

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20773

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-773 SUPPL # _____

Trade Name SUNN RX Generic Name SEMETHICONE COATED CELLULOSE SUSPENSION
Applicant Name BRACCO HFD- 1160

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES / / NO / /

b) Is it an effectiveness supplement?
YES / / NO / /

If yes, what type? (SE1, SE2, etc.) N/A

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")
YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / / NO / /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO /

If yes, explain: _____

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO /

If yes, explain: _____

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 42,440-3A

Investigation #2, Study # 42,440-3B

Investigation #3, Study # 42,440-7

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

- c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # 42,440-3A -200"

Investigation #__, Study # 42,440-3B

Investigation #__, Study # 42,440-7

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND YES / / NO / Explain: _____

Investigation #2

IND # YES / / NO / Explain: _____

IND # INVESTIGATION #3 YES (substantial support)

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ ! NO / / Explain _____

Investigation #2

YES / / Explain ! NO / / Explain

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

Signature
Title: _____

18 SEPT 98
Date

Signature of Division Director

18 SEPT 98
Date

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 20773 **Trade Name:** SONORX (SIMETHICONE COATED CELLULOSE SUS
Supplement Number: **Generic Name:** SIMETHICONE COATED CELLULOSE SUSPENSION
Supplement Type: **Dosage Form:** LIQ
Regulatory Action: 10-29-98 **Proposed Indication:** An orally administered gas shadowing reduction agent that is indicated to enhance the delineation of upper abdominal anatomy in conjunction with ultrasound imaging.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

What are the INTENDED Pediatric Age Groups for this submission?

 Neonates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Status -
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:

Phase 4 commitment by sponsor dated October 28, 1998 , to file a labeling supplement containing the pediatric dosing recommendations W/I 12 months.

A Phase 4 commitment to file a labeling supplement containing the pediatric dosing recommendations within 12 months. This will be based on oral volume information contained in medical references and literature.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RUBYNELL JORDAN

 Signature **Date** 10-30-98

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-773 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5
SE6

HFD-1160 Trade and generic names/dosage form: SEMIFRACONS LIMITED CELLULOSE SUSPENSION Action: AP AE NA

Applicant BRACCO Therapeutic Class 35

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application _____ (For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

JSI _____ 8-29-97 _____
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-773
HFD-1160 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFICATION

STATE OF NEW JERSEY)
)
 COUNTY OF MIDDLESEX) ss:


I, Frank M. Didato, hereby certify that I represent BRACCO DIAGNOSTICS INC. ("Bracco") in the capacity of Senior Director, Regulatory Affairs, and, as such, am authorized to certify and represent by on behalf of Bracco the following:

a. that I personally am not now, nor never have been, debarred under Section 306(a) or 306(b) of the Federal, Food, Drug and Cosmetic Act (i.e., 21 USC § 306 et seq.) for any conduct relating to the development or approval of any drug application submitted to the U.S. Food and Drug Administration.

b. that Bracco has made a diligent effort to ensure that no person who is or has been debarred has either provided or will provide any services in connection with this application.

c. that all employees of Bracco connected with this application have already and/or will be required to certify to Bracco that he or she has not been debarred.

d. that all persons not employed by Bracco who provide services in connection with this application will be required to certify to Bracco in connection with this application that no person employed by them has been debarred and that no debarred person will in the future be employed by them.


 Signature

9/25/96
 Date

Sworn to before me on

September 25, 1996


NOTARY PUBLIC

(Seal)

POST APPROVAL INFORMATION FOR NDA 20-773

- a. NDA 20-773 (SonoRx)
- b. SonoRx (simethicone-coated cellulose)
- c. Bracco Diagnostics Inc.
- d. This new drug application provides for the use of SonoRx (simethicone coated cellulose suspension) an orally administered gas shadowing reduction agent that is indicated to enhance the delineation of upper abdominal anatomy in conjunction with ultrasound imaging.
- e. For oral administration only
SonoRx (simethicone coated cellulose suspension) is an orange-flavored, aqueous suspension, which consists of 22-micron cellulose fibers coated with 0.25% simethicone that is intended for oral administration.
- f. Rx only
- g. 3S

**APPEARS THIS WAY
ON ORIGINAL**

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY
AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: November 18, 1996

To: Mei-Ling Chen, Ph.D., Director
John Hunt, Deputy Director/Acting Team Leader

From: David G. Udo, Ph.D., Reviewer

Subject: Pre-45 Day Filing Meeting for NDA 20-773
Simethicone Coated Cellulose Suspension (SonoRx®)

Date of Meeting: 11/20/96. Time: 11:00 AM
Place of Meeting: Dr. Mei-ling Chen's Office

SYNOPSIS/BACKGROUND

NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) was submitted by the sponsor on September 30, 1996. SonoRx® is proposed as an oral ultrasound agent for use in the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen, including the upper gastrointestinal tract and the retroperitoneum. Under the Dosage and Administration section of the package insert, the sponsor states that "the minimum recommended dose of SonoRx® is 400 mL".

The active ingredient of SonoRx® is simethicone coated cellulose (7.5 mg/mL [0.25% simethicone]). SonoRx® also contains free simethicone (0.2 mg/mL). Therefore, the recommended minimum dose of SonoRx® (400 mL) contains 7.5 mg of simethicone (7.5 mg as cellulose coating and 80 mg of free simethicone). Maalox Plus®, an approved drug product contains 25 mg of simethicone per tablet. The recommended dose is 1-4 tablets to be taken 4 times daily. Thus, one dose of 4 tablets of Maalox Plus® contains 100 mg of simethicone which is higher than the amount of simethicone in a single dose of SonoRx®. Cellulose, an unbranched polymer of glucose residues linked in β -1,4 linkages, is a plant polysaccharide which serves a structural rather than a nutritional role. It cannot be absorbed by passive diffusion due to its molecular size. Literature information indicates that mammals do not have cellulases, the enzyme that digests cellulose. Therefore, significant digestion of the cellulose component of SonoRx® in patients receiving the diagnostic agent is not expected.

In this NDA the sponsor submits two studies evaluating the safety and potential bioavailability of SonoRx® in patients with impaired bowel motility and/or impaired bowel mucosa (Protocol 42,440-5) and in normal volunteers (Protocol 42,440-06). These studies were recommended by the Division of Biopharmaceutics (currently Office of Clinical Pharmacology and Biopharmaceutics) in the review of IND - dated July 13, 1994. In the submitted studies, blood and urine samples were analyzed for silicon (the surrogate marker for simethicone) by Fecal elimination of the cellulose component of SonoRx® was also assessed in both studies. Summaries of the studies and the analytical methods are herewith attached (Attachment I).

Adequate information has been provided to permit a substantive review of the NDA.

RECOMMENDATION

NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) submitted by the sponsor on September 30, 1996 has been reviewed for filing by the Office of Clinical Pharmacology and Biopharmaceutics. From a pharmacokinetic perspective, the sponsor has provided sufficient information to permit a substantive review of the NDA. Therefore, the NDA is considered acceptable for filing.

cc: NDA 20-773, HFD-160, HFD-870 (M. Chen, Hunt and Udo), HFD-870 (Drug, Chron, Reviewer [Clarence Bott, PKLN Room 13B-31]).

Jordan

MEMORANDUM OF TELECON

DATE: November 6, 1997, 4:15 PM

APPLICATION NUMBER: NDA 20-773; SonoRx

BETWEEN:

Name: Madhu Anant, Norman La France, T. Mingot, K. Bense, and R. Muse
Phone: (609) 514-2262
Representing: Bracco Diagnostics Inc.

AND

Name: Patricia Love, Victor Raczkowski, A. Eric Jones, Robert Yaes,
Mohammed Al Osh, Michael Welch and Rubynell Jordan
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clinical/Statistical Issues for SonoRx from September 30, 1997 NA Letter

The teleconference began with HFD-160 requesting that Bracco clarify their indication,

The two parties then proceeded to discuss the meaning of delineation.

BRACCO: SonoRx eliminates gas shadowing artifact, enhancing the physics of the modality.

HFD-160: The division indicated that Bracco needs to submit more information on the intent to treat (ITT) analysis and the assessment of the technically inadequate images.

BRACCO: The sponsor acknowledged this.

HFD-160: Please note paragraph 4 on page 5. The responses to Item #1 of the Blinded Reader Comparison Image Evaluation are confounded. Both parties discussed exactly what was meant by confounding in this instance.

BRACCO: The sponsor explained their 3 tier indication.

HFD-160: The division indicated that they were comfortable with the first tier only and that the other 2 were not as clear.

HFD-160: The division explained how they viewed the product. The product removes the interference to allow ultrasound to go further and do its job, but SonoRx does not go any further itself to do anything more.

BRACCO: The sponsor noted that both parties agreed on the gas shadowing aspect of the indication. We eliminate gas shadowing and allow things to be better seen but we want to say more. What do we do to include this other information?

HFD-160: The division explained that it depends on what additional information the sponsor wants to include in the indication. This set of data remains with a composite endpoint and this could pose a problem.

BRACCO: How can we get around this confounding issue?

HFD-160: The division explained that Bracco would need to show how they acquired a nonconfounding answer. The sponsor should look at technical features (e.g., sharpness of margins, contour, echogenicity, homogeneity).

BRACCO: Should we replace the word "delineation with "facilitation of visualization"?

HFD-160: The best advice the division can give is that you need to uncouple the composite endpoints to be separate components.

BRACCO: Look at table X volume 16 section 8 page 137.

HFD-160: The division agreed to look at the table mentioned but if you want more precision we need more information on delineation.

BRACCO: The sponsor offered to do additional teleconferences and/or face to face meetings to further explain the data.

Next, there was some discussion about a portion of the last paragraph on page 7 of the NA letter.

HFD-160: We need the worst case analysis of the Intent To Treat. We also need to determine just how important certain words are to the sponsor, i.e., delineation, anatomy, etc. The division noted that this paragraph would be discussed later in more detail. We will discuss how many patients were missing, how many were technically inadequate and why; these patients need to be included in the data. We will discuss this further via a teleconference with your statisticians at a later date. Please provide a safety update for us, even if there is no additional data, no additional patients, just write it as such. Please answer questions 1-8 on page 9 completely in your resubmission.

BRACCO: The sponsor agreed to answer all clinical/statistical issues in the NA letter completely and requested that the division expedite the review of their resubmission once received.

HFD-160: The division agreed to review the resubmission in as timely a manner as possible. They also reminded the sponsor that not just the clinical/statistical issues need to be completely addressed prior to resubmission, but all items noted in the NA letter need to be adequately addressed(a complete response) upon resubmission of the NDA for approval.

The meeting concluded at this time with both parties agreeing to deal with other issues in the NA letter via a subsequent teleconference.

JS

Rubynell Jordan
Project Manager, HFD-160

cc: Original NDA 20-773
HFD-160/Div. File
HFD-160/Rubynell Jordan,

TELECON

Sevan

**Division of Medical Imaging and Radiopharmaceutical Drug Products
Industry CMC Meeting for SonoRx (NDA 20-773) NA Letter(9/30/97)**

SPONSOR: Bracco Diagnostics Inc.

PRODUCT: NDA 20-773
SonoRx® (simethicone coated cellulose suspension)

DATE: November 12, 1997
2:30 PM, Conference Room 18B-37

FDA ATTENDEES:

Victor Raczkowski, MD, Deputy Director, HFD-160
Eldon Leutzinger, Ph.D., Chemistry Team Leader, HFD-160
David Place, P.h.D., Chemistry Reviewer, HFD-160
John Gibbs, Director, Office of New Drug Chemistry
Rubynell Jordan, MPA, Regulatory Project Manager, HFD-160

BRACCO DIAGNOSTICS ATTENDEES:

Larry Callan, Director, Regulatory Operations
Melanie Benson, Senior Manager, Regulatory Operations
R. Muse
A. Betournay
Madhu Anant, Senior Manager, Regulatory Affairs

PURPOSE: For HFD-160 and Bracco to discuss the CMC deficiencies listed in the September 30, 1997, NA letter.

DISCUSSION: After brief introduction of all participants the meeting began. The meeting proceeded by going through and discussing each deficiency in the order listed in the NA letter. Please note that first the deficiencies will be listed in italics. Following the deficiency any discussion of the issues will be noted.

A. Drug Substance Deficiencies

1. *The application lacks adequate information about the reference standard that serves as the benchmark for the regulatory specifications. Its identification, method of preparation, and details of its analytic examination are not described. Please provide the following:*
 - a. *The identity of the drug substance reference standard and its lot number.*
 - b. *The full details of any manufacture and the specifications that are used if an extra purification step or an alternate synthesis is implemented for the reference standard.*

2. *The application lacks sufficient information to validate Method III, entitled: "Determination of Particle Size of Simethicone Coated Cellulose", submitted in the Amendment dated 8/26/97. Please submit data on the calibration of the instrument and the ruggedness of the assay.*
3. *The application lacks sufficient information about the container/closure systems used to control humidity in the drug substance. Please submit the schematics for the drums and lids used.*

DISCUSSION: HFD-160 thoroughly discussed why having a reference standard was essential and what is acceptable for ruggedness. The sponsor confirmed that they understood. The sponsor indicated that the schematics for the drums and lids used were not available at the time the NDA was initially filed. However, the sponsor confirmed that the schematics are available now and will be submitted in the resubmission. Next the Drug Product deficiencies were discussed.

B. DRUG PRODUCT DEFICIENCIES:

1. *The methodology lacks*

Please develop specifications and in process controls for impurities. Also please submit data on the identification, and the amount of the lubricant and grease that was inadvertently introduced into the final drug product.

DISCUSSION: Bracco explained that an investigation was done reference the lubricant in the product and the related batch. Bracco reports that the operator was over zealous in using lubricant to oil the pistons used to make the batches and thus the excess lubricant ended up in the product. Bracco has since modified its product specifications for checking for foreign particles in their lab reports. HFD-160 advised that Bracco needs to submit the SOP that shows how this was done and also include the report that shows how the lubricant got into the batch. Bracco agreed to provide the data in the resubmission.

2. *The application lacks a description and validation on the method for container evaluation.*

Please provide a full description of all applicable methods, documentation, data, and their validation. This should include all methods for evaluation of the caps and cap liners, both for qualification and acceptance as well as for performance during stability studies.

DISCUSSION: The sponsor indicated that the container evaluation for caps and cap liners was sent to the previous chemistry reviewer unofficially and that they would submit the same data officially to the NDA with the resubmission. The failures were from inbound and not due to specifications. HFD-160 asked if Bracco had all caps without pinholes now or if they still had some of both (with and without pinholes). Bracco confirmed that they were not using any caps with pinholes and that they changed their screening methods to use _____ Bracco explained that they were using _____ HFD-160 inquired as to whether Bracco was doing their own _____ test or if it was being done by someone else. Bracco indicated that the test was being done by both and that they were doing their own test for statistical significance. HFD-160 asked that they submit all of the data officially with the resubmission.

3. *The application lacks sufficient information to qualify the stability and integrity of the drug product. The submitted stability data tables contain an unusually high percentage of uncollected data. They also contain a substantial number of failures due to container/closure issues. The sum of these deficiencies renders the data presented to date incomplete. (We note you have recognized these problems and are beginning to resolve them).*

a. Please provide a full description of all applicable methods, documentation, data, and validation.

b. Please include all methods for evaluation of the caps and cap liners, both for qualification and acceptance as well as for performance during stability studies.

DISCUSSION: Bracco explained that the data is time driven and the computer that tells you when to pull the samples was set improperly by the previous supervisor. HFD-160 asked Bracco what had they done to correct the misses. Bracco stated that the new supervisor has mastered the process of setting the computer and also has manual reminders in place. HFD-160 requested that the sponsor submit the protocol that outlines this to the NDA as soon as possible to insure that everything is okay for the batches Bracco has up on stability now. Bracco agreed to submit this data to the NDA right away. Bracco also agreed to resubmit the data being requested in 3b. above, as they felt it had already been submitted during the submission of the original NDA.

4. *The drug product samples for this application lack specific stability sampling procedures. Please provide the following information about the sampling plan:*

- a. *A specific accounting of the sampling plan used in the drug product for each batch produced.*
- b. *The number of individual drug product samples, per container size, that have been analyzed in each test.*
- c. *A description of the sampling plan(s) for production batches, specifying the number of samples to be evaluated.*

DISCUSSION: HFD-160 explained that 4a. refers to the stability batches, 4b. explains what should be in the plan, and 4c. denotes the specific information needed for the NDA.

5. *The CMC methods lack descriptions of the methodology used for determining the appearance, pH, and viscosity of the drug product specifications. Please fully describe these methods and their validation.*

DISCUSSION: Both parties agreed that a specific description of methods and validation needs to be developed for lab workers to follow explicitly. Bracco asked if this means explaining the appearance. HFD-160 suggested that this be handled in the form of a SOP to show appearance, color, consistency, etc.

6. *The application lacks validation information for Method II: "Determination of Particle Size of Simethicone Coated Cellulose". Please provide the following:*

- a. *The full validation of the methods for Method II, and a discussion of the calibration of the instrument and the ruggedness of the assay.*
- b. *If this procedure will be performed in laboratories that are not those used for Method III in the drug substance section of the NDA, then independent validation of the method in the corresponding laboratories should be submitted.*

7. *The final total batch mass calculations lack sufficient mathematical consistency to determine the appropriateness of the final mass and volume.*
- a. *Please confirm that the specific gravity of the product is exactly or submit a value to a greater degree of precision.*
 - b. *Please submit appropriate adjustments to the manufacturing instructions and the batch record that take the specific gravity into account in the calculation to arrive at the correct final adjusted mass (through q.s. of water) of the batch. For example, if the exact specific gravity of the drug product were , then the mass of a full Liter batch should be Kg not Kg, as stated in the application.*

DISCUSSION: After a brief discussion, Bracco agreed to make the necessary changes and submit them to the NDA with the resubmission.

C. ESTABLISHMENT INSPECTION DEFICIENCIES

DISCUSSION: The sponsor confirmed that they will include the report that outlines what happened with the liners, caps and the lubricant with their resubmission of the NDA. Bracco reported that they had 3 batches with the same lot of caps for February and September, 1997. The sponsor then asked if they could submit 3 months accelerated data and send the rest later, instead of the six months worth of stability data referred to in the last paragraph above. HFD-160 indicated that the full six months worth of stability data needs to be collected and that when the application is resubmitted it needs to be a complete response. However, the Chemistry team stated that even though this was a policy issue (resubmissions being complete responses), they would consult with Dr. Love and Dr. Cheever reference the 3 months worth of accelerated data vs 6 months worth of data. The chemistry team leader indicated that 6 months worth of data was generous and that the key here is to be sure enough data is available to do a complete review of the NDA once resubmitted.

The meeting concluded with Bracco confirming that they will provide all CMC information requested in the paragraph below and fully address all 3 items listed below. They further stated that they had no issues with this request from HFD-160 and that all data would appear in their resubmission for this NDA.

Also, in order to complete the administrative record of the NDA, please provide clarification on whether an assay is performed on the bulk drug product prior to bottling to determine if any manufacturing failures occurred. If an assay is performed, please submit details of the assay and its validation. If an assay is not performed and reprocessing will not occur, please so state. In addition:

- 1. Please list the concentration of drug substance in the drug product in the header of all forms of labeling.*
- 2. Please state the minimum time for shaking of the bottle to resuspend the drug product on the immediate container label and in the package insert.*
- 3. Please provide the full addresses of the manufacturers of both the mil low density polyethylene bags and the cylindrical fiberboard drums.*

Minutes recorded by: Rubynell Jordan, Consumer Safety Officer, HFD-160

cc:

Orig NDA 20-773
HFD-160/ Div. File
HFD-160/Jordan

Jordan

MEMORANDUM OF TELECON

DATE: November 20, 1997 (10:30 AM)

APPLICATION NUMBER: NDA 20-773; SonoRx

BETWEEN:

Name: Madhu Anant, Melanie Benson, Eldon Fritz, Susan Cousounis, A. Betournay, and Lucas Makris
Phone: (609) 514-2262
Representing: Bracco Diagnostics Inc.

AND

Name: Victor Raczkowski, Michael Welch, Mohammed Al Osh, Robert Yaes, and Rubynell Jordan
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clinical/Statistical Issues in September 30, 1997, NA Letter
(mainly issues on pages 6-7)

After a brief introduction of all participants, the teleconference began with the sponsor indicating that the purpose of the meeting was to discuss issues noted on pages 6-7 in the September 30, 1997 NA letter. Next HFD-160's Deputy Director noted some key points from the letter prior to the in-depth discussion.

First, he informed Bracco that they made the claim for the decreased gas shadowing indication and that any resubmission should be focused on the data for reduction of gas shadowing artifact. The sponsor was asked to include a worst case analysis of the intent-to treat-analysis and comparison to water or the vehicle used. Please clearly identify the individuals by whom images were deemed to be technically inadequate. Please submit a proposal for analyses and the agency can provide guidance.

Secondly, he indicated that from the review of the NDA data it was possible but not completely clear that the Bracco could get a delineation claim. In order to get the claim the sponsor would need to do some image rereads though.

Lastly, it was pointed out that with respect to pathology the sponsor needs to do another or more trials in order to get the claim. These were the main issues HFD-160 was attempting to communicate both in the NA letter and via the November 6, 1998 teleconference. Please note that the 6 items on pages 6-7 of the NA letter were included for completeness but addressing them alone will not solve other problems with the overall application.

The second sentence of the last paragraph on page 7 of the NA letter (*"The clinical trials description should include the imaging parameters identified in the study reports, the responses to Item # 3a on the delineation of anatomy, and the results in comparison to water or vehicle"*) was thoroughly discussed and appeared to be understood by both parties.

The division discussed the last page of the blinded read Case Report Forms (CRF). Focus on the results of Item # 3a for delineation of anatomy. The CRF should include all areas for completeness, give a complete analysis of all patients and comparators.

The sponsor indicated that water was used for safety not efficacy. HFD-160 stated that this was okay but that they wanted to see the data and that they won't prejudge. Please show statistical comparison and qualify it in your narrative. The sponsor asked if they should compare SonoRx against water. HFD-160 confirmed this and explained that the sponsor has 2 issues going here; one issue is what is in their submission or what is going to be in the resubmission, the other is what is in their proposed package insert. The division noted that any analysis of water will only be used in a supportive realm. HFD-160 further pointed out that at this time it is not known what will be in the package insert.

The sponsor indicated that they understood that it will be necessary to include a worst case analysis of the ITT analysis. The division then discussed what is meant by a real ITT analysis. A real ITT analysis is any patient enrolled in the trial whether they receive drug or not. In clinical trials we usually get all patients that received drug and had at least one efficacy endpoint measured. We want to see how robust the data is; we want to look at it conservatively.

Bracco asked if they could use the phrase "all patients as dosed analysis". The division indicated that this was okay. HFD-160 explained that there was a concern about the number of patients being excluded from the analysis and that they want to be sure the data is robust. They also noted that Bracco could include other additional data if they chose to. It was also explained that there should not be a large variation in numbers between investigators and readers, none actually.

Both parties discussed the technically inadequate images and how the sponsor will score them. HFD-160 asked is worst score to predose and best score to postdose? Bracco confirmed this. Bracco indicated that they will compare SonoRx to a vehicle. HFD-160 stated that they just want the most conservative analysis. Compare pre dose and post dose score, Example of worst case analysis: (+1= better, 0 = no change, and 1=worst, visualization = excellent, good, and none.) Please focus on gas shadowing and Item 3a on delineation of anatomy. Please show us a real worst case analysis. We do not want this data to place it into a public package insert but we need to see the data internally. With 3a the worst case analysis is not an issue; we made a composite table from your tables (Q, AH, AJ, and AK). The sponsor indicated that they would address these issues internally and get back to the agency with a proposal. Bracco further noted that they do not want to compare SonoRx to a control here. HFD-160 suggested that Bracco should apply

the same decision rules to both.

The sponsor discussed their proposed format for resubmission (discuss results, list end of text tables, new clinical trials for package insert. HFD-160 stated that the format appeared to be okay on the surface. However, the sponsor must provide all data and in electronic format, data SAS, line listing, etc. The sponsor asked if safety data was needed. HFD-160 confirmed that this was indeed the case and suggested that if Bracco wanted any claim about delineation they will need to do more analysis. It was also suggested that Bracco send in a written proposal first and after FDA reviews it, the CSO can arrange for both parties to communicate again about the NDA.

Rubynell Jordan
Project Manager, HFD-160

cc: Original NDA 20-773
HFD-160/Div. File
HFD-160/Rubynell Jordan

TELECON

DF

Minutes of Meeting

Drug: Sonorx, IND
Sponsor: Squibb Diagnostics
Date: April 13, 1994, 12:00 PM
Purpose of Meeting: End-of-Phase 2 Pre-Meeting

FDA Attendees:

Roy Blay, Ph.D., Consumer Safety officer
Joe Pierro, M.D., Medical Officer
Hsien Ju, M.D., Medical Officer
Patricia Love, M.D., M.B.A., Acting Division Director
Norman See, Ph.D., Pharmacologist
Nancy Smith, Ph.D., Supervisory Statistician
Michael Welch, Ph.D., Statistician
Eric Sheinin, Ph.D., Supervisory Chemist
Hasmukh Patel, Ph.D., Reviewing Chemist
David Udo, Ph.D., Reviewing Biopharmacologist
A. Eric Jones, Supervisory medical Officer
Lydia Martynec, M.D., Medical Officer

- Dr. Patel expressed concerns regarding the Phase 1 pharmacokinetic study. He questioned the in-vivo stability of the C-14 labeled simethicone-coated cellulose and whether the simethicone coating would remain intact. He also expressed concern over the composition of the placebo since it is not of the same composition as in the original IND.
- Dr. See said that complete nonclinical studies were submitted by the sponsor. He said that the intraperitoneal studies had some deficiencies but that the firm had committed to correcting the problems and would also be doing teratology studies.
- Dr. Pierro indicated that there might be problems regarding the wording of the indication. He said that the sponsor had not developed a statement regarding the optimal dose of the agent. He said that Phase 3 studies would only include "evaluable" patients: what about the "non-evaluable" patients? He said that more information would be needed on clinical parameters and what values would be considered normal or abnormal. He said that efficacy endpoints would need to be expanded.

- Dr. Love said that there would need to be differentiation between drug and placebo effects, and that a decision would need to be made on the nature of the placebo (orange-flavored water, water, etc.)
- Dr. Smith suggested that a crossover study might provide statistical advantages.
- Dr. Love noted that there were 20 patients per dose and that if one made allowances for body habitus, the resultant study groups would be small. She said that criteria would need to be established for dosage selection.
- Dr. Jones said that the use of centrally located labs might not allow for notification of the investigators in sufficient time for follow-up of the patient. How will this potential problem be addressed?
- Dr. Love said there was no information on EKGs. She said that a subset of patients should be followed and that the sponsor could propose the number of patients that would receive EKGs. The medical need for an ultrasound study should be included as an entry criteria.
- Dr. Pierro said that there was no mention of tolerance to ingestion of the agent, and bowel habits before and after administration of the agent were not addressed.
- Dr. Smith said that Question 13 on page 39 of the CRFs should be moved to page 36 while leaving the latter part of the question. She said that question 8 should only have the option of being answered "yes" or "no". She said that Question 8 was not a good endpoint and that the blinded reader should see the water images. She also noted the need for 2 Phase 3 trials.
- Dr. Love said that blood levels of the agent should be determined in inflammatory bowel subjects.
- Dr. Udo said that the timing of samples as described in the submission was acceptable.

Page 3
IND

- There was discussion regarding acceptable comparative diagnostic modalities (e.g.; surgery, endoscopy, CT, etc.) so as to have a standard for data analysis, sensitivity, specificity, etc.
- Dr. Jones noted that the use of C-14 for absorption studies is discouraged. Current research in this area utilizes C-13 labeled products in ongoing IND studies. The use of ¹³C for both nonclinical and clinical studies is safer than use of C-14 and will avoid the possibility of clinical hold actions because of safety concerns.

CC:
IND
IND

HFD-160/Sheinin/Patel/See/Love/Jones/Ju/Pierro/Martyneć

HFD-713/Smith/Welch

HFD-161/Blay

HFD-426/Udo

Acknowledgements: Jones/Ju/Martyneć 4/21/94,
Pierro/Patel 4/14/94, See/Sheinin 4/15/94,
Smith 5/3/94, Udo 5/17/94, Love 5/27/94

F/T by: CWilson 6/1/94

September 18, 1998

NDA 20-773
SONORX SUMMARY

The complete response to the September 30, 1997, NA letter was submitted on April 29, 1998.

All reviews are complete and the NDA recommended action is Approval (AP).

Action Package Format: The action package is formatted such that the major sections are clearly identified with the most recent review and current information on the top in front of the pink divider sheets. The index and tabulation is by discipline. The summary table follows the discipline tabulation. The Division summary section contains the Division Director's Memo.

ISI
~~_____~~
Rubynell Jordan, CSO

Date: 18 SEPT 98

NDA 20-773
SONORX SUMMARY

The original NDA was submitted on September 30, 1996.

All reviews are complete and the NDA recommended action is not approvable (NA).

Action Package Format: The action package is formatted such that the major sections are clearly identified with the most recent review and current information on the top in front of the blue sheets. The index and tabulation is by discipline. The summary table follows the discipline tabulation. The Division summary section contains the Division Director's Memo.

/S/
~~Robynell Jordan, CSO~~ Date: SEPT 30, 1997

DIVISION DIRECTOR MEMO TO THE FILE

NDA: 20-773
DRUG: SonoRx (simethicone-coated cellulose suspension)
ROUTE: Oral
INDICATION: Gas Shadow Reduction to Delineate Anatomy During Ultrasound
CATEGORY: 1S - Resubmission Response to Non-approval Action
SPONSOR: Bracco Diagnostics, Inc.
SUBMITTED: April 30, 1998
PDUFA DATE: October 31, 1998
COMPLETED: October 28, 1998

RELATED REVIEWS:

Division Summary - V. Raczowski, 09/30/97
Chemistry - D. Place, 09/18/97 & 6/04/98
Clinical - B. Yaes, 09/12/97 & 07/21/98
Pharmacokinetics - D Udo, 09/25/97
Pharmacology - N Sadrieh, 07/17/97
Statistics - M Al-Osh, 07/18/97 & 08/05/98
Project Manager - Ruby Jordan

BACKGROUND:

SonoRx was originally submitted Sept 30, 1996. The review resulted in a non-approval letter on Sept 30, 1997 because of chemistry, clinical and statistical deficiencies. As stated in the letter the chemistry deficiencies included, " but were not limited to, problems with the container/closure system (pinholes in cap liners that result in discoloration and rust spots of the cap), inadequate documentation or acquisition of stability data, manufacturing errors, and lubricant or grease in samples of the drug product". Clinical and statistical deficiencies focused on the inability of the data to support a pathology detection indication; however, the letter stated that the data appeared to support a more limited indication of gas shadowing reduction and delineation of anatomy. Also, the letter contained preliminary requests for labeling clarifications. On April 30, 1998 the sponsor submitted responses to these deficiencies. The application has been reviewed and is found to be acceptable for approval.

CHEMISTRY:

Dr. Place reviewed the chemistry responses and found them to be acceptable for the 400 mL fill size. The originally requested mL fill size is not approved because new data were not submitted for this container. During the first review cycle the environmental assessment was found to be acceptable and a FONSI was finalized on 9/11/97. A repeat inspection was acceptable on 9/22/98.

MICROBIOLOGY: Approval recommendation during first review cycle

PHARMACOLOGY / TOXICOLOGY: During first review cycle recommended approval with labeling to advise of “granulomatous inflammation after intraperitoneal administration”.

PHARMACOKINETICS / PHARMACODYNAMICS: TOXICOLOGY: During first review cycle recommended approval with labeling revisions for clarity.

CLINICAL - STATISTICAL:

As noted in the above background section, during the first review cycle it was determined that SonoRx appeared to be approvable for gas shadowing reduction and anatomic delineation. SonoRx contains simethicone, an over-the-counter approved drug as an anti-flatulent for gastrointestinal gas reduction. It is not absorbed into the areas of normal or abnormal anatomy or pathology. Nor is it providing a new or unique property to the organs themselves (e.g., supplying new contrast). Instead, SonoRx's affect is on the intraluminal GI contents as it reduces the gas that could cause anechoic areas that interfere with the ability of ultrasound waves to reach their intended targets. Therefore, it allows existing acoustic impedance differences to be detected as they would if gas were not present or were minimized. As such, SonoRx is considered as a potential ultrasound “contrast” agent for an anatomic indication.

The two pivotal studies (42,440-3A and 42,440-3B Studies A & B; referred to as study A and B) are identical randomized, parallel, multicenter, vehicle controlled studies of adult patients who were highly suspect of having abdominal pathology and had an indication for an ultrasound examination. Patients received a dose of 400 mL SonoRx or 400 mL of the SonoRx vehicle (a formulation without simethicone coated cellulose, simethicone, xanthan gum and sodium lauryl sulfate). In the analysis the results of the ultrasound images before and after SonoRx were compared by 4 blinded readers. Of these two read static images and two read static and video images. Although both types of image sets can be evaluated in clinical practice, the combination is considered more complete.

During the first review cycle data on the delineation of anatomy were derived from case report form question # 3. The delineation was scored on a 5 point scale of 0 = none and 4 = excellent. However, the descriptions of delineation included phrases that referenced diagnosis and pathology¹. (See Dr. Raczowski's review page 38 - 39, Yaes 7/31/98 review, page 11-12). However, for specific anatomic regions both the sponsor's analysis (*using the Wilcoxon signed rank test*), and the statisticians analysis (*a determination of the number of patients whose image scores improved by at least one unit (see Al-Osh page 32-35)*) showed consistent statistical

¹For example, none = “nondiagnostic, cannot identify area of interest, cannot exclude nor detect pathology”; excellent = “diagnostic, excellent delineation, high level of confidence in excluding or detecting pathology”.

significance across all readers. The statisticians results are reproduced from Dr. Al-Osh's review² in the table below. An excerpt of this appears in the package insert.

IMPROVEMENT in ULTRASOUND ANATOMIC DELINEATION BEFORE and AFTER SONORX							
Anatomical Area:	Blinded Reader	Study 42,440-3A (N=64) ^a			Study 42,440-3B (N=81) ^a		
		N ₁ ^b	N ₂ ^c	d=N ₂ -N ₁ (d / N %)	N ₁ ^b	N ₂ ^c	d=N ₂ -N ₁ (d / N %)
Stomach	3	1	47	46 (72%)	1	65	64 (79%)
	4	6	41	35 (55%)	0	60	60 (74%)
Gastric Wall	3	1	46	45 (70%)	1	62	61 (75%)
	4	6	37	31 (48%)	1	65	64 (79%)
Pylorus	3	1	44	43 (67%)	2	51	49 (60%)
	4	10	30	20 (31%)	0	54	54 (67%)
Duodenum	3	0	43	43 (67%)	1	45	44 (54%)
	4	8	28	20 (31%)	0	42	42 (52%)

^a N is the number of patients considered in the analysis (images for 29 patients in Study 42,440-3A and 13 patients in Study 42,440-3B) were not included in the analysis because of protocol violations).

^b N₁ is the number of patients for whom before SonoRx delineation score is better than after SonoRx.

^c N₂ is the number of patients for whom the after SonoRx delineation score is better than before SonoRx.

Prepared by Dr. Al-Osh

² The above table was prepared by Dr. Al-Osh and is similar to table 14 & 15 of his 7/18/97 review page 34-35. The difference is that the review table used assumptions on the missing data, the above table used the actual scores.

On further reflection and discussion with Dr. Raczkowski during this review cycle, since SonoRx is not providing new contrast, then the readers are making interpretations that normally would be made on ultrasound examinations. As such this question is acceptable with the caveat that the pathologic determinations were not confirmed in this study. Therefore, SonoRx cannot be promoted for the detection of pathology.

To further support the application the sponsor submitted a worst case analysis of the gas shadowing data from the two pivotal studies (A and B) and from a cross over study (42,440-7, subsequently referred to as #7). During the first review cycle, there appeared to be sufficient information to support approval for gas shadowing reduction. This appeared to be based on studies A, B and study 7. (See Raczkowski, page 18, 27-28, Yaes 07/21/98 review page 18). The sponsor's reanalyzed data by the Wilcoxon signed rank test, and the statistician's analysis of all patients who improved by at least one unit reveals statistically significant improvement in all 4 readers of study B. However, in study A the two blinded readers with static images had statistically significant improvement after SonoRx. For the two blinded readers with the static and video images, one reader found similar gas shadowing before and after SonoRx, the other reader found the before SonoRx images to have less gas shadowing. Therefore, study B strongly supports gas shadowing reduction. Study A is weaker and depends upon the images reviewed.

Study # 7 is a randomized cross over of 53 patients who were suspected to have abdominal pathology. The patients received 400 mL of SonoRx and 400 mL of water. The image scores after each treatment were compared. An analysis against baseline was not submitted. The results of study #7 are sensitive to the statistical methodology. Specifically, the sponsor again used the Wilcoxon signed rank test to evaluate the statistical difference in gas shadowing for SonoRx and water images. The reviewing statistician used an imputed worst case analysis of the number of patients who improved or worsened by at least one unit (see Dr. Al-Osh's review page 6-8). If the results of the sponsor's analysis is used, then SonoRx results are better than those of water. If the statistician's results are used, then SonoRx gas shadowing appears to be similar to that of water (an active control). Unfortunately before and after dosing image comparisons were not performed in study 7, so the interpretation can not be the same as that of study A and B. Therefore, study #7 is not sufficiently supportive of gas shadowing reduction.

Safety Update - The sponsor has not studied any additional patients since the original review cycle.

DSI - Acceptable during the first review cycle.

Special Populations: Pediatric studies were not conducted. Pediatric patients especially infants are apt to vomit if large volumes are ingested. Dose adjustment should be studied in phase 4.

CONCLUSIONS:

Ultrasound of the abdomen typically is a screening test. If it is inconclusive, additional studies are likely. Abdominal ultrasound studies can be obscured by gas shadowing in the gastrointestinal tract. SonoRx contains known ingredients that are approved for over-the-counter use to reduce gas (simethicone) and provide bulk (cellulose). Phase 1-2 studies are supportive of pharmacodynamic effects on gas shadowing. Although the delineation endpoint is somewhat confounded, it is acceptable. The adverse event risk profile is low. Chemistry manufacturing and control deficiencies have been resolved. Therefore, The NDA contains adequate information for approval of SonoRx as a gas shadow artifact reducing agent to enhance the visualization of upper abdominal anatomy.

ACTION: APPROVAL with a PHASE 4 Commitment to determine the volume for ingestion in pediatric patients.

PS

10/29/98

Patricia Y. Love, M.D.

07/21/98 1

SonoRx MO Review R. J Yaes.

NDA#20,773 00-773

Response to NA letter of 9/30/97

SonoRx™ Oral Suspension

Simethicone Coated Cellulose Suspension

Submitted: 4/29/98

Dosage: 400 mL P.O. Single Dose

Received: 4/30/98

Sponsor: Bracco Diagnostics, Princeton, NJ

Assigned: 5/7/98

Medical Officer Review

Completed: 7/21/98

MO Robert J. Yaes, Sc.D., MD

Review Team

Medical officer: R. Yaes

Pharmacology/Toxicology: . Sadrieh/Myers

Biopharmaceuticals: D. Udo

Chemistry: S. Gilman/Place

Statistics: M. Al Osh

Microbiology: P. Stinavage

CSO: R. Jordan

Regulatory background:

NDA 20,773 was received on Sept 30,1996. This submission was reviewed and deficiencies were found in the clinical/statistical section and in the chemistry section of the submission. An NA letter was sent to the sponsor, dated Sept 30,1997 .

Submission:

This resubmission consists of 2 volumes. Volume 1 deals with clinical and statistical issues. Volume 2 deals with chemistry issues. The chemistry issues will be addressed by the chemistry reviewers. This review will be limited to the clinical and statistical issues contained in volume 1. Statistical issues will also be addressed by the statistical reviewer. This Volume contains no new data but consists of a reanalysis of the data obtained in the clinical trials, particularly the two pivotal phase 3 trials, 42,440-3A and 42,440-3B. Data from the supporting study 42,440-7 is also reanalyzed. An integrated safety analysis including all adverse data from all Phase 1, 2, and 3 clinical studies is also included The resubmission also contains a revised proposed draft of package insert.

Proposed Indication (revised)::

Robert J. Yaes, MD., Sc.D, Medical Officer

Handwritten signature and initials "RS" and "11"

Handwritten date 7/21/98

Background Material

Abstract of Original MO Review of NDA 20-570 Dated 9/12/98

Ultrasound imaging is an inexpensive, portable diagnostic modality that does not expose the patient to ionizing radiation. Its usefulness in imaging the upper abdomen is limited by the effect of gas shadowing, which results in image degradation. SonoRx is a new, orally administered ultrasound contrast agent which adsorbs and displaces gas in the upper GI tract, and is therefore expected to improve the quality of ultrasound images of the upper abdomen. Since images are to be obtained shortly after ingestion, its effect will be primarily on gas in the stomach. Images of only those structures affected by shadowing by gas in the stomach would be expected to --be improved. These structures are the stomach, gastric wall, duodenum and the head, body and tail of the pancreas.

The sponsor has undertaken two phase 1 trials, one phase 2 dose ranging trial, two pivotal phase 3 trials, and one phase 3 supporting trial, with a total of 426 subjects, in order to demonstrate the safety and efficacy of SonoRx. While these studies were well designed to demonstrate safety, there were major problems with the design and implementation of the pivotal trials in the demonstration of efficacy. Blinded reads were not performed according to protocol. The first pair of readers were not given both static and video images, as the protocol required. A second pair of readers did not receive the scans from all patients. The questions asked of the readers were highly subjective, and this was reflected in the wide disparity of answers given by the blinded readers. The pivotal trials were not control agent controlled for efficacy.

There does not appear to be any major safety concern. The active ingredients in SonoRx, cellulose and simethicone, are known to be safe for oral ingestion in the doses given. Pre-clinical studies show that these ingredients remain in the gut and are excreted unchanged in the feces. There were no deaths in any of the studies that could be attributed to the study agent. The number and pattern of adverse events did not raise any particular safety concerns. There was a slight excess of mild adverse events, involving the GI system, such as diarrhea and nausea and vomiting, which would be expected with this type of agent.

The two pivotal trials were identical in design and implementation and were carried out simultaneously. Patients ingested 400 mL SonoRx. Blinded readers compared ultrasound scans taken immediately after SonoRx ingestion (post-dose scan) to scans obtained just before ingestion (pre dose scans). The sponsor's primary outcome variable was the readers answer to the question "Overall did the post dose images provide additional information over the pre- dose images?" The sponsor claims that efficacy has been demonstrated because the percentage of patients for which the answer was yes, was greater than 1% for all blinded readers in both pivotal studies. By pure chance the expected percentage would be 50%.

In conclusion, there are no substantial safety concerns. The sponsor however has not provided substantial evidence of efficacy for the proposed indication, based on the primary outcome variable in the pivotal trials. There is substantial evidence presented in these studies that SonoRx does improve visualization of the stomach duodenum and pancreas, which are those organs whose visualization would be most affected by shadowing by gas in the stomach. The NDA is therefore approvable with the narrower indication.

This reviewer's recommendation is that this NDA is approvable with the indication "SonoRx is an orally administered ultrasound contrast agent indicated for the reduction of gas shadowing effects, and the enhancement of the visualization of anatomical structures in the upper abdomen" Labeling should be modified to reflect this narrower indication, and to indicate that the enhanced visualization was not conclusively demonstrated when SonoRx was compared to water control agent in the supporting study.

Clinical Rationale

When compared to MRI or CAT scanning, ultrasound imaging has the advantages of low cost, portability and lack of ionized radiation or high magnetic fields.. However ultrasound is limited as a screening test for pathology in the upper abdomen, by the image degradation by gas shadowing by gas in the stomach. SonoRx is an ultrasound contrast agent containing ultra small particles of cellulose coated with simethicone, designed to displace and adsorb gas. Gas shadowing by gas in the stomach can be reduced and the stomach can be made transparent to ultrasound, improving visualization of the stomach, and of structures posterior to the stomach, and in particular the pancreas

SonoRx was assessed in 2 phase 1 studies, 1 phase 2 dose ranging studies and 3 phase 3 studies with a total of 426 subjects (see table 1) The 2 pivotal phase 3 studies were *not* controlled for efficacy

Dosage and Formulation

SonoRx is an orally administered ultrasound contrast agent for the delineation of normal anatomy and the detection of pathology in the upper abdomen. According to the sponsor, the active ingredient is 22 micron fiber length cellulose coated with Simethicone The cellulose is manufactured from wood and is considered safe (GRAS). The proposed dose of SonoRx is 400 ml PO The sponsor states that the amount of Simethicone in 400 ml SonoRx is 80 mg, which is less than the amount of Simethicone in the maximum recommended doses of common over the counter medications (see pharm-tox review) The composition of SonoRx is given in table 1.A

TABLE 1-A COMPOSITION OF SonoRx

INGREDIENT	gm/L
22 micron cellulose with 0.25% Simethicone coating (active ingredient)	7.5
Xanthan Gum	
Medical anti Foaming Agent A (Simethicone USP)	
Sodium Laurel Sulfate NF	
Citric Acid USP	
Orange Oil Florida Type	
FD&C Yellow #6	
Fructose USP	
Sodium Benzoate (preservative) NF	

*The mixture is brought to a volume of 1 liter with purified water USP

In the pivotal trials (42,440-3A and 42,440-3B), the placebo agent consisted of SonoRx with four ingredients (simethicone coated cellulose, xanthan gum, simethicone and sodium laural sulfate) omitted

Reviewer's comment: The sponsor has not described the function of xanthan gum and sodium laural sulfate nor have they stated the reason that these (presumably inactive) ingredients have been excluded from the placebo agent. Thus, even if the sponsor could demonstrate a clear advantage of SonoRx over placebo, this would not support a claim that implies that simethicone coated cellulose is the only active ingredient in SonoRx

TABLE 1-B COMPOSITION OF PLACEBO IN PHASE 3 PIVOTAL TRIALS*

INGREDIENT	gm/L
Citric Acid USP	
Orange Oil Florida Type	
FD&C Yellow #6	
Fructose USP	
Sodium Benzoate (preservative) NF	

*The mixture is brought to a volume of 1 liter with purified water USP

In the phase 3 supporting study, 42,440-7, the control agent was water

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Trials

All clinical trials are listed in table 2 The 2 pivotal phase 3 studies were *not* control agent controlled for efficacy. Data on patients who received control agent was used in the safety analysis only (the placebo patients are included in the sponsor's efficacy reanalysis of the pivotal studies in the resubmission)

Table 2 SonoRx CLINICAL STUDIES

PHASE 1 EFFICACY-STUDIES				
NUMBER	DATES	DESIGN	DOSES	SUBJECTS
42,440-1	7/93- 7/93	Phase 1 Single Center Randomized, Placebo Controlled, Double Blind, Parallel, dose Escalating Safety and Efficacy Study in Normal Healthy Adult Male Volunteers	200-1000ml.....SonoRx	5
			“ Placebo	3
42,440-4	11/93- 12/93	Phase 1 Single Center Randomized, Placebo Controlled (Water vs. SonoRx), Single-Blind Crossover Safety and Efficacy Study in Normal Healthy Adult Male Volunteers	SonoRx 800 ml	24
			Placebo 800 ml	24
PHASE 1 PHARMACOKENETIC STUDIES				
42,440-5	11/94- 3/95	Randomized, Single Dose Placebo Controlled, Double -Blind Study in Male and Female Patients With Impaired Bowel Motility	SonoRx 400ml	12
			Placebo 400 ml	3
42,440-6	1/95- 1/95	Randomized, Single Center Single Dose Placebo controlled, Double Blind Study in Normal Volunteers	SonoRx 400 ml	7
			Placebo 400ml	3
Total Phase 1 Patients			Both (crossover)	24
			SonoRx only	24
			Placebo only	9
PHASE 2 DOSE SELECTION STUDY				
42,440-2	9/93- 3/94	Multicenter, Randomized, Uncontrolled, Dose Ranging Study	SonoRx 200-1000 mL	99
PHASE 3 CLINICAL TRIALS				
PIVOTAL STUDIES				
42,440-3A	6/94- 12/94	Multicenter Randomized Double-Blind Parallel Study	SonoRx 400 mL	93
			Control Agent 400 mL	24
42 440-3B	7/94- 11/94	Multicenter Randomized Double-Blind Parallel Study	SonoRx 400 mL	94
			Control Agent 400 mL	28
Total Patients in Pivotal trials			SonoRx 400 mL	187
			Control Agent 400 mL	52
PHASE 3 SUPPORTIVE STUDY				
42,440-7	10/94- 2/95	Multicenter, Randomized, Placebo Controlled, Single-Blind, Crossover Study	Both SonoRx 400 mL and Water 400 mL (crossover)	51
			Water only	2

NA letter of Sept.30,1997

The NA letter of Sept 30, 1997 specifies the deficiencies in the Chemistry /Manufacturing section and in the Clinical/Statistical section of the submission. Chemistry/Manufacturing deficiencies will be addressed in the chemistry review and will not be discussed here. Specific quotations from the NA letter of Sept. 30, 1977 are shown in italics below;

Clinical /Statistical Issues

Delineation of anatomy and gas shadowing

"..the submitted application appears to support SonoRx's use to decrease gas shadowing in the upper abdomen The data marginally demonstrates SonoRx's efficacy to facilitate the detection or exclusion of pathology".

"question 3a of the Blinded Reader Comparison Image case report form is the only question that directly asks for information on the delineation of anatomy. Specifically, in reference to the question on the nature of the additional information provided by the post dose images over the pre dose images, one of the responses could be improved delineation of abdominal anatomy".

" the other question that assesses the delineation of anatomy is Item#1 of the Blinded Reader Comparison Image Evaluation.However the possible responses are composites....Therefore responses to this item are confounded"

"another item of the case report form asks the degree to which gas obscures the image(item #2 of the Blinded Reader Comparison Image Evaluation) Responses to this item provide acceptable data".

"item #15 on the Blinded Reader case report form from study 42-440-7 requests information on the impact of gas shadowing.....This item provide acceptable supporting data"

Detection or Exclusion of Pathology

"The studies lacked adequate "standards of truth" by which the interpretation of pathological findings could be validated"

"The procedures used to identify diagnostic "matches" or "mismatches" were not adequate to minimize the effects of possible biases"

Reviewer's comment: *The lack of a "standard of truth", and biases in the determination of matches and mismatches can not be remedied by reanalysis of the existing data*

"The values of sensitivity ...in Studies #42,440-3A and #42,440-3B were not consistent between the two studies"

"the values of specificity in Studies #42,440-3A and #42,440-3B were based on...an insufficient number of subjects".

"Sensitivity and specificity were calculated only with data from the per protocol subset of subjects"

"The analyses used to evaluate the response rate for the primary outcome variable...did not include data from the entire group of subjects randomized to receive SonoRx, or from the entire group of subjects that actually received SonoRx".

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"The results of the intent to treat analysis of the blinded image evaluation were highly variable..... values for the kappa statistic for agreement between the blinded readers were not far from what is expected from chance agreement alone."

Reviewer's Comment: *It should be emphasized that the clinical issues raised in the NA letter of Sept 30, 1997, are all related to the demonstration of efficacy. No issues relating to safety were considered to be of sufficient concern to affect the approvability of the application. The letter implies that the data submitted could support an indication of "decrease of gas shadowing in the upper abdomen" and of "delineating anatomy", but were insufficient to support an indication for "facilitation of detection or exclusion of pathology". Thus the letter of Sept. 30, could be interpreted to imply that, if the chemistry issues were satisfactorily resolved, the application could be approvable with an indication for reduction of gas shadowing and delineation of anatomy.*

SPONSOR'S RESPONSE

Proposed Indication: The revised proposed package insert contains a revised indication (pg,6):

Sponsor's Original Proposed Indication from NDA submitted Sept 30, 1996:

Reviewer's Comment: *The revised proposed indication differs from the original proposed indication the following significant ways;*

The NA letter clearly stated that the data submitted in NDA 20,570 could not support an indication for detection or exclusion of pathology. There were fundamental deficiencies in the study design that could not be remedied by a reanalysis of existing data. These deficiencies included the lack of a single "standard of truth" to which the ultrasound diagnoses could be compared, the bias introduced by not having a blinded reviewer determine whether diagnoses matched or not, and the lack of sufficient patients without pathology to determine the specificity, or to support a claim for detection or exclusion of pathology. Even before the reanalysis of the data is addressed, it is clear that

an indication for these studies.

cannot be supported by the data produced by

The readers were asked to rate the visualization of specific structures in the upper abdomen (stomach, duodenum, head of the pancreas, etc.). The reader's response could be used to justify an indication for either "delineation of anatomy in the upper abdomen" or for "facilitates visualization of the upper abdomen". While these statements might be considered to be equivalent, the first seems less vague and therefore more preferable. When the readers were asked about the nature of additional information in those cases where the post dose images provided additional information, one of the possible choices was "Improved delineation of abdominal anatomy" and it would be desirable to retain that wording in the statement of the indication

The readers were asked to rate the effects of gas shadowing on a 5 point scale as, not obscured, mildly obscured, moderately obscured, markedly obscured or completely obscured. Only the response "not obscured" would support the claim "eliminates gas shadowing". Using a Wilcoxin log-rank test to show a statistically significant difference between pre dose and post dose images would only justify a claim of "reduces gas shadowing"

In the reviewer's opinion only an indication such as "SonoRx is an orally administered contrast agent that reduces gas shadowing artifact and facilitates ultrasound visualization of anatomical structures in the upper abdomen" can be justified unless additional clinical data (not a reanalysis of previously submitted data) is provided. } ✓

Active Ingredient: In the clinical pharmacology section of the revised proposed package insert. The sponsor makes the claim that "The active ingredient in SonoRx, simethicone coated cellulose, rapidly adsorbs and disperses gas in the stomach and the bowel, therefore eliminating shadowing artifacts, creating uniform echogenicity and improving transmission of the ultrasound beam"

Reviewer's Comment: In order to claim that simethicone coated cellulose is the "active ingredient" in SonoRx., the sponsor would have to demonstrate that there is a statistically significant difference in efficacy between SonoRx and SonoRx with all ingredients except simethicone coated cellulose. In the pivotal phase 3 studies, placebo patients were included for safety analysis only. For efficacy analysis SonoRx images were compared to pre dose images, not to control agent images. In the supporting phase 3 study, SonoRx was compared to water not to vehicle. In the pivotal studies, control agent was the vehicle with 3 ingredients besides simethicone cellulose (simethicone, sodium laurel sulfate and xanthan gum) omitted.

In the same sentence the sponsor is again making the claim that SonoRx eliminates gas shadowing artifacts and creates a uniform echogenicity in the stomach and bowel. As discussed above the sponsor should only be able to claim that SonoRx reduces gas shadowing. The uniformity of the echogenicity was not directly addressed in any of the 3 phase 3 studies, and since imaging begins immediately after ingestion, it is unlikely that SonoRx will get much beyond the stomach and duodenum during imaging. Most of the effect probably occurs in the stomach, not the large or small bowel. This entire sentence should be deleted from the package insert.

Reanalysis of the Data

Efficacy

In the original clinical report of the data from the 2 Phase 3 pivotal trials, 42,440-3A and 42-440-3B and the supporting Phase 3 trial, 432,440-7, the "intent to treat population" was defined as "all patients who ingested any volume of at least one study agent and had images of acceptable technical quality". Technical quality was evaluated by a "technical reviewer" and those images found to have unacceptable technical quality were removed from the set and were not read. In both pivotal studies the first 2 readers (readers 1 and 2) did not see the video images as required per protocol. A second reading was then arranged with readers 3 and 4 where both static and video images were read together, however video images could not be located for all patients. Patients who ingested less than 350 ml

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SonoRx were also excluded. Consequently, of the 93 patients who ingested any volume of SonoRx in Study 42,440-3A (the intent to treat population as usually defined in a contrast agent study) the images from 85 patients were evaluated by readers 1 and 2, and the images from 76 patients were evaluated by readers 3 and 4 in the "intent to treat analysis" in the original submission. In study 42,440-3-B, all 94 patients who ingested any volume of SonoRx, had images evaluated by blinded readers 1 and 2 and 85 had images evaluated by blinded readers 3 and 4. In the supportive study 42,440-7, 51 patients ingested any volume of SonoRx. 50 sets of SonoRx images were evaluated by blinded readers 1 and 2 and 48 sets of images by blinded readers 3 and 4. Consequently a worst case analysis including all patients who ingested any dose of SonoRx was requested for these studies in the NA letter.

The sponsor has presented such a worst case analysis in the re-submission, for the question concerning gas shadowing where the possible reader responses were: "not obscured", "mildly obscured", "markedly obscured" or "completely obscured". In studies 42,440 3A and 3B imputed worst case data, for the question concerning gas shadowing, where images were not read, for both SonoRx and control agent (pg.22) was "pre-dose images were not obscured and post dose images were completely obscured."

Reviewer's comment: "Worst case" should always mean "worst for SonoRx", and imputed worst case data should always tend to make SonoRx look worse than the control agent. However if for both agents, all pre dose images were called "not obscured" and all post dose images were called "completely obscured", this imputed data alone would tend to make SonoRx and control appear equivalent, whereas in the "worst case" control agent would look better than water. Thus, for the SonoRx images, "worst case" should mean "pre-dose images were not obscured and post dose images were completely obscured." However for the control agent it should mean precisely the opposite, "pre-dose images were completely obscured and post dose images were not obscured." This "worst case" analysis described by the sponsor is not really a worst case analysis and would tend to make control agent look worse and therefore make SonoRx look better, in comparison to control agent, than would a real worst case analysis. If the sponsor wishes only to compare pre-dose SonoRx images to post-dose SonoRx images this "worst case" data would be acceptable. However this imputed "worst case" data is not acceptable for comparing SonoRx to control agent

For supportive study 42,440-7 where SonoRx was compared to water, for missing water image data, "worst case" was defined as water images more obscured than SonoRx, and for missing SonoRx image data, "worst case" was defined as SonoRx more obscured than water.

Reviewer's Comment; which ever image data is missing, "worst case" should always mean SonoRx images are more obscured than water images (see reviewer's previous comment) What the sponsor is actually doing is ascribing "worst case" data when the SonoRx images were missing, and "best case" data when the water images were missing. Such an analysis would obviously make SonoRx appear better in comparison to water than would a true worst case analysis.

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The results of the analysis of the data from the original submission, and the sponsor's "worst case analysis are shown for 42,440-3A (tables 3-6), for 42,440-3B.(tables 7-10), and for 42,440-7 (table 11)

42,440-3A

The patient disposition for pivotal study 42,440-3A is given in table 3

TABLE 3 42,40-3A PATIENT DEPOSITION FOR EFFICACY ANALYSIS	
Total Number of patients planned	100
Total Number of patients enrolled	119
Dropped Out Before Ingestion	2 (both SonoRx)
Patients Available For Safety Analysis (SonoRx 93) (Placebo 24)	119-2=117
Patients Available For Efficacy Analysis (SonoRx patients only*)	117-24=93
Intent to Treat Analysis By Investigators	93
Technically inadequate per technical reviewer	8
Intent to Treat Analysis By Blinded readers 1 and 2	93-8=85
Video Images Missing or Not Readable	9
Intent to Treat Analysis By Blinded readers 3 and 4 (primary efficacy endpoint only)	85-9=76
Patients Who Ingested <350 mL	12
Per Protocol Analysis By Blinded readers 1 and 2	85-12=73
Video Images Missing or Not Readable	9
Per Protocol Analysis By Blinded readers 3 and 4	73-9=64

*placebo data used for safety analysis only

Reviewer's Comment: A true intent to treat analysis should have included all 93 patients who received any dose of SonoRx. The results for the 24 patients who received placebo should also have been analyzed. The intent to treat analysis for readers 1 and 2 involved 85 patients for the primary outcome variable, the answer to the question "Overall did the post dose images provide additional information over the pre dose images" (It should be noted that the revised proposed indication contains no specific statement concerning "additional information" and is therefore not directly related to the primary outcome variable of the pivotal studies). A per protocol analysis only was performed for all other outcome variables including the questions related to gas shadowing artifact and delineation anatomy. For these outcomes only 73 patients were available for analysis by blinded readers 1 and 2 and 64 patients by blinded readers 3 and 4

In table 4 responses to the question in which the readers were asked to rate the SonoRx images for gas shadowing artifact, on a 5 point scale, are given for the investigators and the blinded readers. The possible reader responses were: "not obscured", "mildly obscured", "markedly obscured" or "completely obscured". This table represents data presented in the original submission. Note that data is presented for the SonoRx patients only. Since the placebo group was included in the analysis of safety only and the study was not powered to show a statistically significant difference in efficacy between SonoRx and placebo, the efficacy data for the patients who received placebo was not included in the analysis in the original submission

Gas Shadowing	Investigators		Blinded Readers							
	N=79		Reader #1 N=73		Reader #2 N=73		Reader #3 N=64		Reader #4 N=64	
	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose
Completely Obscured	1	1	0	0	0	0	3	2	0	0
Markedly Obscured	14	4	7	4	1	0	15	15	3	3
Moderately Obscured	42	30	19	19	18	3	29	20	10	14
Mildly Obscured	20	39	38	32	52	60	14	17	50	46
Not Obscured	2	5	9	18	2	10	3	10	1	1

In the sponsor's reanalysis all 93 patients who received SonoRx and all 24 patients who received placebo were included in the analysis. The sponsor also changed the outcome variable to a 3 point scale, whereby the pre dose image was more obscured, equally obscured or less obscured than the post dose image (e.g. If the pre dose image was markedly obscured and the post dose image was mildly obscured then pre was more obscured than post) The sponsor does not provide a rationale for changing from a 5 point scale to a 3 point scale. The results of the sponsor's "worst case" reanalysis is given in table 5.

Readers	SonoRx N=93			Placebo N=24		
	pre more obscured than post	equal	post more obscured than pre	pre more obscured than post	equal	post more obscured than pre
investigators	40 (43%)	47 (51%)	6 (6%)	17 (71%)	7 (29%)	0 (0%)
Reader 1	27 (29%)	47 (51%)	19 (20%)	8 (33%)	9 (38%)	7 (29%)
Reader 2	27 (29%)	58 (62%)	8 (9%)	8 (33%)	12 (50%)	4 (17%)
Reader 3	17 (18%)	43 (46%)	33 (35%)	3 (13%)	14 (58%)	7 (29%)
Reader 4	4 (4%)	53 (57%)	36 (39%)	2 (8%)	13 (54%)	9 (38%)

Sponsor's outcome variable for this analysis is the difference in the number of patients whose pre dose images were more obscured than the post dose images. This difference is statistically significant (pre worse than post) for the investigators ($p=0.0001$) and for reader #2 ($p=0.0019$), and statistically significant (post worse than pre) for readers 3 ($p=0.0328$) and reader 4 ($p=0.0001$)

Reviewer's comment: The results for this endpoint would be the most relevant to the indication "Reduces gas shadowing artifact" No clear advantage of SonoRx over placebo in reducing gas shadowing artifact is demonstrated. The data shows pre SonoRx more obscured than post in more cases for readers 1 and 2, but post more obscured than pre in more cases for readers 3 and 4. No clear advantage for post dose

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images over pre dose images is demonstrated. However given the large number of patients excluded from the readings (readers 3 and 4 only evaluated 64 out of 93 patients) to whom "worst case" data had to be assigned, this would be almost a foregone conclusion.

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 6 NATURE OF ADDITIONAL INFORMATION IN SonoRx POSTDOSE IMAGES 42,440-3A

	Investigators N=46*	Blinded Readers			
		Reader#1 N=32*	Reader#2 N=72*	Reader#3 N=42*	Reader#4 N=15*
Improved delineation of abdominal anatomy	32/46 69 %	23/32 72%	72/72 100%	40/42 95%	15/15 100%
Improved delineation of abdominal anatomy (worst case analysis calculated by reviewer)**	46/93 49 %	32/93 24%	72/93 77%	42/93 43%	15/93 16%
Improved confidence in exclusion of pathology	19/46 41%	15/32 32%	72/72 100%	15/42	0 0%
Improved delineation of pathology	17/46 37%	9/32 28%	0 0%	5/42 11%	0 0%
Improved evaluation of extent of disease pathology seen	5/46 10%	1/32 3%	0 0%	0 0%	0 0%
Other	2/46 4%	1/32 3%	0 0%	0 0%	0 0%
Placebo	N=14	N=13	N=19	N=12	N=66
Improved delineation of abdominal anatomy	11/14 79%	12/13 92%	19/19 100%	11/12 92%	6/6 100%

*N = number of patients with additional information (information in the post dose image that was not in the pre dose image) according to each individual reader

** The reviewer has performed a simple worst case analysis by dividing the total number of patients with improved delineation of abdominal anatomy by the total number of patients (93) who received any dose of SonoRx

Reviewer' Comment It should be noted that, in the per protocol analysis, in those cases where the readers said that the post dose images provided additional information, the additional information included "improved delineation of anatomy", for between 100% and 69% of the cases. In contrast, "improved delineation of pathology" was included in only 41% to 0% These results provide evidence in support of the claim for "improved delineation of abdominal anatomy" However, comparing the first and last rows of table 6 there appears to be no advantage of SonoRx over placebo in providing improved delineation of abdominal anatomy

42,440-3B

TABLE 7 PATIENT DISPOSITION FOR EFFICACY ANALYSIS 42,440-3B	
Total Number of patients planned	100
Total Number of patients enrolled	123
Dropped Out Before Ingestion	1 (SonoRx)
Patients Available For Safety Analysis (SonoRx 94) (Placebo 28)	123-1=122
Patients Available For Efficacy Analysis (SonoRx patients only*)	122-28=94
Intent to Treat Analysis By Investigators	94
Technically inadequate per technical reviewer (8))	9
Intent to Treat Analysis By Blinded readers 3 and 4	94-9=85
1 image miscoded for readers 1 and 2	1
Intent to Treat Analysis By Blinded readers 1 and 2	85-1=84
Intent to Treat Analysis By Blinded readers 3 and 4 (primary efficacy endpoint only)	85
Patients Who Ingested <350 mL	3
Per Protocol Analysis By Investigators	88**
Per Protocol Analysis By Blinded reader 1	80**
Per Protocol Analysis By Blinded reader 2	78**
Per Protocol Analysis By Blinded readers 3 and 4	81**

*placebo data used for safety analysis only

** Images were evaluated for technical acceptability by both the technical reviewer and the individual blinded readers. The number of images excluded as technically unacceptable varied from reader to reader.

Reviewer's Comment: A true intent to treat analysis should have included all 94 patients who received any dose of SonoRx. The results for the 28 patients who received placebo should also have been analyzed. The intent to treat analysis for readers 1 and 2 involved 84 patients for the primary outcome variable. A per protocol analysis only was performed for all other outcome variables including the questions related to gas shadowing artifact and delineation anatomy. For these outcomes only 80 and 78 patients were available for analysis by blinded readers 1 and 2 respectively and 81 patients by blinded readers 3 and 4

SonoRx MO Review R. J Yaes.

In table 8 responses to the question regarding the gas shadowing artifact are given for the investigators and the blinded readers. The overall image was evaluated with respect to gas shadowing artifact. The possible reader responses were: "not obscured", "mildly obscured", "markedly obscured" or "completely obscured". This table represents data presented in the original submission. Note that data is presented for the SonoRx patients only. Since the placebo group was included in the analysis of safety only and the study was not powered to show a statistically significant difference in efficacy between SonoRx and placebo, the efficacy data for the patients who received placebo was not included in the analysis in the original submission

Gas Shadowing	Investigators		Blinded Readers							
	N=88		Reader #1 N=73		Reader #2 N=73		Reader #3 N=64		Reader #4 N=64	
	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose
Completely Obscured	6	0	0	0	9	4	9	2	0	0
Markedly Obscured	25	5	25	6	18	20	22	7	7	2
Moderately Obscured	41	22	32	23	32	32	26	20	30	13
Mildly Obscured	16	49	22	45	17	19	16	26	39	49
Not Obscured	0	12	1	6	2	3	8	26	5	17

In the sponsor's reanalysis all 94 patients who received SonoRx and all 28 patients who received placebo were included in the analysis. The sponsor also changed the outcome variable to a 3 point scale, whereby the pre dose image was more obscured, equally obscured or less obscured than the post dose image (e.g. If the pre dose image was markedly obscured and the post dose image was mildly obscured then pre was more obscured than post) The sponsor does not provide a rationale for changing from a 5 point scale to a 3 point scale. The results of the sponsor's "worst case" reanalysis is given in table 9.

Readers	SonoRx N=94			Placebo N=28		
	pre more obscured than post	equal	post more obscured than pre	pre more obscured than post	equal	post more obscured than pre
investigators	63 (67%)	30 (32%)	1 (1%)	13 (46%)	13 (46%)	2 (7%)
Reader 1	44 (47%)	37 (39%)	13 (14%)	11 (39%)	11 (39%)	6 (21%)
Reader 2	20 (21%)	58 (62%)	16 (17%)	7 (25%)	16 (57%)	5 (18%)
Reader 3	54 (57%)	27 (29%)	13 (14%)	13 (46%)	8 (29%)	7 (25%)
Reader 4	32 (34%)	49 (52%)	13 (14%)	11 (39%)	10 (36%)	7 (25%)

Sponsor's outcome variable for this analysis is the difference in the number of patients whose pre dose images were more obscured than the post dose images. This difference is statistically significant (pre more obscured than post > post more obscured than pre) for the investigators (p=0.0001) and for reader #1 (p=0.0001), for readers 3 (p=0.0001) and reader 4 (p=0.0066) For reader4 #2 the difference is NS

Reviewer's comment: It should be noted that all readers found a higher percentage of SonoRx images with the pre dose image more obscured than post dose images, than with the post dose images more obscured than the pre dose images. The difference is statistically significant for readers 1, 3 and 4 and for the investigators. However the same is true for the placebo images. These results could be interpreted as supporting the conclusion that SonoRx is effective in reducing gas shadowing but no more effective than the placebo (from which the claimed active ingredient, simethicone coated cellulose, has been excluded).