

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20773

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-773

OCT 29 1998

Bracco Diagnostics Inc.
Attention: Madhu Anant
Associate Director, Regulatory Affairs
P.O. Box 5225
Princeton, NJ 08543-5225

Dear Ms. Anant:

Please refer to your new drug application (NDA) dated April 29, 1998, received April 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoRx (simethicone coated cellulose suspension) aqueous suspension .

We acknowledge receipt of your submissions dated October 8, November 5, 1997, December 4 and 17, 1997, April 29, September 28, October 8, 26, 27 (via facsimile), and 28 (via facsimile) 1998 . Your submission of April 29, 1998 constituted a full response to our September 30, 1997, action letter. The user fee goal date for this application is October 31, 1998.

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.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-773." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your fax dated October 28, 1998. This commitment, along with any completion dates agreed upon, is listed below.

"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".

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Rubynell Jordan, Consumer Safety Officer, at (301) 443-1560.

Sincerely,

/S/

Patricia Y. Love, M.D., M.B.A.

Director

Division of Medical Imaging and Radiopharmaceutical
Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVABLE LETTER



Div

Food and Drug Administration
Rockville MD 20857

NDA 20-773

SEP 30 1997

Bracco Diagnostics Inc.
P.O. Box 5225
Princeton, NJ 08543-5225

Attention: Madhu Anant
Senior Manager, Regulatory Affairs

Dear Ms. Anant:

Please refer to your new drug application dated September 30, 1996, received September 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SonoRx[®] (simethicone-coated cellulose suspension).

We acknowledge receipt of your submissions dated January 15, April 29, June 12 and 23, July 3 and 17, August 14 and 26, and September 2, 8, and 11, 1997. We also refer to your June 3 and September 5, 1997, telephone conferences with this Division. The User Fee goal date for this application is September 30, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Deficiencies were noted in the chemistry, clinical, and statistical sections of the application. The deficiencies may be summarized as follows:

I. CHEMISTRY, MANUFACTURING , AND CONTROLS (CMC)

A. DRUG SUBSTANCE

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 [] 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.

B. DRUG PRODUCT

1. The methodology lacks a specification and in process controls to document []

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.

2. The application lacks a description and validation on the method for container evaluation. (This is a particularly critical deficiency because of the reported failures in the cap liners, and the resulting oxidation of the []

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.

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.
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.
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.
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.

C. ESTABLISHMENT INSPECTION DEFICIENCIES

During recent inspections of the manufacturing facilities for your SonoRx NDA, a number of critical deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved. Also, in the resubmission, please include a summary of the corrective actions that were taken to resolve the deficiencies encountered during the inspection of the drug product manufacturing site.

We note that several of the above deficiencies are linked (I.B.2, B.6, B.7 and I.D.) and are particularly critical. These include a) _____ cap liner, b) impurities, c) manufacture of stability lots with caps that were not screened _____ s, and; d) non-validated methods to screen for _____ These deficiencies could be resolved by implementation of a number of CGMP methods.

We acknowledge your commitments to resolve these deficiencies in future stability studies, both in timely data collection and with new closure utilization. Ideally resolutions to these problems should include the acquisition of cap liners that do not have pinholes. Less optimally, (if this is not possible), validated screening and confirmatory tests should be developed that are able to detect _____ accurately, reproducibly, and with sensitivity. Cap liners with _____ could then be identified and not used in the packaging of SonoRx. Once the problems with manufacturing and with the container/closure system have been resolved, stability testing using validated caps and an appropriate sampling protocol should be performed on at least two batches of the drug product.

For a revised application to be considered by the Agency, the resubmission should include a minimum of six months of stability testing (both room-temperature and accelerated storage) on at least two batches of the drug product. These stability data should be derived from batches that are manufactured with the revised methodologies that are developed to address the above deficiencies.

II. CLINICAL AND STATISTICAL

SonoRx was submitted with a proposed indication for

SonoRx's mechanism of action is to decrease gas shadowing (and, thereby, increase the clarity of the acoustically-derived images).

After extensive review of the data and the case report forms from which the data are derived, and a consideration of the clinical trial and statistical concerns stated below, the submitted application appears to support SonoRx's use to decrease gas shadowing in the upper abdomen. The data marginally demonstrate SonoRx's efficacy in delineating anatomy. The data do not sufficiently demonstrate that the SonoRx-enhanced ultrasound images facilitate the detection or the exclusion of pathology. The deficiencies in the analyses of the two principal phase-3 clinical trials (Studies #42,440-3A and #42,440-3B) are summarized as follows.

A. Delineation of Anatomy and Gas Shadowing:

Question 3a of the Blinded Reader Comparison Image Evaluation 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 post-dose images over pre-dose images, one of the responses could be "improved delineation of abdominal anatomy". Responses to this question do provide categorical assessments. However, they do not provide an assessment of the range of improvement, the type of imaging technical features (e.g., sharpness of margins, contour, homogeneity), or the location of the improved features. Thus, responses to this item are potentially useful, but incomplete.

The other question that assesses the delineation of anatomy is Item #1 of the Blinded Reader Comparison Image Evaluation. The question asked for the completion of a table on the delineation of abdominal anatomy in specific abdominal areas (e.g., stomach, gastric wall). However, the possible responses are composites that range from "0 = none (nondiagnostic, cannot identify area of interest, cannot exclude nor detect pathology)" to "4 = excellent (diagnostic image, excellent delineation, high level of confidence in excluding or detecting pathology)". While this question is intended to be supported by the individual questions in #3a, the responses are not mutually exclusive (e.g., it is possible to make a diagnosis or detect pathology despite limited delineation). Therefore, responses to this item are confounded.

Another item of the case report form asks about the degree to which gas obscures the image (item #2 of the blinded reader Comparison Image Evaluation). Responses to this item provide acceptable data.

In addition, item #15 on the Blinded Readers' case report from study #42-440-7 requests information on the impact of gas-shadowing artifacts in specific abdominal anatomic areas on post-SonoRx and post-water images. This item provides acceptable supportive data.

B. Detection of Pathology, Exclusion of Pathology, the Evaluation of the Extent of Disease or Pathology, and the Impact of the Information on Patient Management or Therapy.

The studies lacked adequate "standards of truth" by which the interpretation of pathologic findings could be validated, and the studies did not ensure that these standards were applied consistently. Instead, for purposes of analysis, the diagnostic assessments performed by the investigator were utilized de facto as standards of truth. Hence, across subjects, neither the adequacy of the standard of truth for a particular condition nor its consistent application was ensured. Likewise for the impact on patient management or therapy, the assessments need confirmation that the decisions are clinically appropriate.

C. Clinical Trials and Statistics

There are a number of confounding issues that affected the assessment of pathology that are reflected in the sensitivity and specificity results. Resolving these will not, however, overcome the lack of adequate standards of truth. These issues are listed for completeness.

1. The procedures used to identify diagnostic "matches" or "mismatches" were not adequate to minimize the effects of possible biases on the values obtained for sensitivity and specificity. Specifically, independent blinded reviewers were not used to determine whether the diagnoses (i.e., pathology) made from the SonoRx images and the diagnoses made from other modalities constituted a match or not.
2. The values of sensitivity obtained by the blinded image evaluations in Studies #42,440-3A and #42,440-3B were not consistent between the two studies. In the comparison of the images obtained after SonoRx administration to those obtained before SonoRx administration, the values for sensitivity showed a slight increase in Study 42,440-3B, whereas they either decreased or did not change in Study 42,440-3A.
3. The values of specificity obtained by the blinded image evaluation in Studies #42,440-3A and #42,440-3B were based on the evaluation of images from an insufficient number of subjects (i.e., 9 patients and 10 patients, respectively) to draw reliable conclusions.

4. The analyses used to determine sensitivity and specificity were incomplete. Sensitivity and specificity were calculated only with data from the "per protocol" subset of subjects, and not with data from other sets of interest (e.g., a true intent-to-treat analysis) and not with data imputed to test whether the calculated values are robust (e.g., a "worst-case" analysis).
5. The analyses used to evaluate the response rate for the primary endpoint were incomplete. A substantial number of subjects were excluded from these analyses. Although some analyses of the response rate were performed with "worst-case" data imputed to test whether the results were robust, these analyses 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.
6. The results of the "intent-to-treat" analysis of the blinded image evaluation were highly variable. The lower limits of the confidence interval ranged from about 11% to 97% in Study 42,440-3A (Blinded Readers #4 and #2, respectively) and from about 32% to 62% in Study 42,440-3B (Blinded Readers #2 and #3, respectively). Similarly, in the per-protocol analysis, values of the Kappa statistic for agreement between the blinded readers were not far from what is expected under chance agreement alone.

Therefore, when the NDA for SonoRx is resubmitted, please include a revised Indication and Clinical Trials labeling that focuses on the data for reduction of the gas shadowing artifact in the upper abdomen. 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. Please include a worst case analysis of the intent-to-treat analysis of these data (i.e, include all patients enrolled, include all patients who received study drug, include all patients whose images were excluded for technical inadequacy, etc.). Also, for all images that were judged to be technically inadequate and were not forwarded to the blinded readers, please provide the number that were technically inadequate before SonoRx administration, after SonoRx administration, or both. Similar information should be provided for the images that the blinded readers found to be technically inadequate. It might be possible to expand the indication for SonoRx if a blinded re-evaluation of the images is performed that captures information of the technical features that support the blinded readers' interpretations.

Final labeling will not be considered until the NDA for SonoRx is otherwise approvable; however, the following comments are offered for your consideration.

1. The application does not provide adequate pre-clinical or clinical evidence that the activity of the SonoRx is solely due to simethicone-coated cellulose. Although phantom studies suggest that the acoustic properties of simethicone-coated cellulose are optimized with median fiber lengths of approximately 22 microns, the simethicone-coated cellulose may not be the only, or even the most important, factor that determines the activity of the drug product. The unbound simethicone and the vehicle of the product (water) may also contribute substantially to the drug's activity. Additionally, the vehicle controls used in the clinical studies eliminated simethicone-coated cellulose, simethicone, xanthan gum, and sodium lauryl sulfate.
- If you wish to claim that simethicone-coated cellulose is the "active ingredient" of SonoRx, additional preclinical and clinical studies should be conducted to establish the relative contributions of the simethicone-coated cellulose, free simethicone, and water to the overall clinical activity of the drug.
- If not, then references in the package insert that state or imply that simethicone-coated cellulose is the "active ingredient" should be modified to indicate that the unbound simethicone and the vehicle of the product may contribute to the drug's activity.

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

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update any resubmission to the NDA by submitting all safety information you then have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of any NDA resubmission. In addition to the format used in your initial submission, this should include analyses and composite summary tables of all subjects who received SonoRx in any clinical trial (e.g., pooled data for the entire NDA database, not just the phase 2 & 3 trials). These tables should reflect full demographic data and adverse event by subgroups, including by body size and dose ingested. Tables comparing adverse reactions at the time the NDA was submitted versus the updated information will facilitate review.
2. Similarly, retabulate the exposure data by dose of SonoRx received. As above, this should include analyses and composite summary tables of all subjects who received SonoRx in any clinical trial (i.e., pooled data for the entire NDA database, not just for the phase 2 & 3 trials).
3. Fully characterize adverse events related to the gastrointestinal system (e.g., diarrhea, nausea, vomiting) with regards to their duration, onset, severity, seriousness, etc. Please provide an analysis of these adverse events by the dose ingested and by body size.
4. Similarly, please fully characterize any episodes of aspiration or possible aspiration. Please provide an analysis of these adverse events by the dose ingested and by body size.
5. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.
6. Provide details of any significant changes or findings, if any.
7. Summarize worldwide experience on the safety of this drug.
8. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug applications with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including (1) those involving indications not being sought in the present submission; (2) other dosage forms, and; (3) other dose levels, etc.

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Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Rubynell Jordan, Consumer Safety Officer, at (301) 443-1560.

Sincerely yours, 


Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research