

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20773

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-773

SUBMISSION DATE: 07/17/97

SIMETHICONE COATED CELLULOSE
SONORX®

BRACCO DIAGNOSTICS, INC.
P.O. BOX 2552
PRINCETON, NJ 08543-5225

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL SUBMISSION CODE 3S

SYNOPSIS/BACKGROUND

This amendment to NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) was submitted by the sponsor on July 17, 1997. 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.

This amendment contains the sponsor's response to the Agency's request for additional information on the pharmacokinetic evaluation of SonoRx® that were needed to complete the review of the original NDA. The reviewer's desk copy of this amendment was reviewed along with the originally submitted NDA and its contents were taken into consideration in the Recommendation that was made in this review. Accordingly, no further action related to this amendment is necessary.

RECOMMENDATION

The amendment to NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) submitted by the sponsor on July 17, 1997 has been reviewed by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics. Since the contents of this amendment have already been reviewed and taken into consideration in the Recommendation that was made in the review of the original NDA submission, no further action related to this amendment is necessary.

/S/ 09/24/97
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee, Ph.D.
FT Initialed by David Lee, Ph.D.

/S/ 9/25/97
/S/ 9/25/97

cc: NDA 20-773, HFD-160, HFD-160 (Jordan), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, and Udo), CDR (Attn: Barbara Murphy).

Jordan
AUG - 5 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-773

SUBMISSION DATE: 09/30/96

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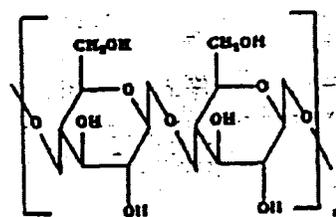
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SYNOPSIS/BACKGROUND

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. In the **Dosage and Administration** section of the package insert, it is stated that **"the minimum recommended dose of SonoRx[®] is 400 mL"**. The sponsor states that this dose was selected because in the Phase II clinical trials, **a greater degree of image contrast enhancement was obtained with SonoRx[®] doses** as compared to the other tested doses

The active ingredient of SonoRx[®] is simethicone coated cellulose (7.5 mg/mL [0.25% simethicone]). SonoRx[®] also contains free simethicone, USP (0.2 mg/mL). Therefore, the recommended minimum dose of SonoRx[®] (400 mL) contains mg of simethicone (7.5 mg as cellulose coating and 80 mg as free simethicone, USP) and approximately g g) of cellulose. In the NDA, it is stated that SonoRx[®] contains the crystalline form of cellulose (manufactured from wood). It is further stated that unlike the microfibril form of cellulose present in vegetables and ripe fruits, the crystalline form of cellulose is not digested by the bacteria in the large bowel. In the **Clinical Pharmacology section of the package insert**, it is stated that following SonoRx[®] administration, (i) simethicone acts to reduce the surface tension of gas bubbles in the bowel lumen thereby causing them to coalesce, (ii) cellulose acts to create uniform echogenicity within the bowel lumen and (iii) these actions of simethicone and cellulose culminate in improved transmission of the ultrasound beam and ultrasound images that are free of shadowing artifacts.

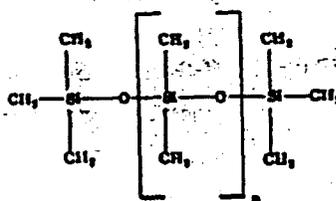
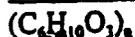
The structures of simethicone and cellulose are presented below.



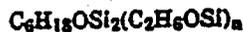
Cellulose



Molecular Formula



Simethicone



Molecular Formula



The information presented in the next three paragraphs was not provided in the NDA. It has been obtained, by this reviewer, from the literature and/or the labeling of approved oral agents containing the same or similar active ingredients as SonoRx[®] in order to have sufficient grounds to make a rational approval related recommendation on the NDA.

Simethicone, USP (that is used in SonoRx[®]), a mixture of dimethicones and silicon dioxide with a molecular weight between 14,000 and 21,000, is a translucent, gray, viscous fluid. It is used as an oral antifoaming agent in gastroscopy. It is also used as an antiflatulent and as a releasing agent in some pharmaceutical preparations. Silicon (all forms considered) ranks second only to oxygen in abundance

in the earth's crust. Maalox Plus[®], an approved oral antacid/antigas agent 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. This is higher than the amount of simethicone (87.5 mg) in a single dose of SonoRx[®].

Citrucel[®], an FDA approved bulk forming laxative contains 2 g of methylcellulose per dose and can be taken three times per day (a maximum daily dose of 6 g of methylcellulose). Another approved, fiber laxative, Matamucil[®] (containing 3.4 g of 95% psyllium husk per dose) is recommended to be taken three times per day (i.e., 9.7 g psyllium husk daily). Thus, the recommended dose of cellulose (3 g) in SonoRx[®] is less than the amount of fiber present in the daily dose of each of these approved, fiber laxatives. The onset of fecal elimination of Citrucel[®] and Matamucil[®] is 12-72 h postdose.

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. Mammals do not have cellulases, the enzymes that digest cellulose. Cellulose is not likely to be absorbed passively from the gut due to its large molecular size. Therefore, it is reasonable to expect that following the administration of SonoRx[®] to patients, its cellulose component would be eliminated in feces.

In this NDA, the sponsor submits two, placebo-controlled, pharmacokinetic studies in which the safety and potential bioavailability of SonoRx[®] were evaluated in 15 patients with impaired bowel motility or impaired bowel mucosa (Protocol 42,440-5) and in 10 healthy subjects (Protocol 42,440-06). The to-be-marketed SonoRx[®] formulation was used in these studies and in the Phase III clinical studies. In the pharmacokinetic studies, blood and urine samples were analyzed by

The analytical methods were specific for silicon (the surrogate marker for simethicone). The minimum quantifiable limit (MQL) of silicon was $\mu\text{g/mL}$ for blood and $\mu\text{g/mL}$ for urine. The weight of the dietary fiber (pre-dose) or dietary fiber plus the cellulose component of SonoRx[®] (postdose) eliminated in feces was determined following acid digestion, filtration, drying.

In healthy subjects (Protocol 42,440-6) and in patients with impaired bowel motility or impaired bowel mucosa (Protocol 42,440-5), significant silicon levels were observed pre-dose and postdose in healthy subjects/patients treated with SonoRx[®] or placebo (see pages 3-7). Therefore, in this review, it was concluded that the silicon levels observed in the SonoRx[®] treated healthy subjects/patients could be partially or totally from sources other than simethicone. Thus, these silicon levels were not considered a reliable indicator of absorption of the simethicone component of SonoRx[®]. The frequency at which silicon was detected in blood or urine in both studies would not allow for an accurate evaluation of its kinetics.

In healthy subjects as well as in bowel impaired patients, the onset of fecal elimination of SonoRx[®] (Day of dosing to Day 3 postdose in patients with impaired bowel motility or impaired bowel mucosa and Day 2 postdose to Day 3 postdose in individuals with normal bowel function) was similar to the elimination onset of 12-72 h postdose stated for Citrucel[®] or Matamucil[®] in the drug product labeling. Based on the limited data obtained in the submitted pharmacokinetic studies, the rate of elimination of dietary fiber (pre-dose) or dietary fiber plus SonoRx[®] (postdose) was lower in patients with impaired bowel motility or impaired bowel mucosa as compared to healthy subjects.

From a clinical pharmacokinetic perspective, the NDA is considered approvable.

II. SUMMARY OF INFORMATION ON BIOAVAILABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, DRUG-DRUG INTERACTIONS, ETC.

1. **BIOAVAILABILITY OF SIMETHICONE:** Two placebo-controlled studies (Protocol 42,440-6 [in healthy subjects, n=10] and Protocol 42,440-05 [in patients with impaired bowel motility or impaired bowel mucosa, n=15]) were conducted to evaluate the potential bioavailability of SonoRx®. The design of these studies is presented on page 16. In each study, 3 subjects/patients were treated with a control agent (placebo). The analytical methods were specific for silicon, the surrogate marker of simethicone (MQL = $\mu\text{g/mL}$ for urine and $\mu\text{g/mL}$ for blood). In Protocol 42,440-5, a total of 18 patients were dosed (see page 19). However, Patients 122 (SonoRx® treated), 123 (placebo treated) and 125 (placebo treated) were not evaluated due to withdrawal of consent after dosing (Patient 125) and positive drug screen results (Patients 122 and 123).

In Protocol 42,440-6, silicon was observed in the blood of 2 of 7 SonoRx® treated subjects pre-dose $\mu\text{g/mL}$, 4 of 7 SonoRx® treated subjects postdose $\mu\text{g/mL}$, 1 of 3 placebo treated subjects pre-dose $\mu\text{g/mL}$ and 2 of 3 placebo treated subjects postdose $\mu\text{g/mL}$ (see Table 1).

In the same study (Protocol 42,440-6), silicon was also observed in the urine of 3 of 7 SonoRx® treated subjects pre-dose $\mu\text{g/mL}$, 3 of 7 SonoRx® treated subjects postdose $\mu\text{g/mL}$, 1 of 3 placebo treated subjects pre-dose $\mu\text{g/mL}$ and 1 of 3 placebo treated subjects postdose $\mu\text{g/mL}$ (see Table 2).

In Protocol 42,440-5, silicon was observed in the blood of 1 of 12 SonoRx® treated patients pre-dose $\mu\text{g/mL}$ and 4 of 12 SonoRx® treated patients postdose $\mu\text{g/mL}$. Silicon was not detected in the blood of any placebo treated patients (see Table 3).

In the same study (Protocol 42,440-5), silicon was observed in the urine of 11 of 12 SonoRx® treated patients pre-dose $\mu\text{g/mL}$, 10 of 12 SonoRx® treated patients postdose $\mu\text{g/mL}$, 3 of 3 placebo treated patient pre-dose $\mu\text{g/mL}$ and 1 of 3 placebo treated patients postdose $\mu\text{g/mL}$ (see Table 4).

In each study (Protocol 42,440-6 or Protocol 42,440-5), for the SonoRx® treated healthy subjects/patients, the pre-dose and postdose blood or urine silicon levels were comparable. Furthermore, the postdose silicon levels in the blood and urine of the SonoRx® treated healthy subjects/patients were comparable to those in the blood of the placebo treated subjects. These findings suggest that the silicon observed in the SonoRx® treated healthy subjects/patients could be partially or totally from sources other than SonoRx®. Thus, these silicon levels were not considered a reliable indicator of absorption of the simethicone component of SonoRx®. Based on literature information, silicon (all forms considered) ranks second only to oxygen in abundance in the earth's crust. Therefore, "other sources" of the silicon observed in the blood and urine of the healthy subjects/patients in these studies could include some components of the drug formulation (e.g. water) and meals that were served to the healthy subjects/patients prior to and during the studies.

2. **PHARMACOKINETICS OF SIMETHICONE:** The individual subject blood and urinary excretion profiles of silicon in Protocols 42,440-6 and 42,440-5 were not adequate for a pharmacokinetic evaluation of silicon.

TABLE I
WHOLE BLOOD SILICON ($\mu\text{g/mL}$)

	Pre-dose						Post-dose									
<i>SonoRx</i> [®] Subjects	Day -5	Day -4	Day -3	Day -2	Day -1	-0.5 hr.	+0.25 hr.	+0.5 hr.	+1 hr.	+2 hr.	+3 hr.	+6 hr.	+10 hr.	+15 hr.	Day +2	Day +3
Sb. 101																
Sb. 102																
Sb. 104																
Sb. 105																
Sb. 108																
Sb. 109																
Sb. 110																
<i>Control Agent Subjects</i>																
Sb. 103																
Sb. 106																
Sb. 107																

-- = Below the minimum quantifiable limit of 5.3 $\mu\text{g/mL}$.

X = No sample submitted.

|| = Dosing point.

TABLE 2

TOTAL URINE COLLECTED AND CONCENTRATION OF URINARY SILICON ($\mu\text{g/mL}$)

SonoRx® Subjects	Pre-dose										Post-dose									
	Day -5		Day -4		Day -3		Day -2		Day -1		Day +1								Day+2/Day+3	
	Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	+0-1 hr.	+1-3 hr.	+3-6 hr.	+6-24hr.	≥ +24 hr./+48 hr.					
Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc			
Sb. 101																				
Sb. 102																				
Sb. 104																				
Sb. 105																				
Sb. 108																				
Sb. 109																				
Sb. 110																				
Control Agent Subjects																				
Sb. 103																				
Sb. 106																				
Sb. 107																				

^a = Total urine collected by volume (mL).
^b = Concentration of silicon in urine ($\mu\text{g/mL}$).
 — = Below quantifiable limit of 2.65 $\mu\text{g/mL}$.
 X = No sample submitted.
 || = Dosing point

TABLE 3

WHOLE BLOOD SILICON ($\mu\text{g/ml.}$)

SonoRx® Patients	Pre-dose						Post-dose									
	Day -5	Day -4	Day -3	Day -2	Day -1	-0.5 hr.	+0.25 hr.	+0.5 hr.	+1 hr.	+2 hr.	+3 hr.	+6 hr.	+10 hr.	+15 hr.	Day +2	Day +3
Pt. 102																
Pt. 104																
Pt. 105																
Pt. 111																
Pt. 112																
Pt. 114																
Pt. 116																
Pt. 120																
Pt. 128																
Pt. 203																
Pt. 204																
Pt. 205																
<i>Control Agent Patients</i>																
Pt. 107																
Pt. 117																
Pt. 202																

— = Below the minimum quantifiable limit of 5.3 $\mu\text{g/ml.}$
 X = No sample submitted
 || = Dosing point

6
205

TABLE 4

TOTAL URINE COLLECTED AND CONCENTRATION OF URINARY SILICON ($\mu\text{g/mL}$)

SonoRx® Patients	Pre-dose										Post-dose									
	Day -5		Day -4		Day -3		Day -2		Day -1		Day +1								Day +2 /Day +3	
	Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	+0-1 hr.	+1-3 hr.	+3-6 hr.	+6-24hr.	≥ +24 hr./+48 hr.					
Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc			
Pt. 102																				
Pt. 104																				
Pt. 105																				
Pt. 111																				
Pt. 112																				
Pt. 114																				
Pt. 116																				
Pt. 120																				
Pt. 128																				
Pt. 203																				
Pt. 204																				
Pt. 205																				

^a = Total urine collected by volume (mL).
^b = Concentration of silicon in urine ($\mu\text{g/mL}$).
 -- = Below quantifiable limit of 2.65 $\mu\text{g/mL}$.
 X = No sample submitted.
 || = Dosing point.

TABLE 2

TOTAL URINE COLLECTED AND CONCENTRATION OF URINARY SILICON ($\mu\text{g/mL}$)

Control Agent Patients	Pre-dose										Post-dose									
	Day -5		Day -4		Day -3		Day -2		Day -1		Day +1								Day +2 /Day +3	
	Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	+0-1 hr.	+1-3 hr.	+3-6 hr.	+6-24hr.	≥ +24 hr./+48 hr.					
Vol ^a	Conc ^b	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc	Vol	Conc			
Pt. 107																				
Pt. 117																				
Pt. 202																				

^a = Total urine collected by volume (mL).
^b = Concentration of silicon in urine ($\mu\text{g/mL}$).
 -- = Below quantifiable limit of 2.65 $\mu\text{g/mL}$.
 X = No sample submitted.
 || = Dosing point.

3. **FECAL ELIMINATION OF CELLULOSE:** In the submitted pharmacokinetic studies (Protocols 42,440-5 and 42,440-6), for each healthy subjects/patient, fecal elimination of dietary fiber was assessed pre-dose (from Days -5 through Day -1). Elimination of the total fiber ingested (dietary fiber plus 3 g of cellulose from SonoRx[®]) was assessed following SonoRx[®] administration (Days +1 through Day +3). The design of these studies is presented on page 16. For each healthy subject/patient receiving the placebo, fecal elimination of dietary fiber was assessed pre-dose and postdose. The placebo contained no cellulose. The carmine red marker was administered 6 h following the dose of SonoRx[®]/placebo to determine the onset of fecal elimination of SonoRx[®]/placebo.

In Protocol 42,440-6, on Day -5, for each subject, the amount of dietary fiber recovered in feces was less than the ingested amount. These results suggest that a portion of the ingested dietary fiber was retained in the gut. The amounts of dietary fiber recovered in feces were comparable to or greater than the amounts ingested for the day in 4 of 6 subjects evaluated on Day -2 and in 3 of 4 subjects evaluated on Day -1. The amounts of fiber (dietary fiber plus cellulose) recovered in feces were comparable to or greater than the amounts ingested for the day in 2 of 5 subjects evaluated on Day +1 and in 5 of 6 subjects evaluated on Day +2 (see Table 5). These results suggest that ultimately, the presence of SonoRx[®] in the gastrointestinal tract does not adversely affect the elimination of dietary fiber. Based on the presence of the carmine red marker in feces, the onset of SonoRx[®] elimination was on Day 2 postdose for 4 of 7 subjects and on Day 3 postdose for 2 of 7 subjects. In one subject, SonoRx[®] was not eliminated in feces during the study. The onset of placebo elimination was on Day 2 postdose for 1 of 3 placebo treated subjects and on Day 3 postdose for the other 2 placebo treated subjects.

For the patients with impaired bowel motility or impaired bowel mucosa receiving SonoRx[®] or placebo (Protocol 42,440-5), except for Patient 104 (Day +1) and Patient 111 (Day +2), for each day of the study, the amount of fiber recovered in feces was lower as compared to the total amount of fiber ingested for the day (see Table 6). These results suggest that rate of fecal elimination of dietary fiber or the cellulose component of SonoRx[®] is lower in patients with impaired bowel motility or impaired bowel mucosa as compared to individuals with normal bowel function. The onset of SonoRx[®] elimination was on Day 1 postdose for 4 of 12 patients, on Day 2 postdose for 3 of 12 patients, on Day 3 postdose for 1 of 12 patients. In 4 SonoRx[®] treated patients, SonoRx[®] was not eliminated in feces during the study. The onset of placebo elimination was on Day 2 for 1 of 3 patients and on Day 3 for 1 of 3 patients. In 1 placebo treated patient, the placebo was not eliminated in feces during the study.

Patient #112 (Day -5 dietary fiber intake of 2.8 g versus fecal fiber output of 28.51 g) and Subject 103 (Day -5 dietary fiber intake of 11.08 g versus fecal fiber output of 16.92 g) had high amounts of dietary fiber prior to the beginning of the study. Thus, for these individuals, pre-study fiber intake contributed more significantly to the fecal fiber output observed in the studies as compared to the other healthy subjects/patients.

The onset of SonoRx[®] elimination in healthy subjects (Day 2 to Day 3 postdose) or in patients with impaired bowel motility or impaired bowel mucosa (Day of dosing to Day 3 postdose) is similar to the elimination onset of 12-72 h postdose stated for the approved fiber laxatives, Citrucell[®] and Matamucil[®] in the drug product labeling. These results suggest that SonoRx[®] is similar to Citrucell[®] and Matamucil[®] in onset of elimination.

Table 5

Intake and Fecal Excretion of Fiber in Normal Subjects Administered SonoRx[®] or Placebo

Protocol No: 42,440-6

	Pre-dose														
	Day -5			Day -4			Day -3			Day -2			Day -1		
	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c
<i>SonoRx[®] Subjects</i>															
101															
102															
104															
105															
108															
109															
110															
<i>Placebo Subjects</i>															
103															
106															
107															

	Post-dose								
	Day +1 ^a			Day +2			Day +3		
	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c
<i>SonoRx[®] Subjects</i>									
101									
102									
104									
105									
108									
109									
110									
<i>Placebo Subjects</i>									
103									
106									
107									

a - On the first day of dosing, the total intake of fiber equals the dietary cellulose plus 3 g of cellulose from SonoRx[®]

b - The day carmine fecal marker was excreted c - Fecal fiber/intake fiber

NS - No sample (sample not collected, not provided, or missing)

Table 6

Intake and Fecal Excretion of Fiber in Impaired Bowel Patients Administered SonoRx[®] or Placebo

Protocol No: 42,440-15

	Pre-dose														
	Day -5			Day -4			Day -3			Day -2			Day -1		
	Intake	Feccs	FF/IF ^c	Intake	Feccs	FF/IF ^c	Intake	Feccs	FF/IF ^c	Intake	Feccs	FF/IF ^c	Intake	Feccs	FF/IF ^c
<i>SonoRx[®] Subjects - Patients</i>															
102															
104															
105															
111															
112															
114															
116															
120															
128															
203															
204															
205															
<i>Placebo Subjects</i>															
107															
117															
202															

NS - No sample (sample not collected, not provided, or missing)

c - Fecal fiber/intake fiber

Table 6
continued

Intake and Fecal Excretion of Fiber in Impaired Bowel Patients Administered SonoRx® or Placebo

Protocol No: 42,440- 5

	Post-dose											
	Day +1 ^a			Day +2			Day +3			Day +4		
	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c	Intake	Feces	FF/IF ^c
<i>SonoRx® Patients</i>												
102												
104												
105												
111												
112												
114												
116												
120												
128												
203												
204												
205												
<i>Placebo Patients</i>												
107												
117												
202												

a - On the first day of dosing, the total intake of fiber equals the dietary cellulose plus 3 g of cellulose from SonoRx®

b - The day carmine fecal marker was excreted c - Focal fiber/intake fiber

NS - No sample (sample not collected, not provided, or missing)

4. **METABOLISM:** No studies were conducted to evaluate the metabolism of SonoRx®. Based on the findings of Protocols 42,440-5 and 42,440-6, it could not be established that SonoRx® is significantly absorbed from the gut. Furthermore, SonoRx® contains the crystalline form of cellulose which is not likely to be metabolized in the gut. Therefore, further studies to evaluate the metabolism of SonoRx® are not necessary.

5. **PLASMA PROTEIN BINDING:** No studies were conducted to evaluate the plasma protein binding of SonoRx®. In the submitted pharmacokinetic studies (Protocols 42,440-5 and 42,440-6), it has not been established that SonoRx® is significantly absorbed from the gut. Therefore, further studies to evaluate the plasma protein binding of SonoRx® are not necessary.

6. **FOOD EFFECT:** No studies were conducted to evaluate the effect of food on the disposition of SonoRx®. Such studies are not necessary since abdominal ultrasound is usually performed in fasted patients.

7. **GENDER DIFFERENCES:** In the submitted pharmacokinetic studies (Protocols 42,440-5 and 42,440-6), it has not been established that SonoRx® is significantly absorbed from the gut. Therefore, an evaluation of gender differences in SonoRx® bioavailability and kinetics was not feasible.

8. **SPECIAL POPULATIONS:**

(a) **Patients with Impaired Bowel:** The potential bioavailability of the package insert dose of SonoRx® (400 mL) was evaluated in 12 patients with impaired bowel motility or impaired bowel mucosa (Protocol 42,440-5). Like in the healthy subjects (Protocol 42,440-6), absorption of the simethicone component of SonoRx® could not be established. The cellulose component of SonoRx® was eliminated in feces. Based on the limited data obtained in Protocols 42,440-5 and 42,440-6, it was concluded that these patients were similar to healthy subjects in onset of SonoRx® elimination but had a lower rate of SonoRx® elimination.

(b) **Pediatric Patients:** Studies have not been conducted to assess the disposition of SonoRx® in pediatric patients. In the proposed package insert, it is stated that "the safety and effectiveness of SonoRx® in children have not been established".

9. **DRUG-DRUG INTERACTIONS:** Potential interactions of SonoRx® with drugs that could increase gastric motility and accelerate its fecal elimination have not been conducted. In the package insert, it is recommended that "abdominal ultrasound imaging begin immediately after dosing". Therefore, it appears that an early onset of SonoRx® elimination would not significantly affect its efficacy. Since drugs that decrease bowel motility would increase the bowel residence time of SonoRx® thereby enlarging the imaging time window, it appears that such drugs would not adversely affect the efficacy of SonoRx®. Subsequently, studies to investigate potential interactions of SonoRx® with drugs that could increase or decrease bowel motility are considered unnecessary.

10. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONS: SonoRx® is administered for local effect in the gastrointestinal tract. In the proposed package insert, it is recommended that **imaging be performed immediately following the administration of SonoRx®** suggesting that this is when images of the best quality are obtained. In the Adverse Events section of the proposed package insert, it is stated that in a total population of 385 normal healthy subjects and patients treated with SonoRx®, the following adverse events were observed in at least 1% of the study population (for each adverse event, the actual percentage of study population affected is stated in parentheses): headache (1.8%), abdominal pain (2.0%), back pain (1.0%), diarrhea (5.4%), eructation (1.0%), nausea (3.4%) and vomiting (2.1%). Adverse events that occurred in less than 1% of the study population are also listed in this section of the package insert. The percentage of each adverse event occurring in each sub-population (normal healthy subjects or patients) was not provided.

11. SAMPLE ANALYSIS: See Appendix I (page 17) and Appendix II (pages 21-22).

12. PHARMACOKINETIC ANALYSIS: See Appendix I (page 17).

13. FORMULATION: The compositions of SonoRx® and the placebo are presented below. Both formulations were similar in composition except that unlike SonoRx®, the placebo did not contain cellulose, simethicone, xanthan gum and sodium lauryl sulfate.

SonoRx® Formulation:

<u>Component</u>	<u>grams/L</u>
22-micron cellulose with 0.25% simethicone coating	7.5
Xanthan gum, NF	
Medical anti-foaming agent A (simethicone, USP)	
Sodium lauryl sulfate, NF	
Citric acid, USP	
Orange oil Florida-type	
FD and C Yellow #6	
Fructose, USP	
Sodium benzoate (preservative), NF	
Purified water, USP	

Control Agent Formulation:

<u>Component</u>	<u>grams/L</u>
Citric acid, USP	7.5
Orange oil Florida-type	
FD and C Yellow #6	
Fructose, USP	
Sodium benzoate (preservative), NF	
Purified water, USP	

III LABELING COMMENT

1. In the **Dosage and Administration** section of the proposed package insert, the following is stated:

This statement gives the impression that doses higher than 400 mL can also be administered. If this is the case, then all recommended doses (or the recommended dose range) need to be explicitly stated. If the only recommended dose is 400 mL, then the word "should" should be deleted from the above quoted statement. Furthermore, the exact method of dose administration needs to be stated. If the 400 mL of SonoRx® is to be ingested all at once, it should be so stated. The time over which the whole dose is to be ingested should also be stated. If the dose is to be administered in aliquots that are separated by specific time intervals, then the dose aliquots and the time intervals separating them should be stated in the package insert.

2. Under **Pharmacokinetics-Normal Volunteers**, the following is stated:

This statement should be replaced with the following:

3. Based on the limited data obtained in the pharmacokinetic studies (Protocols 42,440-5 and 42,440-6), it was observed that overall, the rate of fecal elimination of fiber (including the cellulose component of SonoRx®) was lower in patients with impaired bowel motility or impaired bowel mucosa as compared to individuals with normal bowel function. Therefore, in the package insert, following the last sentence under "**Pharmacokinetics - Special Populations**", the following statement should be added:

Under this sub-section, the following statement is made:

This statement should be replaced with the following:

IV. GENERAL COMMENT

In the NDA (Volume 1.15 [page 6.28]) it is stated that Patients 122 and 123 were dosed but were not evaluated in the pharmacokinetic study (Protocol 42,440-5) due to "**positive drug screen results**". Conventionally, drug screen precedes dosing. In this study, were the **drug screen results** received after the subjects had been dosed?

V. RECOMMENDATION

NDA 20-773, for simethicone coated cellulose (SonoRx®) submitted by the sponsor on September 30, 1996, has been reviewed by the Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics. From a clinical pharmacokinetic perspective, the NDA is considered approvable. However, the issue raised in Labeling Comments 1, 2 and 3 (page 14) need to be satisfactorily addressed by the sponsor.

Please convey this Recommendation and Labeling Comments 1, 2 and 3 (page 14), as appropriate, to the sponsor. The General Comment above should be brought to the attention of the reviewing medical officer and may be communicated to the sponsor if he deems it appropriate.

Appendices I and II are retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

/S/ 08/04/97

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by David Lee 07/28/97

FT Initialed by David Lee" */S/* 8/5/97

Clinpharm/Biopharm. Briefing: 08/04/97 at 2.00 p.m. in PKLN Room 13B-17 (Attendees: Chen, M. (HFD-870), Hunt (HFD-870), Lee (HFD-870), Jones A.E. (HFD-160), Yaes (HFD-160))

cc: NDA 20-773, HFD-160, HFD-160 (Jordan), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).

VI. APPENDIX I: SUMMARY OF INDIVIDUAL PHARMACOKINETIC STUDIES

1. PROTOCOL 42,440-6

A. TITLE: A Phase I Safety, Pharmacokinetic Evaluation of SonoRx® in Normal Subjects.

B. PRINCIPAL INVESTIGATOR AND CLINICAL STUDY SITE:

C. ANALYTICAL INVESTIGATOR AND SITE: Fecal and Food Samples:

Serum and Urine Samples:

D. OBJECTIVES: The objective of the study was to establish the pharmacokinetic profile of SonoRx® after a single oral dose of 400 mL in normal subjects.

E. DOSAGE FORM: An aqueous suspension (400 mL) of SonoRx® or control agent (placebo) in a 473 mL vial (see page 13 for SonoRx® and placebo compositions). The to-be-marketed formulation was used for the study. The Lot numbers for SonoRx® and placebo were, 12GX01 and 12GX03, respectively. The batch size of SonoRx® was 500 L ($\geq 13.9\%$ of the commercial size batch [500-3600 L]). The batch size of the placebo was 100 L.

F. DESIGN: 1. TYPE OF STUDY: This was a double blind, randomized, placebo controlled study conducted at a single center.

2. STUDY POPULATION: The study population consisted of 2 white, 2 hispanic and 6 black healthy healthy subjects ($\delta=8$, $\text{♀}=2$), aged 18-40 years and weighing 68.4-99.1 kg. The complete subject demographic data are presented in Appendix II (page 19).

3. FEEDING OF SUBJECTS: Five days prior to drug administration (Study Day 1), each subject was placed on a special, low fiber diet containing a maximum of 10 g of dietary fiber per serving. Each serving was prepared in duplicate. One was served to the subject and the other was stored at -20°C . Any uneaten portion of the served food was also stored at -20°C .

3. DOSAGE AND ADMINISTRATION: On the 6th day of the study (Day +1), the subjects received either 400 mL SonoRx® ($n=7$ [$\delta=5$, $\text{♀}=2$]) or placebo ($n=3$ [$\delta=3$, $\text{♀}=0$]). At 6 h postdose, each subject ingested a carmine red fecal marker as an aid to determining when feces containing SonoRx® or placebo is eliminated.

4. BLOOD SAMPLE COLLECTION: Pre-dose blood samples were obtained at 24 h intervals for 5 days (Days -5 to -1) and within 30 min of dosing on Day +1. Postdose blood samples

were obtained on Day +1 at 15, 30, min, 1, 2, 3, 6, 10, 16 h postdose and, thereafter, at 24 h intervals up to Day +3.

5. **URINE SAMPLE COLLECTION:** Cumulative 24 h urine samples were obtained pre-dose on Days -5, -4, -3, -2 and -1. Postdose urine samples were collected at the following time intervals: 0-1 h, 1-3 h, 3-6 h, 6-24 h and 24-48 h (or as many times points that the subject was able to provide a sample).

6. **FECAL SAMPLE COLLECTION:** Cumulative 24 h fecal samples were obtained beginning from Day -5 and continuing through 72 h postdose.

G. **SAMPLE ANALYSIS:** In both studies (Protocols 42,440-5 and 42,440-6), whole blood and urine samples were analyzed for silicon (the surrogate marker for simethicone) by

The summary of analytical methods provided by the sponsor is presented below. No information was provided on the accuracy of the analytical method. Since the blood or urine silicon levels were not adequate for pharmacokinetic evaluation, re-analysis of data to obtain information on assay method accuracy is not necessary. The blood and urine silicon data are presented on pages 4-7.

Fecal elimination of dietary fiber (pre-dose) and dietary fiber plus the cellulose component of SonoRx® (postdose) was assessed by acid digestion, filtration, drying and weighing. Individual subject/patient dietary fiber intake was determined by analysis of the stored serving duplicate and any uneaten portion of the food that was served. The results are presented on pages 9-11.

IN VIVO ANALYTICAL METHODS SUMMARY

Study Number	Type of Biological Sample	Method	Linear Range (µg/mL)	MQL (µg/mL)	Specificity
42,440-5 42,440-6	Urine	Homogenization, dilution, stabilization → ICP-MS	2.65 - 79.5	2.65	2R _{SI}
42,440-5 42,440-6	Blood	Homogenization, digestion, dilution, stabilization → ICP-MS	5.3 - 65.0	5.3	2R _{SI}
42,440-5 42,440-6	Food	Acid digestion, filtration, drying, determination of cellulose by weight	—	—	—
42,440-5 42,440-6	Feces	Acid digestion, filtration, drying, determination of cellulose by weight	—	—	—

H. **PHARMACOKINETIC ANALYSIS OF SILICON:** The frequency at which silicon was observed in blood and urine (see pages 4-7) in both studies (Protocols 42,440-5 and 42,440-6) would not allow for a pharmacokinetic analysis of SonoRx®.

2. PROTOCOL #42,440-5

Protocol 42,440-5 was similar to Protocol 42,440-6 except for the following:

TITLE: A Phase I Safety, Pharmacokinetic Evaluation of SonoRx® in Patients with Impaired Bowel Motility or Impaired Bowel Mucosa.

STUDY POPULATION: The study population consisted of 14 white and 1 hispanic patients with impaired bowel motility or impaired bowel mucosa ($\delta=7$, $\text{♀}=8$), aged 24-52 years and weighing 51.0-103.8 kg. The complete subject demographic data are presented in Appendix II (page 20).

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ON ORIGINAL**

Pt. No.	Treatment Group	Age	Sex	Race (W,B,H,A,O)	Height	Weight	Inf. Cons. M/D/Y	Exclusion Y/N	Med.Hist.	Med.Hist.	Med.Hist.
									EENT N/A	EENT Describe	Cardiac N/A
101	SonoRx	29	M	W	185.0	72.9	1/4/95	Y	N	n/a	N
102	SonoRx	35	M	H	182.2	74.1	12/28/94	Y	N	n/a	N
103	Control Agent	27	M	H	191.8	99.1	12/28/94	Y	N	n/a	N
104	SonoRx	40	M	W	188.0	85.6	1/5/95	Y	N	n/a	N
105	SonoRx	38	M	B	170.0	79.3	1/4/95	Y	N	n/a	N
106	Control Agent	30	M	B	173.0	70.2	1/5/95	Y	N	n/a	N
107	Control Agent	18	M	B	175.0	68.4	1/5/95	Y	N	n/a	N
108	SonoRx	39	M	B	183.0	85.0	1/5/95	Y	N	n/a	N
109	SonoRx	32	F	B	163.0	74.0	1/5/95	Y	N	n/a	A
110	SonoRx	32	F	B	170.0	69.3	1/4/95	Y	N	n/a	N
111	Not Dosed	29	M	W	170.0	76.0	1/5/95	Y	A	Tonsillectomy	N
112	Not Dosed	25	M	B	180.0	86.5	1/4/95	N	N	n/a	N
113	Not Dosed	30	M	B	166.0	59.0	1/5/95	N	N	n/a	N
114	Not Dosed	29	M	W	176.0	86.4	1/5/95	N	N	n/a	N
115	Not Dosed	32	M	W	125.0	87.5	12/28/94	N	ND	n/a	n/a
116	Not Dosed	27	M	B	127.0	88.0	12/28/94	N	N	n/a	N
117	Not Dosed	27	M	B	177.0	78.6	12/29/94	N	N	n/a	N
118	Not Dosed	33	M	B	181.0	65.5	12/29/94	N	N	n/a	N

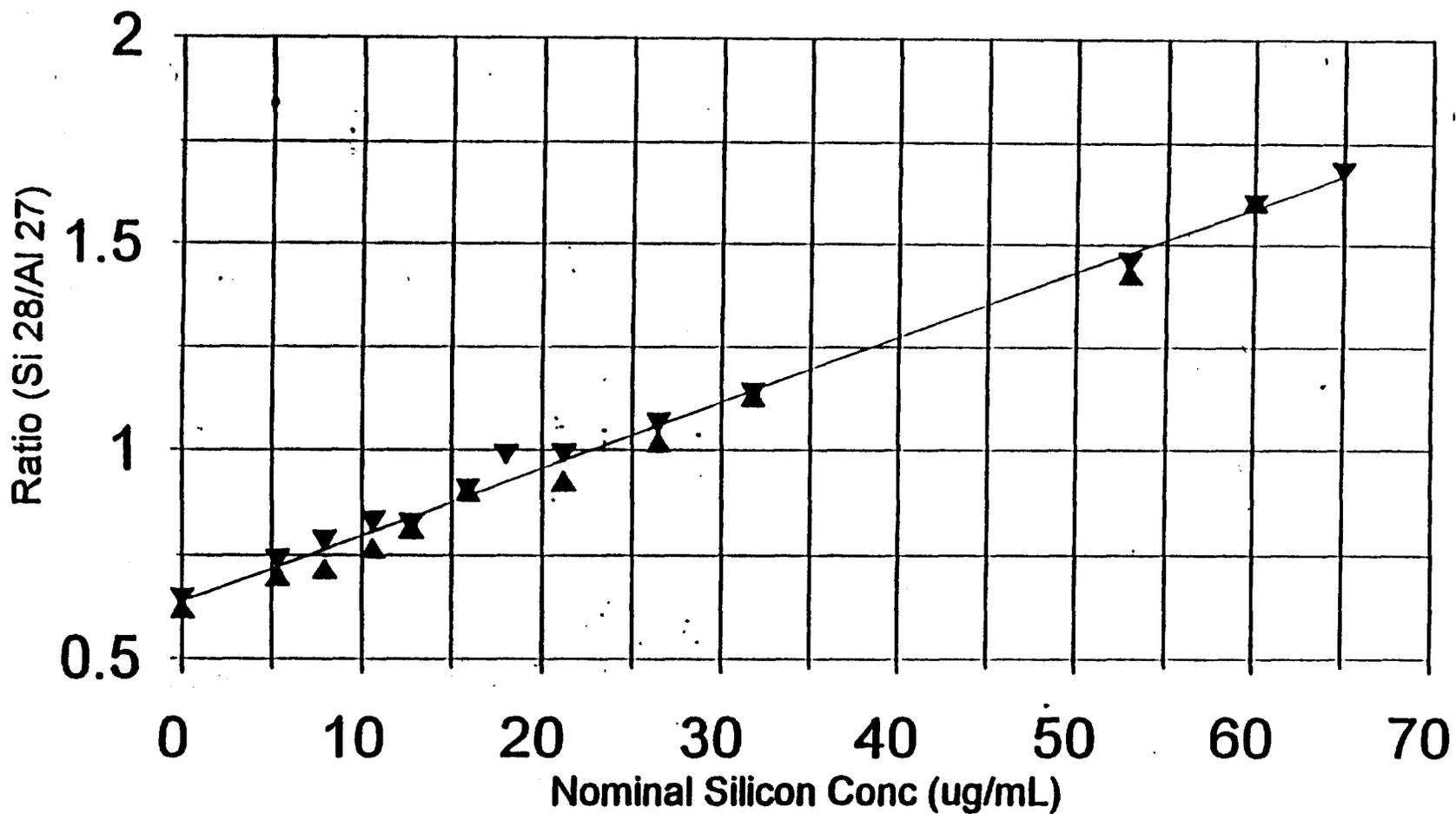
VII. APPENDIX II

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SonoRx Protocol 42,400-5

Patient Number	Treatment	Age	Sex	Race	Height	Weight	Impaired Bowel Motility/Mucosa	Criteria for Diagnosis
		(yrs)			(cms)	(Kg)		
101	Not Dosed	25	M	W	178.0	72.5	Impaired Bowel Mucosa	Colitis
102	SonoRx	37	M	B	184.0	96.5	Impaired Bowel Mucosa	Duodenal Ulcer
103	Not Dosed	41	M	W	182.0	90.7	Impaired Bowel Motility & Mucosa	Duodenal Ulcer & Diarrhea
104	SonoRx	33	F	W	167.5	103.8	Impaired Bowel Mucosa	Chron's Disease
105	SonoRx	31	M	W	172.4	71.0	Impaired Bowel Motility	Diabetes
106	Not Dosed	34	F	W	160.0	78.0	Impaired Bowel Motility	Constipation
107	Control Agent	47	F	W	171.0	60.8	Impaired Bowel Motility & Mucosa	Esophagitis/Gastritis & Diabetes
108	Not Dosed	37	M	B	187.0	109.8	Impaired Bowel Motility	Constipation
109	Not Dosed	26	F	W	ND	ND	Impaired Bowel Mucosa	Irritable Bowel Syndrome
111	SonoRx	37	F	W	159.0	66.2	Impaired Bowel Motility & Mucosa	Ulcerative Colitis/ Constipation
112	SonoRx	40	M	W	181.0	84.0	Impaired Bowel Mucosa	Chron's Disease
113	Not Dosed	43	F	W	162.6	74.4	Impaired Bowel Motility	Constipation
114	SonoRx	45	F	W	162.2	68.0	Impaired Bowel Motility	Chronic Constipation
115	Not Dosed	37	F	W	170.5	64.2	Impaired Bowel Motility	Chronic Constipation
116	SonoRx	24	F	W	166.5	61.5	Impaired Bowel Motility	Chronic Constipation
117	Control Agent	26	M	W	175.3	95.7	Impaired Bowel Motility & Mucosa	Peptic Ulcer Disease/Chronic Constipation
118	Not Dosed	18	M	W	167.0	59.0	Impaired Bowel Mucosa	Chron's Disease
119	Not Dosed	32	M	W	169.0	63.8	Impaired Bowel Mucosa	Ulcerative Colitis
120	SonoRx	37	M	W	172.0	69.7	Impaired Bowel Mucosa	Chron's Disease
121	Not Dosed	22	M	W	180.3	79.8	Impaired Bowel Motility	Chronic Constipation
122	SonoRx	32	F	W	61.5	52.5	Impaired Bowel Motility	Chronic Constipation
123	Control Agent	32	M	H	ND	ND	Impaired Bowel Motility	Chronic Constipation
125	Control Agent	52	F	W	164.0	63.0	Impaired Bowel Mucosa	Chron's Disease
126	Not Dosed	34	F	W	171.0	86.5	Impaired Bowel Mucosa	Irritable Bowel Syndrome
127	Not Dosed	40	F	W	155.0	102.8	Impaired Bowel Mucosa	Duodenal Ulcer
128	SonoRx	47	F	W	162.0	47.7	Impaired Bowel Mucosa	Chron's Disease
201	Not Dosed	49	F	W	160.0	60.5	Impaired Bowel Mucosa	Duodenal Ulcer
202	Control Agent	50	M	W	171.0	92.0	Impaired Bowel Mucosa	Diverticulitis
203	SonoRx	46	F	W	155.0	57.3	Impaired Bowel Mucosa	Ulcerative Colitis
204	SonoRx	39	F	W	173.0	51.0	Impaired Bowel Mucosa	Chron's Disease
205	SonoRx	31	M	W	172.0	65.9	Impaired Bowel Motility	Irritable Bowel Syndrome
206	Not Dosed	42	M	W	172.0	100.2	Impaired Bowel Motility	Irritable Bowel Syndrome

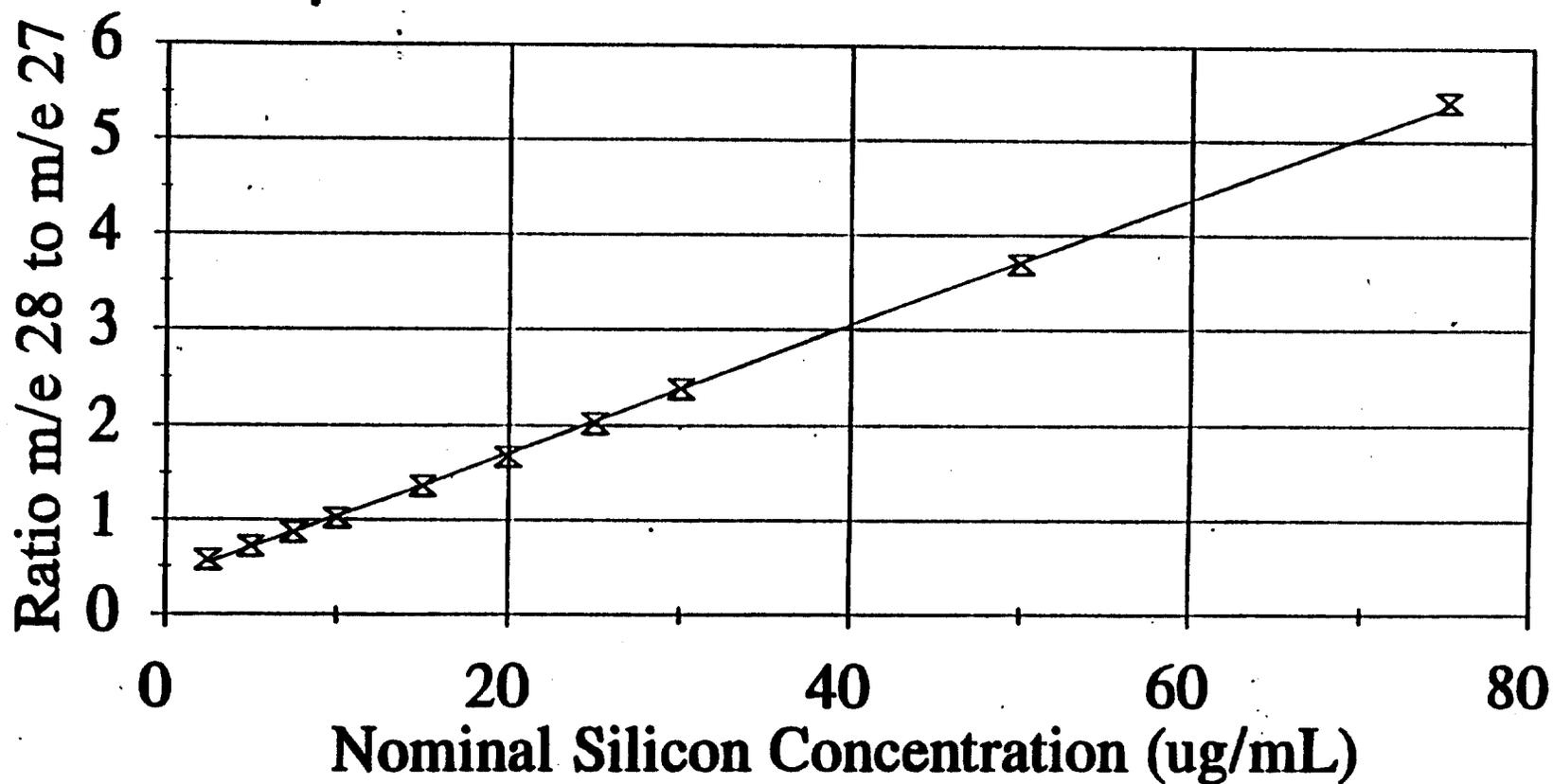
Simethicone in whole blood
ERI File 7392d - March 14, 1995



▼ first curve ▲ second curve — regression line

Silicon In Human Urine

ERI Ref 7217 31Jan95



x Silicon Curve — Regression Line

A. Proposed Text of the Labeling for the Drug—Annotated

Annotated proposed labeling text for SonoRx® (simethicone coated cellulose suspension) is included in this section.

References to the section of this application which support the labeling information have been provided.

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ON ORIGINAL**

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AUG - 5 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-773

SUBMISSION DATE: 07/03/97

SIMETHICOME COATED CELLULOSE
SONORX®

BRACCO DIAGNOSTICS, INC.
P.O. BOX 2552
PRINCETON, NJ 08543-5225

REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: ORIGINAL SUBMISSION CODE 3S

I. SYNOPSIS/BACKGROUND

This amendment to NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) was submitted by the sponsor on July 3, 1997. 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.

This amendment contains the sponsor's response to the Agency's request for additional information on the pharmacokinetic evaluation of SonoRx® that were needed to complete the review of the original NDA. Accordingly, the contents of this amendment were reviewed and taken into consideration in the Recommendation that was made in the review of the original NDA.

RECOMMENDATION

The amendment to NDA 20-773 for Simethicone Coated Cellulose Suspension (SonoRx®) submitted by the sponsor on July 3, 1997 has been reviewed by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics. Since the contents of this amendment have already been reviewed and taken into consideration in the Recommendation that was made in the review of the original NDA submission, no further action related to this amendment is necessary.

/S/ 08/04/97

David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

/S/

8/5/97

/S/

8/5/97

RD Initialed by David Lee
FT Initialed by David Lee

cc: NDA 20-773, HFD-160, HFD-160 (Jordan), HFD-850 (Huang), HFD-870 (M. Chen, Hunt, Lee and Udo), CDR (Attn: Barbara Murphy).