e) Safety (e.g., Contraindications, Warnings, Precautions, and Adverse Reactions sections of the labeling): Preclinical studies revealed chronic inflammatory responses in the abdomen when the drug was administered by intraperitoneal injection. Clinically, a similar response is likely if the drug leaks into the peritoneum. Accordingly, SonoRx should not be administered to individuals with gastrointestinal perforation, suspected gastrointestinal perforation, or those at risk for bowel perforation. It should not be administered to patients with possible gastrointestinal obstruction or to those with a high probability of requiring abdominal surgery within eight hours of administration. These categories of patients were also excluded in the phase-3 trials.

These preclinical findings also indicate that if aspirated, patients may develop a chronic inflammatory response in the lungs. Thus, SonoRx should not be administered to individuals at risk for aspiration (e.g., impaired mental status, impaired gag reflux, trouble swallowing). Pediatric patients may be at higher risk because of their relatively small body size and because of the large volume of SonoRx that must be ingested, particularly because nausea and vomiting are among the most common adverse events.

Patients with precarious fluid status (e.g., congestive heart failure) may not tolerate the 400 ml of SonoRx. For example, in a 40 kg pediatric patient, 400 ml of SonoRx is 10 ml/kg (i.e., the equivalent of a fluid bolus).

Patients with impaired bowel motility or impaired bowel mucosa may be more likely to experience adverse events after administration of SonoRx (see pages 32-33).

Because of the volume of SonoRx that is ingested, comparisons of the safety profile of SonoRx with control agents tend to underemphasize the toxicity of SonoRx. That is, adverse effects from SonoRx are likely related in part to the volume ingested. Thus, if comparisons of adverse events from SonoRx are made to equal volume of water, the adverse event profile may be misleading. Similar issues arise with comparisons of SonoRx to "vehicle," because the vehicle contains other ingredients that may cause adverse events.

f) Dosage and Administration: As in the phase-3 trials, patients should fast four hours prior to the ultrasound examination. The container of SonoRx should be shaken vigorously to resuspend any material that has settled at the bottom. The container should sit for at least two minutes prior to opening. Once opened, the product should be ingested immediately. If resuspension is necessary once the bottle is opened and the vacuum seal is broken, the drug should be stirred or swirled to resuspend. It should not be reshaken. Patients should drink the 400 ml of SonoRx in 15 minutes.

g) Image acquisition: Health professionals should be advised that patients should be imaged in each of the following positions: supine, left posterior oblique, right posterior oblique, and erect (if necessary). Both static and video images should be obtained. Images should be obtained both prior to SonoRx administration as well as afterwards.

h) Marketing: The applicant should be specifically advised that the following is not an appropriate claim: "in clinical practice SonoRx-enhanced ultrasound could potentially obviate the need for many additional studies now required because of residual uncertainty following unenhanced ultrasound." Appropriate data were not submitted in the application to support this statement.

RECOMMENDED ACTION

The application is not approvable. Critical deficiencies were identified in the Chemistry, Manufacturing and Controls portion of the application. Substantial deficiencies were also identified in the Clinical/Statistical portion of the application, and the application is not approvable for the indication sought by the sponsor. However, from the Clinical/Statistical perspective, the application is approvable for decreasing the effects of "gas shadowing" during ultrasound examination of the upper abdomen. The non-approval letter summarizes the deficiencies noted in the Chemistry and Clinical/Statistical sections of the application.

/S/ 9/30/97

Victor F.C. Raczkowski, M.D., M.S.

cc: NDA 20-773
Division file NDA 20-773
HFD-160 CSO (R. Jordan)
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