NDA 070848 FIRM :BIOCRAFT 1 OF 1
TRADE NAME :
GENERIC NAME:SUCRALFATE

Summary Basis of Approval
Cover Form

Appl #: 070848 Firm: BIOCRAFT
Reviewing Div: 600
Trade Name:
Generic Name:
SUCRALFATE

Approval Letter:	Y	Statistician Review:	N
SBA Form:	N	Bio/Dissolution Review:	Y
Final Printed Labeling:	Y	Microbiologist Review:	N
Medical Officer Review:	N	NAS/NRC Review:	N
Chemist Review:	Y	Pharmacologist Review:	N
Federal Register Notice:	N	Completion Date:	27-JUL-96

APPROVAL

LETTER

DIV

ANDA 70-848

Biocraft Laboratories, Inc.
Attention: Maurice Bordoni
18-01 Rover Road
P.O. Box 948
Fair Lawn, NJ 07410

Dear Sir:

This is in reference to your abbreviated new drug application dated November 8, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sucralfate Tablets USP, 1 gram.

Reference is also made to your amendments dated April 16 and July 5, 1990, September 28, 1994, August 23, and October 16, 1995 and January 4, and March 19, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sucralfate Tablets USP, 1 gram, to be bioequivalent and, therefore, therapeutically equivalent to those of listed drug (Carafate Tablets, 1 gram, of Blue Ridge Laboratories, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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LABELING

SUCRALFATE TABLETS USP

DESCRIPTION

Sucralfate is an α-D-glucopyranoside, β-D-fructofuranosyl-, octakis-(hydrogen sulfate), aluminum complex.

$R=SO_3[Al_2(OH)_5(H_2O)_7]$

Tablets for oral administration contain 1 gram of sucralfate.

Inactive Ingredients

Corn Starch, Magnesium Stearate and Microcrystalline Cellulose.

Therapeutic Category: antiulcer.

CLINICAL PHARMACOLOGY

Sucralfate is only minimally absorbed from the gastrointestinal tract. The small amounts of the sulfated disaccharide that are absorbed are excreted primarily in the urine.

Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action. The following observations also appear pertinent:

1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site.
2. *In vitro*, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions.
3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32%.
4. *In vitro*, sucralfate adsorbs bile salts.

These observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14-18 mEq of acid-neutralizing capacity per 1-gram dose of sucralfate.

CLINICAL TRIALS

Acute Duodenal Ulcer

Over 600 patients have participated in well-controlled clinical trials worldwide. Multicenter trials conducted in the United States, both of them placebo-controlled studies with endoscopic evaluation at two and four weeks, showed:

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STUDY 1

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	37/105 (35.2%)	82/109 (75.2%)
Placebo	26/106 (24.5%)	68/107 (63.6%)

STUDY 2

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	8/24 (33%)	22/24 (92%)
Placebo	4/31 (13%)	18/31 (58%)

The sucralfate-placebo differences were statistically significant in both studies at four weeks but not at two weeks. The poorer result in the first study may have occurred because sucralfate was given two hours after meals and at bedtime rather than one hour before meals and at bedtime, the regimen used in international studies and in the second United States study. In addition, in the first study liquid antacid was utilized as needed, whereas in the second study antacid tablets were used.

Maintenance Therapy After Healing of Duodenal Ulcer

Two double-blind randomized placebo-controlled U.S. multicenter trials have demonstrated that sucralfate (1 g bid) is effective as maintenance therapy following healing of duodenal ulcers.

In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analysis presented below.

Drug	n	Duodenal Ulcer Recurrence Rate (%) Months of Therapy			
		1	2	3	4
Sucralfate	122	20*	30*	38**	42**
Placebo	117	33	46	55	63

*p<0.05 **p<0.01

Prn antacids were not permitted in this study.

In the other study, scheduled endoscopies were performed at 6 and 12 months, but for cause endoscopies were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:

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Data from placebo-controlled studies longer than 1 year are not available.

INDICATIONS AND USAGE

Sucralfate is indicated in:

- Short-term treatment (up to

Duodenal Ulcer Recurrence Rate (%)

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INDICATIONS AND USAGE
Sucralfate is indicated in

•*Short-term treatment* (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued *for 4 to 8 weeks unless healing* has been demonstrated by x-ray or endoscopic examination

•**Maintenance** therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short term treatment with sucralfate can result in complete healing of the ulcer, *a successful course of treatment with sucralfate* should not be expected to alter the posthealing frequency or severity of duodenal ulceration

Special Populations: Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin (plasma proteins). Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

Drug Interactions

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following: cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy.

The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, ranitidine, and warfarin), dosing the concomitant medication 2 hours before sucralfate minimized the interaction. Because of the potential of sucralfate to alter the absorption of some drugs, sucralfate should be administered separately from other drugs when alterations in bioavailability are likely to be critical. In these cases, patients should be monitored appropriately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 30 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy

Teratogenic Effects. Pregnancy Category B.

Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,700 patients treated with sucralfate tablets, adverse effects were reported in 128 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system:

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash.

Miscellaneous: dizziness,

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Dermatological: pruritus, rash.

Nervous System: dizziness, insomnia, sleepiness, vertigo.

Other: back pain, headache.

Postmarketing reports of hypersensitivity reactions, including urticaria (hives), angioedema, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported in patients receiving sucralfate tablets. Similar events were reported with sucralfate suspension. However, a causal relationship has not been established.

Bezoars have been reported in patients treated with sucralfate. The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

Inadvertent injection of insoluble sucralfate and its insoluble excipients has led to fatal complications, including pulmonary and cerebral emboli. Sucralfate is not intended for intravenous administration.

OVERDOSAGE

[illegible] experience in humans with overdosage of sucralfate, no specific treatment recommendations can be given. Acute oral toxicity studies in animals, however, using doses up to 12 g/kg body weight, could not find a lethal dose. Sucralfate is only minimally absorbed from the gastrointestinal tract. Risks associated with acute overdosage should, therefore, be minimal. In rare reports describing sucralfate overdose, most patients remained asymptomatic. These few reports where adverse events were described included symptoms of dyspepsia, abdominal pain, nausea, and vomiting.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer

The recommended adult oral dosage for duodenal ulcer is 1 gram four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

Maintenance Therapy

The recommended adult oral dosage is 1 gram twice a day.

HOW SUPPLIED

Sucralfate Tablets USP are supplied as white, scored, capsule-shaped tablets containing 1 gram of sucralfate. Available in bottles of 30 (NDC 0332-2210-04), 100 (NDC 0332-2210-09) and 500 (NDC 0332-2210-13). Tablets are debossed BIOCRAFT on one side and 105 on the other.

Dispense in a tight container as defined in the USP/NF.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Biocraft Laboratories, Inc.
Elmwood Park, New Jersey 07407

October 1994

C H E M I S T ' S R E V I E W

D. V

ANDA 70-848

1. CHEMIST'S REVIEW NO. 11

2. ANDA # 70-848

3. NAME AND ADDRESS OF APPLICANT

Biocraft Laboratories, Inc.
92 Route 46, P.O. Box 200
Elmwood Park, NJ 07407

6. NAME OF DRUG

Sucralfate, USP

9. AMENDMENTS AND OTHER DATES:

Firm:

1) 11-8-85 with original application.
2) 11-25-85 with manufacturing site of for active ingredient, sucralfate
3) 12-16-85 with DMF # for active ingredient
4) 3-18-86 with 1st responding letter
5) 9-9-86 with 2nd responding letter
6) 2-13-87 with amendment for Bio's protocol
7) 2-10-87 with amendment for Bio's protocol
8) 5-15-87 with Bio study
9) 1-13-88 with amendment for meeting
10) 2-1-88 with amendment on new supplier/manufacturer of active ingredient
11) 4-27-88 and 4-28-88 with method validation for active ingredient and the finished product (The source of the active ingredient was from later was withdrawn)
12) 5-4-88 with COA from
13) 5-12-88 with a meeting request
14) 6-20-88 with reformulation, manufacturing and control revision
15) 8-16-88 with 3rd responding letter
15a) 5-18-89 with 4th responding letter
16) 8-18-89 with the revised method validation for both drug substance and the finished product
17) 11-1-89 with draft labeling
18) 11-3-89 with second source and stability data
19) 2-15-90 with Bio material (Vol. 3.3-3.5)
20) 3-5-90 with responding to HFD-180 letter dated 2-14-90
21) 3-14-90 with NC
22) 3-16-90 with 5th responding to chemistry

deficiency letter dated 2-13-90
23) 4-16-90 with Bio amendment
24) 11-14-90 with amendment
25) 1-17-92 with 6th responding to chemistry deficiency letter dated 3-28-91
26) 8-20-92 with amendment
27) 10-23-92 with amendment
28) 2-10-93 with amendment
29) 7-6-93 with amendment
30) 10-27-93 with labeling amendment
31) 7-7-95 with amendment
32) 7-26-95 with fax
33) 7-28-95 with fax
34) 10-16-95 with amendment

FDA:

1) 11-13-85 with acknowledgement
2) 6-11-86 with developing a protocol for Bio
3) 2-13-86 with 1st deficiency letter
4) 8-18-86 with 2nd deficiency letter and deficiency letter to DMF#
5) 9-30-86 with 3rd deficiency letter
6) 12-9-86 with 4th deficiency letter
7) 3-6-87 with acknowledgement and ok for protocol
8) 5-13-88 with Bio protocol comments
9) 4-11-89 with 5th deficiency letter
10) 1-10-90 & 1-19-90 with deficiency letters to DMF# and DMF #
11) 1-25-90 with Bio deficiency letter from mathematical statistician
12) 2-13-90 with 5th deficiency letter
13) 2-14-90 With Bio deficiency letter from HFD-180
14) 4-17-90 with deficiency letter from HFD-180
15) 6-5-90 with clarifications
16) 3-28-91 with 6th deficiency letter
17) 6-24-92 with 7th deficiency letter
18) 10-19-92 with method validation for both drug substance and finished product (OK)
11) 9-2-93 with 8th deficiency letter
12) 6-22-94 with 9th deficiency letter
13) 9-26-95 with 10th deficiency letter

10. PHARMACOLOGICAL CATEGORY

Antiulcer or Duodenal Ulcer

11. HOW DISPENSED

Rx

13. DOSAGE FORM

Tablets

14. POTENCY

1 gram

15. CHEMICAL NAME AND STRUCTURE

Sucralfate USP
$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]_x[H_2O]_y$ in which
x=8 to 10, and y=22 to 31.

α-D-Glucopyranoside, β-D-fructofuranosyl, octa-kis(hydrogen sulfate), aluminum complex.
Sucrose octakis(hydrogen sulfate) aluminum complex.

17. COMMENTS

The formulation has been changed since the site was used as the source of the drug substance on 8-20-88.

The finished products are manufactured using the source drug substance.

The revised formulation (composition)

The indication for maintenance therapy (in healed duodenal ulcer patients at dose of 1 gram twice daily) is covered by exclusivity.

Comments:

Q: 1. The drug product is now an article in USP 23. Please revise the testing specifications accordingly, if applicable. If the drug product does not meet the compendial standards, please address the specific issues.

A: OK (see attached comment 1).

Status:

a. EER status: **Pending**

Requested for updated for applicant (Biocraft),

b. Method Validation status: **satisfactory**

Samples for the raw materials and the finished product have been validated by St. Louis Lab and Philadelphia District and found acceptable on October 19, 1992 and July 12, 1993. Samples for the raw materials and the finished product from lot 16046 were used for the method validation. The special **Chemical Structure Elucidation Work** was performed by St Louis (DDA) and found acceptable. Now Sucralfate is USP product.

c. Bio-review and clinical studies review: **Satisfactory**

Satisfactory per J Henderson reviewed on 1-31-96. Bio and clinical studies found satisfactory per Dr. Stephen Fredd, MD/Gastrointestinal & Coagulation Drug Products and Paula Boststein, MD on 12-8-95.

Clinical studies is from lot 12715. The batch size for lot 12715 is tablets. The raw material used for lot 12715 is from
Sucralfate as the stability indicating assay method is used for stability studies on lot 12715.

d. Labeling review status: **satisfactory**

Satisfactory per C Hoppes reviewed on 12-13-94 and per A Vezza on 2-21-96.

E. DMF **Satisfactory**

DMF have been reviewed and found satisfactory on 9-22-95.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable - Pending EER and Bio-study.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 2-21-96

BIO/DISSOLUTION

REVIEW

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #70-848 SPONSOR: BIOCRAFT
DRUG: SUCRALFATE
DOSAGE FORM: TABLET
STRENGTHS/(s): 1 g
TYPE OF STUDY: COMPARATIVE CLINICAL TRIAL
STUDY SITE: CONDUCTED BY

STUDY SUMMARY:

On 8/16/89 the sponsor submitted the results of a comparative clinical trial conducted from 5/13/88 to 6/26/89 as a three-treatment, randomized, parallel design comparing the test product sucralfate 1 g tablets (Biocraft lot #12715, assay 100.3%) with the reference listed drug (RLD) Carafate® 1 g tablets (MMD lot #N7257, assay 94.3%) and placebo in the treatment of duodenal ulcer disease. The lot of test product used in clinical studies was manufactured (2/16/88, batch size units) prior to the implementation of OGD PPG #22-90 (applicable to applications submitted after 9/1/89).

The clinical trial results were reviewed by the Division of Gastrointestinal and Coagulation Drug Products, HFD-180, and the Division of Biometrics, HFD-713. The clinical end point was duodenal ulcer healing at four weeks. The statistician's original conclusion was that Biocraft sucralfate was more effective than placebo and bioequivalent to Carafate®. The original medical review raised questions concerning the conduct of the trial (randomization and blinding) and clinical significance of low healing rates. Dr. Stephen Fredd, Director, HFD-180, commented on these findings and an inspection was conducted by the Division of Scientific Investigations concerning these issues (randomization, patient assignment, distribution of test drugs, blinding).

These inspection results were reviewed by HFD-180 and their (medical reviewer and Dr. Fredd) resulting comments transmitted to the firm in a deficiency letter issued from the Division of Bioequivalence on 7/27/94. The firm's response was submitted 9/28/94, reviewed by Dr. Fredd, and additional information was requested regarding the databases (letter issued 7/31/95). The firm's response was submitted 8/23/95. Dr. Fredd's final review was completed 11/27/95 and he recommended approval of Biocraft's sucralfate as bioequivalent to Carafate®. Because Dr. Fredd believed that the original medical reviewer and the field inspector considered the application not approvable, he requested concurrence from the Director, ODE III. Dr. Paula Botstein, Director, ODE III, concurred with Dr. Fredd's recommendation on 12/8/95. There was one further

communication to the firm to clarify certain statements made in the 8/23/95 regarding corrections to the databases. The firm's response on 1/4/96 was acceptable to Dr. Fredd and the 7/5/90 database is the basis for approval. The test product is deemed bioequivalent to the RLD

WAIVER/DISSOLUTION: N/A

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: JH DATE 1-24-96

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL: RNP DATE 1/24/96

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Chan, Ph.D.
INITIAL: KKC DATE 1/25/96

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: N/A DATE

END

MD

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

ANDA
70848

ANDA 70-848

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Attention: Maurice Bordoni
18-01 Rover Road
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SUCRALFATE TABLETS USP

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1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site.
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Acute Duodenal Ulcer

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Sucralfate is indicated in:

•Short-term treatment (up to

In the other study scheduled endoscopies were performed at 8 and 12 months, but for cause endoscopies were permitted at symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention to treat analysis for the 94 patients enrolled in the trial had the following res...

INDICATIONS AND USAGE

Sucralfate is indicated in

•Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

•Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.

Special Populations: Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum such as aluminum containing antacids may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum containing products ordinarily excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

Drug Interactions

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following: cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, L-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentration or prothrombin time with the addition of sucralfate to chronic warfarin therapy.

The mechanisms of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, ranitidine, and warfarin), dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of sucralfate to alter the absorption of some drugs, sucralfate should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies of 24 months duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug related tumorigenicity. A reproduction study in rats at doses up to 30 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system:

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash.

4

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system.

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash.

Nervous System: dizziness, insomnia, sleepiness, vertigo.

Other: back pain, headache.

Postmarketing reports of hypersensitivity reactions, including rare instances (hives), angioedema, respiratory difficulty, rhonchi, laryngospasm, and facial swelling have been reported in patients receiving sucralfate tablets. Similar events were reported with sucralfate suspension. However, a causal relationship has not been established.

Bezoars have been reported in patients treated with sucralfate. The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

Inadvertent injection of insoluble sucralfate and its insoluble excipients has led to fatal complications, including pulmonary and cerebral emboli. Sucralfate is not intended for intravenous administration.

OVERDOSAGE

Due to limited experience in humans with overdosage of sucralfate, no specific treatment recommendations can be given. Acute oral toxicity studies in animals, however, using doses up to 12 g/kg body weight, could not find a lethal dose. Sucralfate is only minimally absorbed from the gastrointestinal tract. Risks associated with acute overdosage should, therefore, be minimal. In rare reports describing sucralfate overdose, most patients remained asymptomatic. Those few reports where adverse events were described included symptoms of dyspepsia, abdominal pain, nausea, and vomiting.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer

The recommended adult oral dosage for duodenal ulcer is 1 gram four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

Maintenance Therapy

The recommended adult oral dosage is 1 gram twice a day.

HOW SUPPLIED

Sucralfate Tablets USP are supplied as white, scored capsule-shaped tablets containing 1 gram of sucralfate. Available in bottles of 30 (NDC 0332 2210-04), 100 (NDC 0332 2210-09) and 500 (NDC 0332 2210-13). Tablets are debossed BIOCRAFT on one side and 105 on the other.

Dispense in a tight container as defined in the USP/NF.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Biocraft Laboratories, Inc.
Elmwood Park, New Jersey 07407

October 1994

D. L

ANDA 70-848

1. CHEMIST'S REVIEW NO. 11

2. ANDA # 70-848

3. NAME AND ADDRESS OF APPLICANT

Biocraft Laboratories, Inc.
92 Route 46, P.O. Box 200
Elmwood Park, NJ 07407

6. NAME OF DRUG

Sucralfate, USP

9. AMENDMENTS AND OTHER DATES:

Firm:

1) 11-8-85 with original application.
2) 11-25-85 with manufacturing site of for active ingredient, sucralfate
3) 12-16-85 with DMF # for active ingredient
4) 3-18-86 with 1st responding letter
5) 9-9-86 with 2nd responding letter
6) 2-13-87 with amendment for Bio's protocol
7) 2-10-87 with amendment for Bio's protocol
8) 5-15-87 with Bio study
9) 1-13-88 with amendment for meeting
10) 2-1-88 with amendment on new supplier/manufacturer of active ingredient

11) 4-27-88 and 4-28-88 with method validation for active ingredient and the finished product (The source of the active ingredient was from .ater was withdrawn)
12) 5-4-88 with COA from
13) 5-12-88 with a meeting request
14) 6-20-88 with reformulation, manufacturing and control revision
15) 8-16-88 with 3rd responding letter
15a) 5-18-89 with 4th responding letter
16) 8-18-89 with the revised method validation for both drug substance and the finished product
17) 11-1-89 with draft labeling
18) 11-3-89 with second source and stability data
19) 2-15-90 with Bio material (Vol. 3.3-3.5)
20) 3-5-90 with responding to HFD-180 letter dated 2-14-90
21) 3-14-90 with NC
22) 3-16-90 with 5th responding to chemistry

deficiency letter dated 2-13-90
23) 4-16-90 with Bio amendment
24) 11-14-90 with amendment
25) 1-17-92 with 6th responding to chemistry deficiency letter dated 3-28-91
26) 8-20-92 with amendment
27) 10-23-92 with amendment
28) 2-10-93 with amendment
29) 7-6-93 with amendment
30) 10-27-93 with labeling amendment
31) 7-7-95 with amendment
32) 7-26-95 with fax
33) 7-28-95 with fax
34) 10-16-95 with amendment

FDA:

1) 11-13-85 with acknowledgement
2) 6-11-86 with developing a protocol for Bio
3) 2-13-86 with 1st deficiency letter
4) 8-18-86 with 2nd deficiency letter and deficiency letter to DMF#
5) 9-30-86 with 3rd deficiency letter
6) 12-9-86 with 4th deficiency letter
7) 3-6-87 with acknowledgement and ok for protocol
8) 5-13-88 with Bio protocol comments
9) 4-11-89 with 5th deficiency letter
10) 1-10-90 & 1-19-90 with deficiency letters to DMF# and DMF #
11) 1-25-90 with Bio deficiency letter from mathematical statistician
12) 2-13-90 with 5th deficiency letter
13) 2-14-90 With Bio deficiency letter from HFD-180
14) 4-17-90 with deficiency letter from HFD-180
15) 6-5-90 with clarifications
16) 3-28-91 with 6th deficiency letter
17) 6-24-92 with 7th deficiency letter
18) 10-19-92 with method validation for both drug substance and finished product (OK)
11) 9-2-93 with 8th deficiency letter
12) 6-22-94 with 9th deficiency letter
13) 9-26-95 with 10th deficiency letter

10. PHARMACOLOGICAL CATEGORY — 11. HOW DISPENSED

Antiulcer or Duodenal Ulcer — Rx

13. DOSAGE FORM — 14. POTENCY

Tablets — 1 gram

15. CHEMICAL NAME AND STRUCTURE

Sucralfate USP
$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]_x[H_2O]_y$ in which
x=8 to 10, and y=22 to 31.

α-D-Glucopyranoside, ß-D-fructofuranosyl, octa-kis(hydrogen sulfate), aluminum complex.
Sucrose octakis(hydrogen sulfate) aluminum complex.

17. COMMENTS

The formulation has been changed since the site was used as the source of the drug substance on 8-20-88.

The finished products are manufactured using the source drug substance.

The revised formulation (composition)

The indication for maintenance therapy (in healed duodenal ulcer patients at dose of 1 gram twice daily) is covered by exclusivity.

Comments:

Q: 1. The drug product is now an article in USP 23. Please revise the testing specifications accordingly, if applicable. If the drug product does not meet the compendial standards, please address the specific issues.

A: OK (see attached comment 1).

Status:

a. EER status: **Pending**

Requested for updated for applicant (Biocraft),

b. Method Validation status: **satisfactory**

Samples for the raw materials and the finished product have been validated by St. Louis Lab and Philadelphia District and found acceptable on October 19, 1992 and July 12, 1993. Samples for the raw materials and the finished product from lot 16046 were used for the method validation. The special **Chemical Structure Elucidation Work** was performed by St Louis (DDA) and found acceptable. Now Sucralfate is USP product.

c. Bio-review and clinical studies review: **Satisfactory**

Satisfactory per J Henderson reviewed on 1-31-96. Bio and clinical studies found satisfactory per Dr. Stephen Fredd, MD/Gastrointestinal & Coagulation Drug Products and Paula Boststein, MD on 12-8-95.

Clinical studies is from lot 12715. The batch size for lot 12715 is tablets. The raw material used for lot 12715 is from Sucralfate as the stability indicating assay method is used for stability studies on lot 12715.

d. Labeling review status: **satisfactory**

Satisfactory per C Hoppes reviewed on 12-13-94 and per A Vezza on 2-21-96.

E. DMF **Satisfactory**

DMF have been reviewed and found satisfactory on 9-22-95.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable - Pending EER and Bio-study.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 2-21-96

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #70-848 SPONSOR: BIOCRAFT
DRUG: SUCRALFATE
DOSAGE FORM: TABLET
STRENGTHS/(s): 1 g
TYPE OF STUDY: COMPARATIVE CLINICAL TRIAL
STUDY SITE: CONDUCTED BY

STUDY SUMMARY:

On 8/16/89 the sponsor submitted the results of a comparative clinical trial conducted from 5/13/88 to 6/26/89 as a three-treatment, randomized, parallel design comparing the test product sucralfate 1 g tablets (Biocraft lot #12715, assay 100.3%) with the reference listed drug (RLD) Carafate® 1 g tablets (MMD lot #N7257, assay 94.3%) and placebo in the treatment of duodenal ulcer disease. The lot of test product used in clinical studies was manufactured (2/16/88, batch size units) prior to the implementation of OGD PPG #22-90 (applicable to applications submitted after 9/1/89).

The clinical trial results were reviewed by the Division of Gastrointestinal and Coagulation Drug Products, HFD-180, and the Division of Biometrics, HFD-713. The clinical end point was duodenal ulcer healing at four weeks. The statistician's original conclusion was that Biocraft sucralfate was more effective than placebo and bioequivalent to Carafate®. The original medical review raised questions concerning the conduct of the trial (randomization and blinding) and clinical significance of low healing rates. Dr. Stephen Fredd, Director, HFD-180, commented on these findings and an inspection was conducted by the Division of Scientific Investigations concerning these issues (randomization, patient assignment, distribution of test drugs, blinding).

These inspection results were reviewed by HFD-180 and their (medical reviewer and Dr. Fredd) resulting comments transmitted to the firm in a deficiency letter issued from the Division of Bioequivalence on 7/27/94. The firm's response was submitted 9/28/94, reviewed by Dr. Fredd, and additional information was requested regarding the databases (letter issued 7/31/95). The firm's response was submitted 8/23/95. Dr. Fredd's final review was completed 11/27/95 and he recommended approval of Biocraft's sucralfate as bioequivalent to Carafate®. Because Dr. Fredd believed that the original medical reviewer and the field inspector considered the application not approvable, he requested concurrence from the Director, ODE III. Dr. Paula Botstein, Director, ODE III, concurred with Dr. Fredd's recommendation on 12/8/95. There was one further

communication to the firm to clarify certain statements made in the 8/23/95 regarding corrections to the databases. The firm's response on 1/4/96 was acceptable to Dr. Fredd and the 7/5/90 database is the basis for approval.

WAIVER/DISSOLUTION: N/A

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: JH DATE 1-24-96

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL: RNP DATE 1/24/96

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Chan, Ph.D.
INITIAL: KKC DATE 1/25/96

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: N/A DATE

ANDA
70848

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER CONSULT REVIEW

ANDA [illegible]

Sponsor: Pharmetic

Drug: Famotidine, Oral Tablets, Bioequivalence Study

Submitted to the Division of Generics:

1. Integrated Clinical and Statistical Report
2. Statistical Data
3. Patient Listing
4. Case Report Form Tabulation (archival only)
5. Case Report Form Tabulation (archival only)
6. Case Report Forms (archival only)
7. Case Report Forms for Drop-out Patients (ADRs) (archival only)

Volumes organized into the Division of Gastrointestinal and Coagulation Drug Products: Volumes 1, 2 and 3

Date Volumes filed in Generics: August 16, 1990

Reviewed by Div. of Gastrointestinal: August 21, 1990

Amendment #1 — Received by Generics: February 16, 1990
Received by Gastrointestinal: February 26, 1990

Amendment #2 — Received by Generics: March 5, 1990
Received by Gastrointestinal: March 17, 1990

Amendment #3 — Received by Generics: April 16, 1990
Received by Gastrointestinal: April 30, 1990

Amendment #4 — Received by Generics: July 9, 1990
Received by Gastrointestinal: August 9, 1990

Three Volumes with 31 Case Report Forms of Discontinuations, filed in Amendment #1

Three Volumes with 28 Case Report Forms filed in Amendment #4

Information Filed Relevant to Blinding: July 5, 1991
July 15, 1991
July 31, 1991

Reviewed by Medical Officer: Volumes 1, 2 and 3, Volumes of Four Amendments, 79 Case Report Forms and Information filed July 5-31, 1991

Preliminary Reviews Resulted in Memoranda of January 17, 1990 and May 11, 1990

Medical Officer: Robert Prizont, M.D.

First Draft Presented to Division Director: August 8, 1991
Second Draft Finished: August 28, 1991

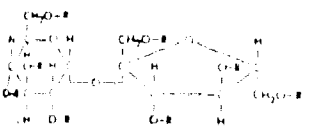
Medical Officer Review Finalized on: September 18, 1991

This Review Includes the Following Sections:

A. Background MO Summary Pages 2-3
B. Descriptive Pages 5-13
C. Reviewer Comments Pages 14-51
D. Reviewer Summary Pages 52-55
The reviewer created 22 Tables called Reviewer Table 1-22
E. Reviewer Recommendations Pages 53-53
F. Appendices 1-4

This ANDA contains the sponsor (Biocraft) report #3810: "Integrated Clinical and Statistical Report of Generic Sucralfate (PMS.011)" of a single study titled "A Comparison of the Efficaciousness and Safety of Generic Sucralfate in the Treatment of Duodenal Ulcer Disease" conducted by the sponsor "to determine the bioavailability of Biocraft's sucralfate and demonstrate its equivalence to Marion's Carafate tablet in support of an 'AB' rating" (Sponsor's Letter of August 10, 1988, Vol. 1).

Background. Chemically, sucralfate is a polymer of a disaccharide esterified with eight sulfate ions in a aluminum salt form known commercially as the aluminum salt of sucrose octasulfate. The chemical formula is the following:



$? = SO_3Al_2(OH)_5(H_2O)_2$

The compound is not absorbed by the gastrointestinal tract. In the presence of a protein, sucrose octanosulfonate precipitates. A similar precipitate has been shown to be present in ulcer craters of experimentally induced gastric ulcers and endoscopically on ulcer craters of duodenal ulcers. Sucralfate does have some acid neutralizing activity which at pH 4, depending of the manufacturing source varies from 13 meq up to 16 meq per 1g of sucralfate. Hitherto, the mechanism whereby the administration of sucralfate tablets leads to the healing of duodenal ulcer has not been elucidated. An oral 1g tablet formulation, manufactured by Marion Laboratories was approved by the FDA on October 30, 1981 (NDA 18-333) and is in the market under the trade name of Carafate®. Carafate is approved for the following indications: 1. Short-term treatment (up to 8 weeks) of active duodenal ulcer. The basis of approval were two U.S. multicenter studies; both of them were placebo-controlled and the endoscopic evaluation showed the following:

Study 1

Ulcer Healing/No. Patients

Treatment Group	2 wk	4 wk (Overall)
Sucralfate	37/105 (35.2%)	82/109 (75.2%)
Placebo	26/108 (24.5%)	68/107 (63.6%)

Study 2

Treatment Group	Ulcer Healing/No. Patients 2 wk	4 wk (Overall)
Sucralfate	8/24 (33%)	22/24 (92%)
Placebo	4/24 (17%)	13/21 (58%)

Tables taken from page 1161, PDR, 45th Edit. 1991. The PDR states that "The sucralfate-placebo differences were statistically significant in both studies at 4 weeks but not at 2 weeks. The poorer results in the first study may have occurred because sucralfate was given 2 hours after meals and at bedtime rather than 1 hour before meals and at bedtime; the regimen used in international studies and in the second United States study. In addition, in the first study liquid antacid was utilized as needed, whereas in the second study antacid tablets were used." Carafate has also been recently approved as maintenance therapy for duodenal ulcer patients at reduce dosage after healing of acute ulcers. Two U.S. double-blind, randomized, placebo-controlled multicenter trials showed efficacy as maintenance therapy. The PDR states that "In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analyses presented below":

Duodenal Ulcer Recurrence Rate (%)					
		Months of Therapy			
Drug	N	1	2	3	4
Carafate	122	20*	30*	38**	42**
Placebo	117	33	46	55	63

*$p < 0.05$, **$p < 0.01$

PRN antacids were not permitted in this study

"In the other study, scheduled endoscopies were performed at 6 and 12 months, but for cause endoscopies were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:"

Duodenal Ulcer Recurrence Rate (%)			
Drug	N	6 months	12 months
Carafate	48	19*	27*
Placebo	46	54	65

*$p < 0.002$

PRN antacids were permitted in this study

II. Descriptive. The Study Protocol. The sponsor contracted , as the third party in charge of the design, implementation and monitoring of the study. The Protocol, included in Vol. 1 of this submission was revised on March 2, 1988 and encompasses the following relevant sections.

A. Study Design (Pages 255 and 257)

This was planned to be a multicenter, third party double-blind, placebo controlled, randomized, parallel clinical trial comparing generic sucralfate, Carafate®, and placebo. Approximately 280 patients was calculated to be enrolled in order to ensure 75 patients in each treatment group. Investigators were requested to enter between nine and twenty-four patients each.

Patients had to be randomly assigned to one of three treatment groups:

1) Generic sucralfate tablets, 1 gm (one tablet), four times daily;

2) Carafate® tablets, 1 gm (one tablet), four times daily;

3) Placebo tablets, one tablet, four times daily.

The sponsor stated on Page 6 of the Study Protocol, Vol. 1, Page 25 "In order to ensure the integrity of the blind, a third-party will dispense test substances to the patients. "Each group will ingest the study test substances for up to eight weeks. Each patient will receive a two-week supply of study medication and return every two weeks for evaluation. Patients whose ulcers heal in four weeks will be discontinued from further study. Those who show little or no improvement will continue taking the assigned study medication for an additional four weeks at which time another evaluation will be performed. The treatment regimen will continue for a total of eight weeks unless healing is previously demonstrated by endoscopic examination."

Antacids

The sponsor amended twice the antacid section. In amendment #2, May 11, 1988, the sponsor states the following:

"NEW - 4. Antacid
Extra Strength Maalox® Tablets will be dispensed to patients for relief of ulcer pain and indigestion.

Note: Extra Strength Maalox tablets will replace Phillips'® Milk of Magnesia tablets during this study. The protocol will be altered to reflect this change wherever use of antacids is mentioned.

B. Administration of Medications.

Regarding the procedures of drug administration the protocol states (pages 288 and 289) the following:

"A patient number and a medication kit will be assigned at the time the patient receives study medication. The medication kit number will be randomly assigned using a computer generated

sequence to contain either generic sucralfate 1 gm tablets, Carafate® 1 gm tablets, or placebo matched tablets. The interval between endoscopy and assignment of medication must not exceed 48 hours."

and

"The investigator is not to discuss the tablet characteristics with the patient nor with the person dispensing the test substance. In like fashion, the patient will be instructed not to discuss the tablets with the investigator(s) or with other patients participating in the study. Particular attention will be devoted to monitoring this third-party system at each monitoring visit."

Inclusion Criteria

The following requirements were needed to enter the study:

1. Males or females 18 to 70 years of age of any race.

2. Patients with an active duodenal ulcer of at least 0.3 cm in diameter and not exceeding 2.5 cm, as diagnosed by endoscopy. Patients may have one or two duodenal ulcers; however, at least one must be 0.3 cm in diameter.

Exclusion Criteria

1. Patients with esophageal or gastric ulcers, or with active bleeding.

2. Patients whose ulcer is due to other diseases (e.g., Zollinger-Ellison Syndrome).

3. Patients with antral, pre-pyloric (> 1 cm proximal to the pyloric channel) or post-bulbar lesions despite possible concomitant lesions in the duodenum.

4. Patients with more than two duodenal ulcers.

5. Patients taking medications within 30 days of study entry that are potentially ulcerogenic, such as corticosteroids, phenylbutazones or other non-steroidal, anti-inflammatory medications. Salicylate consumption (not more than 1300 mg per day within the previous week) for acute problems was not included as a reason for exclusion provided that routine use is not required.

6. Patients who have undergone major trauma or surgery within the previous four weeks or patients scheduled to undergo surgery during the period of time covered by the study.

7. Patients who have undergone previous gastric surgery, or who have previously experienced a perforated ulcer.

8. Patients who are alcohol or drug dependent.

8. Patients being treated with an H_2 receptor antagonist, prostaglandin, cimetidine (≥ 800 mg daily), antacids (≥ 400 mEq daily), ranitidine HCl (≥ 300 mg daily), sucralfate (≥ 4 gm daily), or any other anti-ulcer medication. Patients were not supposed to have ingested these medications for more than three days within the two weeks immediately preceding entrance into the study.

Several points of interest are included in the section of Material and Methods (pages 263-264, Vol. 1). The first point of interest stated in the study protocol is the window (includes endoscopy with biopsy) allowed for the scheduled appointments.

I. Patient Visits (page 263)

"Visits will be scheduled at two week intervals throughout the study. Strict adherence to scheduled visit dates is essential for successful completion of the study. Treatment will continue for eight weeks unless healing is demonstrated earlier by endoscopy.

Both investigators and patients are requested to make every effort to adhere to the schedule for visits, clinical observations and laboratory studies. The possibility of unavoidable delays or conflicts is recognized. The following time limits have been set. Lack of compliance with these time limits will exclude the patient from further study.

Scheduled Visit	Allowable Visit Days Following Start of Coded Medication (Day 0)
Week 2	Days 13 - 15
Week 4	Days 26 - 30
Week 6	Days 40 - 44
Week 8	Days 54 - 58

Extension of patient's participation beyond Week 8 is not anticipated."

The second point of interest are the guidelines set to the P.I. or gastroenterologist to perform endoscopies and establish an ulcer or normal mucosa. The study protocol states in point c and d, pages 265-266 that:

c. "Patients who demonstrate endoscopic healing after four or eight weeks of treatment will receive no further treatment and will be deemed treatment successes. If the patient has <u>two ulcers, both must have undergone endoscopic healing</u> before the patient will be deemed a treatment success. Patients who have not demonstrated endoscopic healing after eight weeks of continuous therapy or patients whose ulcers have increased in severity at four weeks, will be deemed treatment failures, will be withdrawn from the study and will be treated with alternative therapy." and

d. Ulcer HEALING is defined as normal or hyperemic mucosa and FAILURE TO HEAL is defined as erosion or ulcer. Any other gross upper

gastrointestinal pathology seen on endoscopy will be noted on the report form. In addition, each ulcer present will be measured and the information will be recorded on the Case Report Form.

As regards to discontinuation, the sponsor states the following in Vol. 1, Pages 273 and 274: "Patients will be discontinued from the study if they:

1. Develop hypersensitivity to a study drug.

2. Develop ulcer complications (perforation, obstruction or excessive bleeding) at any time during the study.

3. Require hospitalization for a serious illness or surgery.

4. Take an H2-histamine antagonist, prostaglandin, or an anticholinergic agent. (Anticholinergic agents are permitted only as pre-medication for endoscopy.)

5. Wish to discontinue the study for any reason."

The following parts of the protocol sections were included in the Statistical Methods and deal with efficacy assessment and statistical analysis of efficacy.

H. Variables For Efficacy Evaluation (Pages 278 and 279, Vol. 1)

1. The primary efficacy parameter will be the percent of patients whose ulcers have healed at Week 4. A positive response requires endoscopic evidence of complete healing. All other patients who are evaluable based on the criteria above will be considered non-responders at Week 4 and at the final evaluation. The final evaluation will also be tested; however, since spontaneous healing frequently occurs with time, the difference between active and placebo response rates may not be as great as at the earlier time point (Week 4) and thus, not statistically significant.

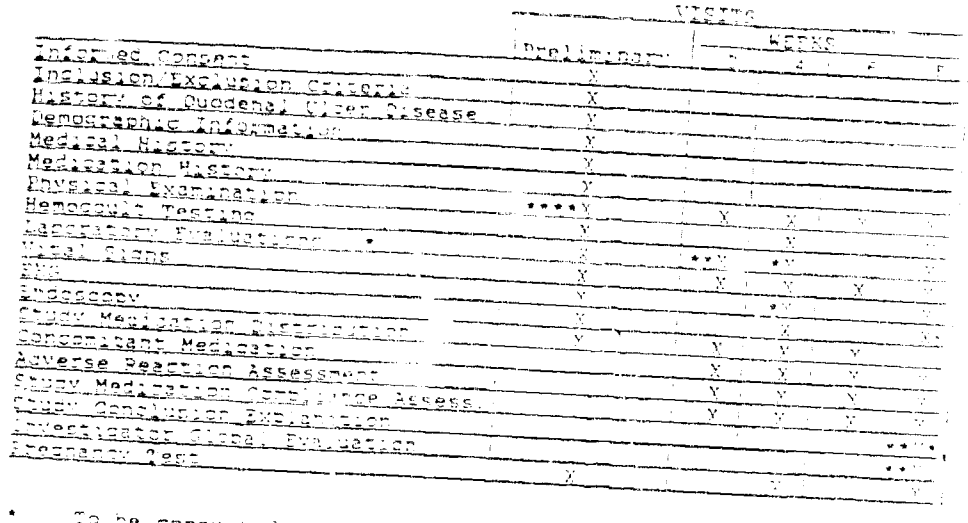
2. Secondary efficacy parameters will include average weekly frequency and intensity of day and night pain and the amount of antacids taken during the study."

The protocol on page 267 includes the laboratory chemistries to be analyzed in blood and urine specimens. Of relevance to safety is the aluminum determination. This paragraph reads as follows:

> "Serum aluminum evaluation. *Serum aluminum levels will be measured at baseline, two weeks and termination. The first 150 patients enrolled into the study will be tested for levels of serum aluminum. Investigators will be notified by Pharmakinetics when the need to collect these samples has ended."

The summary plan shown below was included in page 282, Vol. 1:

STUDY SCHEDULE



	Visits				
	Preliminary	Weeks			
		2	4	6	8
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
History of Duodenal Ulcer Disease	X				
Demographic Information	X				
Medical History	X				
Medication History	X				
Physical Examination	X				
Hemoccult Testing	****X	X	X	X	X
Laboratory Evaluations *	X		X		X
Vital Signs	X	**X	**X		X
ECG	X	X	X	X	X
Endoscopy	X		*X		X
Study Medication Dispensation	X	X	X		X
Concomitant Medication		X	X	X	X
Adverse Reaction Assessment		X	X	X	X
Study Medication Compliance Assess.		X	X	X	X
Study Conclusion Evaluation		X	X	X	X
Investigator Global Evaluation					***X
Pregnancy Test	X				**X
					X

* To be conducted only if ulcer(s) have healed and patients will not continue in the study.

** Serum aluminum measurements only.

*** To be conducted at any point at which the patient discontinues from the study.

**** To include a rectal examination at the preliminary visit.

III. Investigational Plan. In Vol. 1, Pages 5-15, the sponsor presented the Investigational Plan and Statistical Methods used, which encompasses the post-study narrative of the criteria, conduct, procedures, schedule and analyses performed during the study in accordance or in deviation with the pre-established study protocol. There were a number of changes in criteria which the sponsor included post study. These unblinded changes included serum aluminum levels and statistical analyses. Deviations from the study protocol were the following:

A. Patient discontinuation. The sponsor also added the following sentence: "In addition, the medical monitor evaluated study continuation on an individual basis for those patients whose serum aluminum level was greater than 20.0 ng/ml on two consecutive visits."

In the section of Criteria for Efficacy Evaluation there was one post-study change noted. The first change refers to the patients included in the Intent to Treat analysis, which now reads as follows: "An intent-to-treat analysis was conducted on all patients who had a final endoscopy regardless of treatment compliance."

Clarifications about blinding were also noted on Page 5: "There was a difference in the color of Biocraft Sucralfate and Carafate® tablets that necessitated special blister packaging with white opaque-PVC material. The placebo tablets matched Biocraft Sucralfate tablets. The opaque-PVC material prevented identification of the test substance by the person dispensing the

study medication." As relates to the potency of the antacid a clarification was included on page 10: "Antacid tablets (Extra Strength Maalox® 400 mg/400 mg) were provided to the patient for the relief of pain and indigestion."

IV. Disposition of Patients. The sponsor divided this section in subsections. In my descriptive I will follow the sponsor's presentation. All these data was filed in the original ANDA on August 16, 1989.

A. Investigators

"There were 23 investigators who were scheduled to participate in the study. Three investigators (#1056, #1062, #1065) did not enroll patients. Twenty investigators enrolled at least one patient in the study. Eleven sites enrolled less than 10 patients. To reduce the statistical errors associated with small frequencies, the patients from these 11 sites were combined to form group 'NVID 2000." The number of patients enrolled was shown in the sponsor's Table 1, page 35, Vol. 1.

TABLE 1

TREATMENT

INVESTIGATOR	PLACEBO	CARAFATE[2]	Biocraft Sucralfate	TOTAL	
	n (n)	n (n)	n (n)	n (n)*	
1049	2 (2)	2 (2)	2 (2)	6 (6)	
1050	0 (0)	1 (1)	0 (0)	1 (1)	
1051	1 (2)	1 (1)	0 (2)	2 (5)	
1052	13 (15)	12 (15)	13 (15)	38 (45)	
1053	6 (7)	6 (6)	7 (7)	19 (20)	
1054	0 (1)	1 (2)	1 (1)	2 (4)	
1055	7 (9)	6 (8)	6 (10)	19 (27)	
1057	0 (1)	1 (1)	1 (1)	1 (1)	2 (3)
1058	2 (2)	2 (2)	1 (2)	5 (6)	
1059	9 (9)	9 (10)	9 (9)	27 (28)	
1060	3 (4)	3 (4)	3 (4)	9 (12)	
1061	0 (0)	1 (1)	0 (0)	1 (1)	
1063	3 (3)	2 (2)	2 (2)	7 (7)	
1064	4 (4)	3 (3)	3 (3)	10 (10)	
1066	7 (9)	8 (8)	7 (8)	22 (25)	
1067	0 (0)	1 (1)	1 (1)	2 (2)	
1068	1 (1)	1 (1)	1 (1)	3 (3)	
1074	1 (2)	1 (2)	2 (3)	4 (7)	
1075	12 (13)	10 (11)	9 (11)	32 (35)	
1076	7 (9)	8 (8)	8 (9)	23 (27)	
TOTAL	79(93) (:NVID 2000)	80(89)	75(91)	234 (273)	35(45)

* n = # patients with Week 4 endoscopy; (n) = # patients enrolled

b. Number of Patients for Analysis The sponsor stated that 278 patients were randomized into the study. On page 18, Vol 1, the number of patients used in each analysis was specified. They were the following:

SAMPLE TYPES	PLACEBO	CARAFATE®	SUCRALFATE	TOTAL
Safety	93	89	91	273
Intent-to-Treat	88	82	77	248
Primary Efficacy	87	82	76	241

"During the study, the patient disposition included fifty-two patients who were dropped from the study. Of these, twenty-five patients did not return for a subsequent endoscopy after randomization and therefore were not included in the intent-to-treat population. The remaining twenty-seven patients were dropped due to lack of efficacy, adverse reactions, and administrative reasons. Of these, seven patients had a final endoscopy and were included in the intent-to-treat analysis."

In the safety section 27-30, the sponsor inserted a subsection for "Discontinuations" which changed the number of discontinued patients. In the first paragraph of this safety section the sponsor states that "A total of 83 patients, 20 in the placebo treatment group, 14 in the Carafate® treatment group, and 19 in the Biocraft Sucralfate treatment group were discontinued from the study prior to completion." In the following chart, the sponsor offers the reasons for the discontinuations.

	PLACEBO	CARAFATE®	SUCRALFATE
Adverse Reaction	3	0	2
Intercurrent Illness	2	0	2
Patient refused treatment	1	2	1
Lost to follow-up	4	9	6
Administrative	10	3	10
TOTAL	20	14	21

c. Demographics on Background Characteristics. In Tables 4 and 5, Vol. 1, pages 44-47, the sponsor lists the demographics and the total number of patients included for the primary efficacy and intent-to-treat. I will show the table demographics of these risk factors considered to be important in the healing of duodenal ulcer, which are in order of relevance: smoking, history of duodenal ulcer and duration of the disease and sex. The sponsor did not include in the demographics ulcer size. In sequence, the demographics of Table 5 and Table 4 correspond to the total number of patients randomized and those included in the primary efficacy analysis. The Table is shown in total numbers:

Demographic Variables	Placebo	Carafate	Sucralfate	Overall
Smoking in all patients:				
Smoker				
YES	46	42	51	139
NO	47	47	4	134
and in PEA:				
Smoker				
YES	39	35	43	117
NO	44	47	33	124
History of DU in all patients:				
YES	52	53	46	151
NO	39	34	43	116
UNKNOWN	2	2	2	6
and in PEA:				
YES	45	50	36	131
NO	36	30	39	105
UNKNOWN	2	2	1	5
Duration of DU in all patients:				
N	45	49	52	146
MEAN	10.7	12.1	10.1	10.9
STD.	10.8	9.2	8.2	9.3
MIN.	0.3	0.4	0.2	0.2
MAX.	44.9	33.5	31.0	44.9
and in PEA:				
N	35	47	45	127
MEAN	10.0	12.0	9.3	10.5
STD.	8.8	9.3	7.9	8.7
MIN.	0.4	0.4	0.2	0.2
MAX.	38.1	33.5	30.3	38.1

Episodes and Frequency of DU Attacks in all Pts.

Episodes of Ulcer Attacks				
YES	42	41	31	114
NO	14	12	15	41
DO NOT KNOW	26	23	31	80
Frequency of Ulcer Attacks				
Less than or equal to 6 months	21	23	19	63
7-11 months	2	5	2	9
every 12 months	6	1	3	10
Greater than 12 months	13	13	10	36

Demographic Variables and in PEA:	Placebo	Carafate	Sucralfate	Overall
Episodes of Ulcer Attacks				
YES	36	38	24	98
NO	15	11	11	37
DO NOT KNOW	23	21	28	72
Frequency of Ulcer Attacks				
Less than or Equal to 6 Months	5	22	15	52
7-11 months	2	4	1	7
Every 12 months	5	1	2	8
Greater than 12 months	12	13	8	34

Number of males,females in all pts.:

Male	61	62	68	193
Female	31	27	22	79

and in PEA:

Male	55	58	57	170
Female	28	24	18	70

As regards to possible statistical differences in the "all patients" group the sponsor states in Page 19, Vol. 1 the following: "There were no significant differences among the three treatment groups (the total study population) with respect to the variables of age ($p = 0.473$), height ($p = 0.342$), weight ($p = 0.203$), sex ($p = 0.481$), race ($p = 0.354$), occupation ($p = 0.802$), smoking habits ($p = 0.465$) alcohol consumption ($p = 0.314$) and history of duodenal ulcer disease ($p = 0.818$)."

Study Medication Compliance: The overall percent compliance treatment and by week is shown in the sponsor's chart of page 20, Vol. 1. The sponsor states that "of special interest is the percent compliance at Week 4 which ranged from 93.7% to 80.5% among the three treatment groups."

Overall
% Compliance

WEEK	PLACEBO	CARAFATE®	SUCRALFATE
2	90.9	87.2	90.6
4	93.7	86.6	80.5
6	91.8	90.0	96.9
8	87.7	82.1	80.0

In Table 6, page 98, Vol. 1, the sponsor summarizes the "final distribution for study drug compliance".

TABLE 6
OVERALL STUDY DRUG COMPLIANCE - FREQUENCY DISTRIBUTION

TREATMENT	WEEK	LESS THAN 75%	75% TO 125%	GREATER THAN 125%	TOTAL
PLACEBO	2	8 (9.1%)	80 (90.9%)	0 (0.0%)	88
	4	4 (5.1%)	74 (93.7%)	1 (1.3%)	79
	6	5 (8.2%)	56 (91.8%)	0 (0.0%)	61
	8	7 (10.8%)	57 (87.7%)	1 (1.5%)	65
CARAFATE	2	9 (10.5%)	75 (87.2%)	2 (2.3%)	86
	4	11 (13.4%)	71 (86.6%)	0 (0.0%)	82
	6	3 (4.9%)	56 (90.0%)	1 (1.6%)	60
	8	6 (15.4%)	32 (82.1%)	1 (2.6%)	39
SUCRALFATE	2	8 (9.4%)	77 (90.6%)	0 (0.0%)	85
	4	14 (18.2%)	62 (80.5%)	1 (1.3%)	77
	6	1 (3.1%)	31 (96.9%)	0 (0.0%)	32
	8	5 (14.3%)	28 (80.0%)	2 (5.7%)	35

V. Results. The following results were submitted by the sponsor with the original ANDA, filed on August 18, 1988. The text of these results were included in Vol. 1, pages 20-23. The sponsor divided the text presentation in: 1. Primary Efficacy Response, Week 4; 2. Intent-to-treat Response - Final Visit (week 8); 3. Ulcer Healing by Geographic Region; 4. Ulcer Healing by Demographic Characteristics. I will show results for 1, 2 and 4.

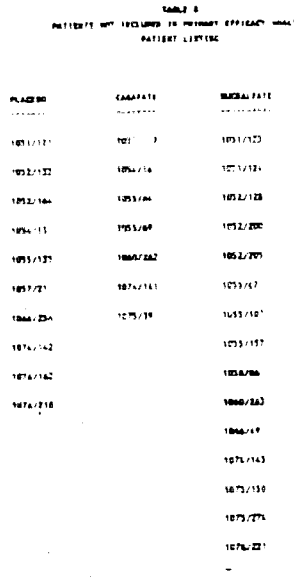
A. Efficacy. Primary Efficacy Response - Week 4. In the first paragraph the sponsor states the following: "The original primary analysis design specified that patients were required to have taken between 75% and 125% of study medication. Patients failed to reliably return medication at the specified intervals. Since it was not possible to determine drug compliance based on tablet count, as stated in the Case Report Forms, for the seven days prior to Week 4, compliance was calculated based on overall tablet counts for the entire four weeks." Out of the total 273 randomized patients, 241 were included in the PEA as shown in the sponsor's Table 7, Vol. 1, page 49.

TABLE 7
PATIENTS INCLUDED IN PRIMARY EFFICACY ANALYSIS

INVESTIGATOR ID	PLACEBO	CARAFATE	SUCRALFATE	TOTAL
1052	13	14	12	39
1053	7	6	7	20
1055	8	6	7	21
1059	9	10	9	28
1060	4	3	3	10
1064	4	3	3	10
1066	8	8	7	23
1075	13	10	9	32
1076	7	8	8	23
2000*	10	14	11	35
TOTAL	83	82	76	241

*Includes investigators 1049, 1050, 1051, 1054, 1057, 1058, 1061.

The sponsor explains that "thirty-two patients did not have a week 4 endoscopy and were not included in the primary efficacy analysis (Table 8)". Table 8 was included in Vol. 1, page 50.



The overall 4 week healing rate for the PEA was shown in the following chart, Page 20, Vol. 1.

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate®	p-value vs. Sucralfate
Placebo	83	18(21.7)	0.000	0.000
Carafate®	82	41(50.0)	-	0.888
Sucralfate	76	39(51.3)	0.888	-

The sponsor concluded the following: "Overall, Biocraft Sucralfate and Carafate® demonstrated clinically and statistically significant healing rates when compared to placebo. In addition, no statistical or clinical differences in healing rates were observed between the two active medications."

The sponsor did not include an intent-to-treat analysis of the 4 week endoscopy results.

Intent-To-Treat Response - Final Visit. The sponsor intent-to-treat analysis of the week endoscopy included 248 randomized patients. The sponsor provided the DU healing rates of patients enrolled by nine investigators in Table 10, pages 51-52. The overall 8 week healing rate in the sponsor intent-to-treat analysis is shown in the following chart (page 21, Vol. 1).

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate®	p-value vs.Sucralfate
Placebo	89	37(41.6)	0.003	0.003
Carafate®	82	55(67.1)	-	0.977
Sucralfate	77	51(66.2)	0.977	-

The sponsor states that in pairwise comparisons the two active sucralfate drugs were significantly better than placebo, but were not significantly different from each other. The sponsor also stated that "deviations from the protocol were not considered a reason to exclude patients from the analysis" (intent-to-treat).

Healing Status by Demographic Variables

The following Tables 13 and 14, show the healing rates at 4 and 8 weeks of the three treatment arms by demographic variables (pages 57 and 58, Vol. 1).

TABLE 13
ULCER HEALING BY DEMOGRAPHIC VARIABLES - VISIT 4

SEX	HEALED	PLACEBO	CARAFATE	SUCRALFATE
MALES	YES	13	31	29
	NO	42	27	27
	%	23.67	53.45	51.79
FEMALES	YES	5	10	10
	NO	23	14	8
	%	17.86	41.67	55.56
RACE				
CAUCASIAN	YES	11	23	26
	NO	40	30	17
	%	21.57	43.40	60.47
NON-CAUCASIAN	YES	7	18	13
	NO	25	11	18
	%	21.87	62.07	41.94
SMOKING				
SMOKERS	YES	7	13	18
	NO	32	22	27
	%	17.95	37.14	41.86
NON-SMOKERS	YES	11	28	21
	NO	33	19	11
	%	25.00	59.57	65.62

TABLE 14
ULCER HEALING BY DEMOGRAPHIC VARIABLES - FINAL VISIT

SEX	HEALED	PLACEBO	CARAFATE	SUCRALFATE
MALES	YES	24	36	36
	NO	36	22	21
	%	40.00	62.07	63.16
FEMALES	YES	13	19	15
	NO	16	5	3
	%	44.83	79.17	83.33
RACE				
CAUCASIAN	YES	25	35	33
	NO	30	18	10
	%	45.45	66.04	76.74
NON-CAUCASIAN	YES	12	20	18
	NO	22	9	14
	%	35.29	68.97	56.25
SMOKING				
SMOKERS	YES	15	20	25
	NO	27	15	18
	%	35.71	57.14	58.14
NON-SMOKERS	YES	22	35	26
	NO	25	12	7
	%	46.81	74.47	78.79

The sponsor did not breakdown the healing rates based on history of duodenal ulcer, duration of disease, frequency of attacks or occupation, all variables included by the sponsor in the baseline demographics.

Changes in the Healing Status Filed in Amendments #3 and 4

In Amendment #3, filed on April 16, 1990, the sponsor made a number of changes; in the first paragraph of the Introduction the sponsor explained the following: "During preparation of responses to FDA requests for additional information (letters received January 26 and

February 14, 1990) of the above-captioned ANDA (70-848), several minor discrepancies were found with respect to ulcer healing status. This document identifies the changes made to the database in correcting these discrepancies and describes the statistical findings as they relate to these changes.

1. Post-Filing Changes in the Week 4 Healing Status

Original Report

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate^{R}	p-value vs. Sucralfate
Placebo	83	18(21.7)	0.000	0.000
Carafate^{R}	82	41(50.0)	-	0.888
Sucralfate	76	39(51.3)	0.888	-

Revised Report

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate^{R}	p-value vs. Sucralfate
Placebo	81	16(19.8)	<0.001	<0.001
Carafate^{R}	82	40(48.8)	-	0.577
Sucralfate	75	40(53.3)	0.577	-

2. Changes in the Week 8 Healing Status

Original Report

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate^{R}	p-value vs. Sucralfate
Placebo	89	37(41.6)	0.003	0.003
Carafate^{R}	82	55(67.1)	-	0.977
Sucralfate	77	51(66.2)	0.977	-

Revised Report

Treatment	N	n (%) Pts. Healed	p-value vs. Carafate^{R}	p-value vs. Sucralfate
Placebo	89	36(40.5)	0.001	<0.001
Carafate^{R}	82	54(65.9)	-	0.840
Sucralfate	77	52(67.5)	0.840	-

The healing status of the following patients was changed in the PEA of week 4:

Pt. 153 (placebo) — From healed to not-healed at Week 4.
Pt. 152 (Carafate®) — From healed to not-healed at Week 4.
Pt. 198 (Carafate®) — Status at final visit from healed to not-healed at Week 8.
Pt. 093 (sucralfate) — From not-healed to healed at Week 4.

3. Endoscopy Window Violations

The sponsor also explains that the following 4 week endoscopies were performed outside the allowed window and therefore the healing status at week 4 of these patients was changed: these patients are: "Patient numbers 070/SAC (sucralfate group), 240/E-H (placebo group) and 264/G-G (placebo group) had final endoscopies at Weeks 3, 3, and 2, respectively. Hence, they were not eligible for inclusion in the primary efficacy sample. It should be noted that these patients are included in the intent-to-treat sample." These changes are summarized in the following sponsor Tables:

TREATMENT GROUP	PAT ID	CHANGE IN STATUS WEEK 4	CHANGE IN STATUS FINAL VISIT
Placebo	153	From healed to not healed	No change
	240	Not included	No change
	264	Not included	No change
Carafate®	152	From healed to not healed	No change
	198	No change	From healed to not healed
Sucralfate	070	Not included	No change
	093	From not healed to healed	No change

The following tables summarize the change in ulcer healing status as a result of the database revisions:

WEEK 4
NUMBER OF PATIENTS

	Original Report		Revised Report	
	Healed	Not Healed	Healed	Not Healed
Placebo	18	65	16	65
Carafate	41	41	40	42
Sucralfate	39	37	40	35

FINAL VISIT
NUMBER OF PATIENTS

	Original Report		Revised Report	
	Healed	Not Healed	Healed	Not Healed
Placebo	37	52	36	53
Carafate	55	27	54	28
Sucralfate	51	26	52	25

Patient 021 - WEEK 8 changed to WEEK 1
Patient 070 - WEEK 4 changed to WEEK 8
Patient 123 - WEEK 8 changed to WEEK 1
Patient 126 - WEEK 8 changed to WEEK 2
Patient 132 - WEEK 8 changed to WEEK 2
Patient 162 - WEEK 8 changed to WEEK 2
Patient 164 - WEEK 8 changed to WEEK 2
Patient 218 - WEEK 8 changed to WEEK 8
Patient 224 - WEEK 8 changed to WEEK 8
Patient 240 - WEEK 4 changed to WEEK 8
Patient 256 - WEEK 8 changed to WEEK 8
Patient 264 - WEEK 4 changed to WEEK 2

4. Additional Changes in Healing Status Reported in Amendment #4

In Amendment #4, filed on July 8, 1990, the sponsor informed us that further changes in the healing status were done by a gastroenterologist who was not part of the present trial. The sponsor explained the following: "Because of the several questions pertaining to healing status and corrections thereof, all CRFs were reviewed blinded by a board certified gastroenterologist with 10 years of experience in conducting clinical trials in acid-related disease for multiple regulatory submissions. Specific instances of CRF changes were noted. Primarily, the changes made were due to the convention of including only one response which was the worst change present. Therefore, if ulcer and hyperemia were checked, the CRF was changed to reflect ulcer. Similarly, if erosion and normal were checked, the CRF was changed to reflect erosion..."

a. Healing Status Changes - Filed in Amendment #4

Investigator 1066, Patient 54 (PLACEBO) Endoscopy performed on Day 30, Week 8 was found to be missing in the data base, and the data was changed from Unhealed at Week 4 to Healed at Week 8.

Investigator 1066, Patient 188 (PLACEBO). Endoscopy report for Week 4 was inappropriately entered. Data was not collected. Week 4 Endoscopy was deleted from data base. Status changed from Healed at Week 4 to Unhealed, lost to follow-up.

Investigator 1050, Patient 133 (Carafate) Healing status changed from Healed at Week 4 to Unhealed at Week 4. Adverse Event reports Ulcer conditions present.

Investigator 1055, Patient (108) (Sucralfate). Endoscopy report for Week 4, Day 14 was found and transcribed to CRF from written report. Status changed from Unhealed at Week 0 to Healed at Week 4.

Investigator 1066, Patient 156 (Sucralfate). Endoscopy form for Week 4 was inappropriately entered. Data was not collected. Week 4 Endoscopy deleted from data base. Status changed from Healed to Unhealed."

VI. Reviewer's Comments and Analyses

The reading of the Descriptive Section points out inconsistencies, discrepancies, contradictions and uncertainties. In view of these, the immediate concern of this reviewer is to attempt to ascertain the possible reasons that led to these irregularities. I will first discuss the conduct of the trial as refers to randomization, blinding, discontinuations, imbalances and window violations which occurred during the first four weeks of the trial. I will then comment and analyze the results of week four. With the exception of withdrawals, I will follow the same sequence for the week eight analyses.

Conduct of the Trial

1. Randomization. The type of randomization was not pre-stated in the study protocol. The randomization code included in the original submission, Vol. 1, Page 384, indicates that patients were randomized in blocks of three patients. The manner this randomization in blocks was executed was not clearly explained in the filed volumes or amendments. At the medical officer's request for more information about randomization, the sponsor filed information on July 18, 1989, related to the procedures used in the implementation of the randomization code. This information had been provided to Dr. Bette Barton, of the Agency's Clinical Information Branch on November 3, 1988. The letter to Dr. Barton and relevant information of center by center randomization is included in Appendix 1. In that letter, Biocraft's Director of Regulatory Affairs, David Zuchero, explains that patient packs were "numbered consecutively" and that each investigator received, before commencing the study, an initial drug shipment of six consecutively numbered patient packs. Since patients were grouped in blocks of three, each center received two complete randomization blocks. David Zuchero further explains that "When an investigator needed more study drug, an additional block of six patient packs were shipped from Biocraft" (paragraph 3, lines 1-2 of letter sent to Dr. Barton). There were 303 patients enrolled and randomized in blocks of three, numbered consecutively from 1-303. Centers were numbered consecutively from 1049 to 1068. The first two digits of center number is always 10; the last two digits designate the center number. Of these 20 consecutive centers, three (1056, 1062 and 1065) did not enroll any patients. The second sequence of centers were numbered from 1074 to 1076. The reason for the skipping of numbers 1069, 1070, 1071, 1072 and 1073 is unknown to this reviewer.

2. Concerns about Implementation of Randomization, Choice of Randomization System and Blinding.

a. Centers were consecutively numbered from 49 to 68, then there was a hiatus of five numbers, 69 to 73, and three more centers were last entered numbered consecutively from 74 to 76. Patient assignments were similarly numbered consecutively from 1 to 303 in random blocks of three and Biocraft shipped to each center two blocks of consecutively numbered assignments. Since there was no centralized first-come first-serve patient allocation of the consecutive numbered assignments but rather each center received two pre-established blocks of assignments in advance, it would be reasonable that the consecutively numbered patient assignments would be matched to the consecutively numbered centers. That is, lower numbered centers would receive the lower numbered patient assignment. This would allow for appropriate implementation of the randomization code. In actuality, consecutively numbered assignments

were not matched with consecutively numbered centers. This reviewer matched assignments, center by center, with the chronological patient entry lists provided to Scientific Investigations and included in Appendix 1. These matchings revealed a pattern of repetitive block sequences, insertion of disrupted blocks and disruption of consecutively numbered assignments. Center 1052 enrolled 45 patients and had the largest enrollment of all centers. In this center, sequence ACB was repeated four times and sequence ABC was repeated another three times Both of these repetitive sequences were always the first block of the six consecutively numbered assignments included in the package shipped to the PI. In one block the numbers were switched around to make an BAC sequence an ABC sequence. In six of the eight packages shipped the first assignment was A=placebo. The reversal of sequence BAC resulted that in seven of eight packages the first assignment was A=placebo. The sequences of this center are shown in the following table.

Reviewer Table 1
Center 1052-Assignment Matching With Patient ID and Chronological Entry Included in Page 19* of Information Sent by Biocraft to Scientific Investigations

NAME	ASSIGNMENT	ENVID	PATID	START DATE	
STONE	→ 1 A	001052	000000	16-JUN-88	
	1 C		000001	17-JUN-88	
	1 B		000002	21-JUN-88	PACKAGE WITH SIX ASSIGNMENTS (#1)
	1 A		000003	27-JUN-88	
	1 C		000004	30-JUN-88	
	1 B		000005	30-JUN-88	
	→ 1 A		000006	01-JUL-88	
	1 C		000113	11-JUL-88	
	1 B		000114	18-JUL-88	PACKAGE WITH
	1 A		000117	18-JUL-88	SIX ASSIGNMENTS (#2)
	1 C		000118	26-JUL-88	
	1 B		000119	01-AUG-88	
	→ 1 A		000120	02-AUG-88	
	1 C		000121	04-AUG-88	
	1 B		000122	07-OCT-88	PACKAGE WITH
	1 A		000128	10-OCT-88	SIX ASSIGNMENTS (#3)
	1 C		000129	10-OCT-88	
	1 B		000130	10-OCT-88	
	→ 1 A		000131	10-OCT-88	
	1 C		000132	11-OCT-88	
	1 B		000133	11-OCT-88	
	→ 1 A		000134	13-OCT-88	PACKAGE WITH SIX ASSIGNMENTS (#4)
	1 C		000143	18-OCT-88	
	1 B		000144	18-OCT-88	
	1 A		000145	18-OCT-88	
	1 C		000146	18-OCT-88	
	→ 1 B		000147	19-OCT-88	
	1 A		000148	19-OCT-88	
	1 C		000175	19-OCT-88	
	1 B		000176	19-OCT-88	PACKAGE WITH SIX ASSIGNMENTS (#5)
	1 A		000177	20-OCT-88	
	1 C		000178	21-OCT-88	
	→ 1 B		000179	21-OCT-88	
	1 A		000180	24-OCT-88	
	1 C		000181	24-OCT-88	
	1 B		000182	24-OCT-88	PACKAGE WITH SIX ASSIGNMENTS (#6)
	1 A		000183	25-OCT-88	
	1 C		000184	25-OCT-88	
	1 B		000185	26-OCT-88	
	→ 1 A		000186	26-OCT-88	
	1 C		000199	27-OCT-88	
	1 B		000200	27-OCT-88	PACKAGE WITH SIX ASSIGNMENTS (#7)
	1 A		000201	27-OCT-88	
	1 C		000202	28-OCT-88	
	1 B		000203	31-OCT-88	
	→ 1 A		000204	31-OCT-88	
	1 C		000205	31-OCT-88	
	1 B		000206	02-NOV-88	FIRST BLOCK OF PACKAGE (#8)
	1 A		000207	02-NOV-88	

The ↕ symbol indicates reversion of consecutive patient assignment.
*Attachment 2

Center 1055 enrolled 27 patients. Sequence CAB was repeated four times and the initial two consecutive assignments CA were repeated five times. In one case the sequence CA was achieved by using an incomplete sequence from another center. Three of the 5 shipped packages started with assignment B=Carafate, while 2 packages started with assignment C=sucralfate. According to the information sent to Scientific Investigations, Biocraft shipped on 5/19/88 two initial packages with

six assignments each (Page 2, Attachment I, Appendix I of this review). These packages, which I will number #1 and #2, had the code numbers 061-072. The PI enrolled six patients using assignments from package #2. The first block of this package had the sequence CAB. Of interest, assignment C=sucralfate healed by week 4, assignment A=placebo finished the trial unhealed and assignment B=carafate was discontinued before the week 4 endoscopy. The next six assignments combined two blocks from two different packages. The first of these two blocks came from package #3 and was shipped to the PI by another PI, (center 1051). The sequence of this first block was CAB. Of further interest, assignment C=sucralfate healed by week 4; assignment A=placebo and B=carafate were unhealed by week 4. The second of these two blocks was the initial block of package #1 and had the assignments ACB. The following table shows this center's sequences.

Reviewer Table 2

Center 1051-Assignment Matching With Patient ID and Chronological Entry Included in Page 1x of Information Sent by Biocraft to Scientific Investigations

October 30, 1989 page 1

8619 INVESTIGATORS WITH PATIENTS BY START DATE

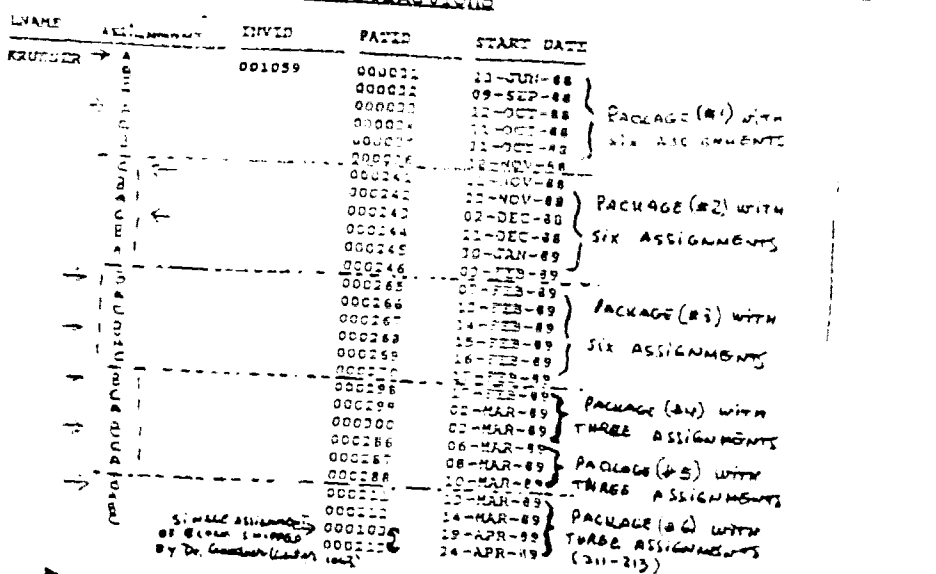
LNAME	Assignment	INVID	PATID	START DATE	
AGRAWAL	→ C	001055	000067	11-OCT-88	Six Assignments From Package #2 (see previous paragraph)
	A		000068	09-NOV-88	
	B		000069	14-NOV-88	
	C		000070	18-NOV-88	
	A		000071	04-FEB-89	
	B		000072	11-FEB-89	
	→ C		000077	11-FEB-89	Three Assignments From Package #3 (see previous paragraph)
	A		000078	11-FEB-89	
	B		000079	11-FEB-89	
	A		000061	13-FEB-89	Six Assignments From Package #1 (see previous paragraph)
	C		000062	18-FEB-89	
	B		000063	22-FEB-89	
	C ←		000064	25-FEB-89	
	A		000065	25-FEB-89	
	A		000066	04-MAR-89	
	C		000280	04-MAR-89	Three Assignments From Package #3
	A		000281	08-MAR-89	
	B		000282	11-MAR-89	
	B ←		000106	15-MAR-89	Three Assignment Package (#4) shipped by Biocraft (see Appendix I discussion)
	A		000107	27-MAR-89	
	C		000108	29-MAR-89	
	C		000124	05-APR-89	Incomplete Block Shipped by Biocraft, Package #5.
	A		000125	06-APR-89	
	B		000126	17-APR-89	Complete Block
	B ←		000127	24-APR-89	First Assignment of Block Shipped by M. Tomaszewski (Center 1058)
	D		000128	24-APR-89	
	C		000157	26-APR-89	

*Attachment 2

Center 1059 enrolled 28 patients. In two consecutive (packages #2 and #3) shipped packages a same sequence was repeated twice in the same package, i.e., CBA, CBA in package #2. The next six assignments had repetitive sequences because shipped packages #4 and #5 had blocks with the same sequence BCA. In each shipped package, the first assignment of the two blocks is always the same, e.g. A.....A..... These sequences are shown in the following table. This center enrolled seven patients who had two ulcers at baseline; assignment A=placebo fell on six of these potentially poor healing patients.

Reviewer Table 3

Center 1059-Assignments Matching With Patient ID and Chronological Entry Included in Page 5* of Information Sent by Biocraft to Scientific Investigations



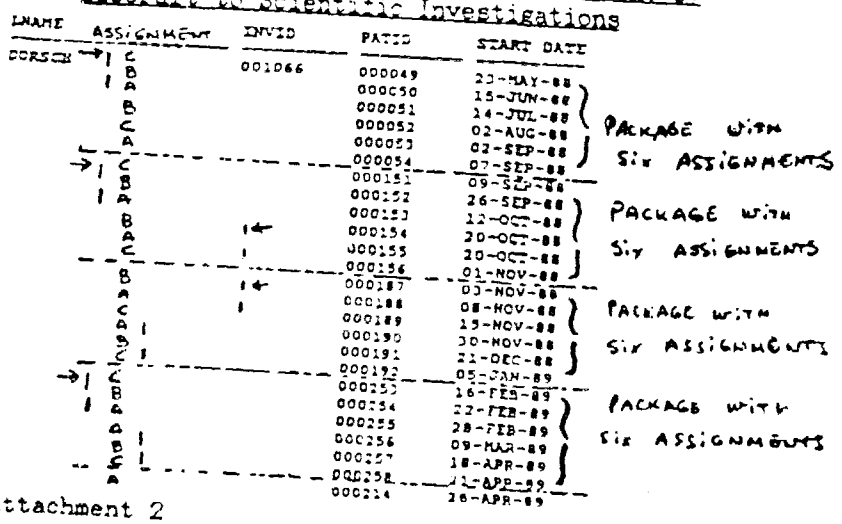
The ↩ symbol indicates reversal of consecutive patient assignment

*Attachment 2

Center 1068 enrolled 25 patients; three of the shipped packages had the same initial block=CBA. The first assignment of 3/4 completed packages started with assignment C=sucralfate. The following table exemplifies this point.

Reviewer Table 4

Center 1066-Assignment Matching With Patient ID and Chronological Entry Included in Page 5* of Information Sent by Biocraft to Scientific Investigations



*Attachment 2

Center 1075 enrolled 35 patients. In this center the sequence ACB was the initial sequence of three consecutive shipped packages. Another sequence, CAB, was repeated four times and was the initial sequence of 3/6 packages. The initial sequence CAB from the second package was obtained by completely disrupting the block's sequence (193-195 or BCA). A repeated consecutive assignment AA was obtained by including in the same shipped package the last assignment of an incomplete block together with the next complete block. The PI enrolled the first two assignments of these consecutive four numbers.

Reviewer Table 5

Center 1075-Assignment Matching With Patient ID and Chronological Entry Included in Page Six of Information Sent by Biocraft to Scientific Investigations

8613 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	ASSIGNMENT	INVID	PATID	START DATE	
KENSTEIN	C ←	001075	000145	13-OCT-88	
	A		000146	14-OCT-88	PACKAGE WITH
	B		000147	19-OCT-88	SIX ASSIGNMENTS (#1)
	B		000148	22-OCT-88	
	A		000149	01-NOV-88	
	C		000150	01-NOV-88	
	C ←		000194	03-NOV-88	
	A		000195	03-NOV-88	PACKAGE WITH
	B		000193	05-NOV-88	SIX ASSIGNMENTS (#2)
	C ←		000196	05-NOV-88	
	A		000197	10-NOV-88	
	B		000198	12-NOV-88	
→	A		000229	17-NOV-88	
	C		000230	22-NOV-88	PACKAGE WITH
	B		000231	29-NOV-88	SIX ASSIGNMENTS (#3)
	B		000232	05-JAN-89	
	C		000233	13-JAN-89	
	A		000234	21-JAN-89	
→	A		000271	21-JAN-89	
	C		000272	21-JAN-89	PACKAGE WITH
	B		000273	24-JAN-89	SIX ASSIGNMENTS (#4)
	C ←		000274	27-JAN-89	
	A		000275	28-JAN-89	
	B		000276	04-FEB-89	
→	A		000037	07-FEB-89	
	C		000038	11-FEB-89	PACKAGE WITH
	B		000039	11-FEB-89	SIX ASSIGNMENTS (#5)
	C		000040	14-FEB-89	
	B		000041	16-FEB-89	
	A		000042	18-FEB-89	
	C ←		000295	22-FEB-89	
	A		000296	25-FEB-89	PACKAGE WITH
	B		000297	25-FEB-89	THREE ASSIGNMENTS (#6)
	A		000075	25-MAR-89	→ INCOMPLETE BLOCK; LAST ASSIGNMENT
	A		000076	13-APR-89	→ COMPLETE BLOCK; FIRST ASSIGNMENT

*Attachment 2
The]↓↑[indicate the adequate sequence of a disrupted block.

A number of centers with low enrollment did not follow the consecutively numbered assignments. That was the case of center 1057. This center enrolled one block with the sequence BCA. The first two assignments were switched around to CB. Of interest, the C=sucralfate patient healed in four weeks; the B=carafate and A=placebo patients did not.

This study was designed with a randomization code which had consecutively numbered assignments from 1 to 339 and centers which were numbered from 49-68 and 74-77. The shipment to centers of packages with arbitrarily selected sequences and incomplete blocks, the disruption of consecutive blocks plus the reversal of consecutive numbered assignments created, in the five aforementioned centers, a pattern of repetitive

sequences which appear not to fit the concept of an appropriate and adequate implementation of a pre-established randomization code.

b Patients were randomized in blocks of three. Blocking by three assures enrollment of all three arms in a block but requires absolute protection of the blinding. Since one of the arms, carafate, was for all practical purposes unblinded, the randomization system used allowed for penetration of the blinding if the blinding of any of the other two arms required unblinding, e.g., for an adverse reaction. Center 105H -turned the block with placebo, 1A. This patient was entered on [illegible] and discontinued six days later for abdominal pain. from was contacted before discontinuation. She was asked about possible alternative therapies by the PI. These alternative therapies were benty'l, additional antacids and hospitalization. Treatments were not acceptable, the patient was withdrawn by PI, hospitalized and the code was broken. The next patient enrolled was 14 and had a carafate assignment which has a tablet with distinguishable pink color. The last assignment in the block could be easily guessed as sucralfate.

c My concerns about the blinding of the trial extends to any knowledge of treatment assignments on the part of monitors, consultants and statisticians. There were three organizations and one statistician consultant involved in the trial. The three organizations were the sponsor, Biocraft Laboratories, which prepared the randomization list for the drug codes and who packaged and labeled the clinical supplies and which was the research organization in charge of running the operation of the trial. The statistician was A total of eight individuals had access to the randomization code. At the request of this reviewer the sponsor explained the blinding of the randomization code in pages 6 and 7, Vol. 1 of the amendment filed to the Agency on July 5, 1990. Nicholas Maselli, Assistant Director of Regulatory Affairs (Biocraft Lab.) stated that the randomization code was blinded and that a code of blind breaker, available only to provided knowledge of treatment assignments. The sponsor stated that neither of them broke the code during the study. I will include the sponsor explanation in Appendix 2. This statement was contradicted by the randomization code and complete blind code breaker filed by Debi Parker, Biocraft's Regulatory Submissions Coordinator, on July 15, 1991. The filed randomization code, included in Appendix 3, designates the treatments as A=placebo, B=carafate and C=sucralfate. This code, generated on February 8, 1988, is identical to the randomization code filed in the original submission. The use of this randomization code was confirmed on July 31, 1991 by Nicholas Maselli in a faxed letter included in the same Appendix. Hence, treatment assignments were unblinded in the randomization code and potentially to all individuals who had access to the randomization code.

d An additional concern related to the blinding is the interaction between monitors, who had access to an unblinded randomization code, and blinded PI's. Aside from contacts due to adverse reactions, which numbered a few, there were numerous interactions between and PI's regarding serum aluminum levels. The study protocol pre-established that blood for aluminum levels will be obtained at scheduled

intervals. My review of the aluminum data in Vol. 3 (included in Appendix 3) indicates that patients were called for numerous unscheduled visits as well. The review of the CRFs also indicates that PI's were discussing by phone patients data with monitors. Sucralfate patient 151/1056 was discontinued by because of an aluminum level of 83 mcg/L in one scheduled visit and one unscheduled visit. There was no pre-established stipulation in the study protocol that a high serum level would be a reason to discontinue a patient. Aluminum levels of 170, 210 and 178 were recorded in sucralfate patients 27/1049, 168/1081 and 172/1183 and all completed the study. Carafate patient 28/1044 had a level of 130 mcg/L at entry and of 45 in an unscheduled visit but was allowed to continue in the trial. Safety concerns with aluminum are potential, do not justify such close interaction between monitors and PIs and even less discontinuation from a trial. The sponsor selected arbitrarily patients for aluminum levels and these patients were in the large majority placebo and sucralfate patients, the two unblinded arms of the trial. If this high monitoring of serum levels relates only to safety, it is then of importance to assure the testing of all patients but foremost of those assigned to the active drugs. The sponsor has not offered any explanation for the arbitrary exclusion of most of the carafate patients. The frequent interaction between monitors and PIs almost exclusively on placebo and sucralfate patients adds to my concern as relates to the conduct of this trial, specifically on blinding. The following table exemplifies the selection of patients for aluminum levels.

Reviewer Table 6
Total Number of Patients Selected for Aluminum Levels

	Placebo	Carafate	Sucralfate
Total number of patients	93	89	91
Patients tested for serum aluminum	66	16	56
Percent	71	18	62
p value		p vs c: 0.001	s vs c: 0.001*
Number of patient/visit	146	48	153

* Two Sided Fisher's Exact Test

The following is an example of interaction between monitors and PIs concerning serum aluminum levels. The CRF of patient 009/1063 shows that at two weeks this patient had a level of <5 mcg/L, that is, undetectable by the sponsor's method. By week 4 the serum level was 8 mcg/L, still extremely low. However, a note states that the serum aluminum levels were "discussed with and "to be observed". The need for any discussion with any monitor for a serum level of 8 mcg/L escapes the reasoning of this reviewer. This patient was a carafate patient who finished unhealed with an erosion at week 8.

e Protection of the blinding is further hampered when investigators are allowed the exchanging of experimental tablets. In the information submitted to Scientific Inves gations, included in Appendix 1 of this review, I counted six instan es in which there was direct transfer of experimental material from one PI to another PI. The sponsor's listing does not include information about communication between centers. These communications would not be unusual. A concern is that these possible communications may have included exchanging of information between investigators about i.e., characteristics of the tablets, PI's experiences of patients acceptance to the experimental drugs and symptomatic or endoscopic responses. All these in a trial that was ongoing and, supposedly, blinded. The sponsor should have taken preventive measures to assure that all shipments of experimental drugs were centralized and confidential.

f The blinding of sucralfate tablets, in a trial which it compared to a generic sucralfate and a placebo yellow tablets, is not feasible. Sucralfate tablets are pink and stamped in one of the tablet surfaces. For all practical purposes, the trial blinding refers to the blinding of the sponsor's sucralfate and to the placebo. At my request, the sponsor filed samples of the sucralfate, placebo tablets and the formulations of the placebo and sucralfate tablets used in the trial. The filing occurred on June 17, 1991 and on July 16, 1991. I have examined the sucralfate and placebo tablets and both appear the same in size and color. In addition to size and color, blinding of the flavor is of relevance for sucralfate tablets have considerable size and require, in many patients, the splitting of the tablet before swallowing. The formulations of the tablets are included in Appendix 4. The sucralfate tablet contains 1 gr of the active compound, It does not contain any edulcorating substance. On the other hand, almost 80% of the placebo tablet is composed of free . This proportion of free is more than ten fold higher than the proportion found in and is equivalent to the edulcorating power of approximately 200 mg of regular In two other applications for generic sucralfate, NDA #19,728 and ANDA #73,171, the composition of the placebo tablets did not include but rather an increase concentration of the inactive ingredients contained in the sucralfate tablet. filed for generic sucralfate, included a placebo tablet with t In his comments about that application this reviewer recommended removal of the nd its replacement by inactive ingredients of the sucralfate tablet (MO review of December 18, 1990). In another recent is reviewer comments on the danger to the blinding which may signify including high concentrations of lactose in a placebo preparation. In that particular formulation, the concentration of was 1/6 of the concentration used in the formulation of the Biocraft's placebo tablets. It is of interest to comment that one placebo patient, 240/1053, removed himself prematurely from the trial after 22 days in the study because he "felt he was receiving placebo and knew he wasn't healed (amendment 4, tabulation list, page 224). This patient's behavior which led to a premature discontinuation does not reassure this reviewer about the blinding protection provided in the placebo tablet formulation.

g In summary, the sponsor had a prospective random code. However, the inadequate and inappropriate implementation of the randomization code,

which created patterns of repetitive assignments in the centers, the unblinding of the randomization code, the number of individuals from different organizations, e.g., coordinators, monitors, statistician, who had access to the unblinded code, the system of randomization used, the frequent interaction between monitors and PIs, the exchange of materials and potential communication between PIs plus the potential distinguishable taste of placebo tablets does not lend for assurance that the measures taken in patient assignment and blinding protection resulted in minimization of bias.

3. Week Four Discontinuations

a) Inconsistencies

In the original filing of [illegible] (Vol. 1), the sponsor reported 52 dropouts on page 18, 55 dropouts on page 27 and 55 in the table included in the same page. In amendment #3 the sponsor informed us that there were 55 dropouts but by the last amendment, amendment #4, the number of dropouts was 53. In table 8, page 51, Vol. 1, which lists discontinued patients not included in the sponsor's primary efficacy analysis, patient 107/1055 is included in the sucralfate arm. The same patient is included in the placebo arm in the tabulation list of page 3, Vol. 3 of the original submission and in the tabulation list, page 225, of amendment #4.

b) Number and Chronology of Patient Discontinuation

The patient tabulation list included in the last amendment on July 9, 1990 shows a total of 53 patients discontinued from the trial. This number of discontinuations accounts for 19% of the total enrollment (53/273). Of the total 53 discontinuations, 43 were discontinued during the first thirty days. This accounts for 81% of the total discontinuations (43/53). The large majority of discontinuations occurred before the protocol's pre-established window. Of the total of 273 patients enrolled, 14% were discontinued between day 1 of enrollment and day 25, one day before the endoscopy window. In fact, most of these discontinuations occurred during the first two weeks of the trial. The considerable number of sucralfate and placebo early departures were not balanced with similar number of departures in the carafate arm. In contrast to these early departures, only five patients were discontinued during the endoscopy window. The following two tables show total departures and the proportion of departures in each arm.

Reviewer Table 7

Total Number of Patients Discontinued

Discontinuation Chronology	Total Enrollment	Total Discontinued	Percent
	273		100
Full length of trial	-	53	19
First 30 days	-	43	16
Day 1-25	-	38	14
Day 26-30	-	5	2
Last 30 days	-	10	5

Reviewer Table 8

Proportion of Discontinued in Each Treatment Arm

Discontinuation Chronology		Placebo	Sucralfate	Carafate
First 30 days	43/273	16/93*	18/91	9/89
Percent	16	17	20	10
p value	-	-	0.094	
Day 1-25	30/273	14/93	17/91	7/89
Percent	14	15	19	8
p value	-	-	0.047**	
Day 26-30	5/273	2/93	1/01	2/89
Percent	2	2	1	2

*Ratio means = Discontinued / Total Number of Patients

**Two Sided Fisher's Exact Test

c. Endoscopy in Discontinued Patients. The study protocol called for an exit endoscopy in every patient discontinued from the study. In the original submission, the sponsor reported that a total of twenty-five patients had not returned for a follow-up endoscopy. My review indicates that there were twenty-six discontinued patients that exited without a follow-up endoscopy. The following table shows the proportion of patients discontinued without endoscopy.

Reviewer Table 9

Patients Discontinued Without Follow-up Endoscopy

Discontinuation	Placebo	Sucralfate	Carafate
Day 1-25	14	17	7
No f/u endoscopy	5	14	7
Percent	36	82	100
p value			
p vs s	0.012*		
p vs c	0.071		
s vs c		0.53	

* Two Sided Fisher's Exact Test

Sucralfate patients (N=14) dropped very early in the trial (Day 1-14) who had no follow-up endoscopy, were patients that had more severe disease or abdominal pain than placebo patients (N=4) discontinued during the same time period without follow-up endoscopy. As can be seen in the previous table, this difference in patient numbers between placebo and sucralfate is significant. Comparison of antacid consumption showed that placebo patients dropped early had a median antacid consumption of 4 tablets/week for the first two weeks while sucralfate patients dropped early had a median antacid consumption of 30 tablets/week for the first week and 38 tablets/week for the second week in the trial (Amendment #1). This apparent bias against placebo enhances the possibility of deficiencies in the blinding protection.

d. Impact of Discontinuations on DU Risk Factors. Two risk factors which were balanced at baseline, were imbalanced as a consequence of patient discontinuations occurring between days 1-30 of the trial. The two risk factors imbalanced as a consequence of the differential dropout were a previous history of DU and the presence of two DU.

1. Discontinuation of Patients With Previous History of DU

There was a numerical difference in favor of sucralfate vs carafate (-9%) in patients randomized who had a previous history of DU. The review of the demographics of all randomized and sponsor's PEA suggests that more sucralfate than carafate patients with previous history of DU were discontinued early in the study. This further imbalances an already numerical difference. The following table demonstrates quantitatively the imbalances.

Reviewer Table 10
Impact of Discontinuations on the Balance of Patients
With Previous History of Duodenal Ulcer as Reported
in Demographics, Vol. 1, Pages 45 and 47

	Placebo	Sucralfate	Carafate
Randomized	93	91	89
Randomized with history of DU	52	46	53
Percent	56	51	60
Patients with history of DU by day 30	45	36	50
Percent	43	40	56
p value			
p vs s	0.300		
p vs c	0.201		
s vs c	0.034*		

* Two Sided Fisher's Exact Test

My review of the CRF's indicates that, in actuality, eleven sucralfate and four carafate patients with history of DU were discontinued by day 30. The ratio and significance remain the same. A previous history of DU is a risk factor considered as unfavorable for DU healing (Van Deventer G.M. et al. A randomized study of maintenance therapy with ranitidine to prevent the recurrence of duodenal ulcer. NEJM 32:1113-1119, 1989). It should be pointed out that a very small number of "naive" sucralfate and carafate patients were also discontinued, but the number was the same in each treatment arm (four).

2. Discontinuation of Patients With Two DUs.

a) Inconsistencies. In the filing of August 16, 1989, Biocraft filed 31 patients enrolled with two DUs (Vol. 3, patient tabulation list): placebo had 24 patients, carafate had 7 and sucralfate had none. On March 5, 1990, Biocraft filed 62 patients enrolled with two DUs" placebo had 27, carafate had 15 and sucralfate had 20. On April 30, 1990, Biocraft filed 52 patients enrolled with two DUs" placebo had 23, carafate had 14 and sucralfate had 15. My revision of the CRFs of eight completed patients listed in the March filing as with two DU revealed that patients 183/1052, 38/1075 and 40/1075, had, in fact, a single DU. Scientific Investigations will have to verify the CRFs of completed patients, not reviewed by this MO claimed by the sponsor as enrolled with two DU.

b) Comments. The presence of multiple ulcers is considered an unfavorable risk factor in the healing of DU (Massarrat S. et al. Risk factor for healing of duodenal ulcer under antacid treatment: do ulcer patients need individual treatment? Gut, 29:291-297, 1988). During the first 30 days of the trial there was a differential dropout of patients enrolled with two DU. This differential dropout favored sucralfate over

over carafate. The following table shows the sequence of dropouts and the imbalances which occurred as a consequence of differential dropouts.

Reviewer Table 11
Patients Randomized With Two Duodenal Ulcers and
Number Dropped by End of Week Four

	Placebo	Sucralfate	Carafate	Total
Total Randomized	93	91	89	273
Number Randomized With 2 DU	24	15	14	53
Percent of All Randomized	26	16	16	19
Number of 2 DU Dropouts by End of Week Four	4	6	0	12
p value	Sucralfate vs Carafate: 6/91 (7%) vs 0/89 (0%); p=0.029*			
Number of Dropouts Without Any Follow-up Endoscopy	2	6	0	
Number of Completed 2 DU by Week Four	20	9	14	43
Percent	22	10	16	81
p value	Sucralfate vs Placebo: 20/93 (22%) vs 9/91 (10%); p=0.042*			

* Two Sided Fisher's Exact Test

The marked imbalances in discontinuation of patients with 2 DU are concentrated in a few centers. In the table shown below I am showing the centers which were involved in these imbalances.

Reviewer Table 12
Centers With Imbalances in the
Dropout of Patients With Two Duodenal Ulcers

Center	Patient	Drug	Disposition by Day 30
1051	121	Placebo	Discontinued after baseline, no f/u endo
	123	Sucralfate	Discontinued after baseline, no f/u endo
	124	Sucralfate	Discontinued at week two visit; treatment failure, no f/u endo
1052	164	Placebo	Discontinued at week 2 visit for lack of efficacy. Meds. dispensed 3 days after entry endoscopy (Protocol violation)
	180	Sucralfate	Unhealed
	182	Carafate	Unhealed
	185	Placebo	Unhealed
	186	Carafate	Unhealed
	189	Placebo	Unhealed
	200	Sucralfate	Discontinued after baseline. LTFU, no f/u endo
1066	052	Carafate	Unhealed
	152	Carafate	Unhealed
	156	Sucralfate	Discontinued after baseline for "inability to tolerate endoscopy".
	255	Placebo	Unhealed
1076	101	Sucralfate	Unhealed
	162	Placebo	Discontinued at week 2 visit. Pt. entered with hepatitis. F/u endo. showed 2 mm erosion.
	209	Sucralfate	Healed
	221	Sucralfate	Discontinued after baseline; "uncooperative patient". No f/u endo
	289	Placebo	Unhealed
	293	Sucralfate	Healed

The review of the above table offers the following observations which may suggest possibility of bias in favor of sucralfate:

1. Four centers (1051, 1052, 1066 and 1076) enrolled 38% of patients with 2 DU (20/53) and accounted for 80% of the 2 DU dropouts (8/10); out of eight dropouts with 2 DU five were sucralfate, three placebo and none carafate. The observed imbalance are against carafate: 5/15 (33%) for sucralfate vs 3/24 (13%) for placebo and 0/14 (0% for carafate.

2. Center 1051 enrolled a total of five patients: three of them with 2 DU (60%). All of the 2 DU patients were discontinued after baseline.

e) Reasons for Discontinuations. My review of the CRFs of discontinued patients revealed relevant information as relates to communication between PIs and monitors as well as interference on the part of monitors in the clinical decisions of PIs. As mentioned, these frequent interactions and interferences are a concern of this reviewer. The CRFs also revealed inconsistencies and uncertainties of the final healing status of some patients and these also adds to the concern. Therefore, it is my belief that this review should contain a comprehensive as well as detail information about the circumstances that led to the discontinuation of patients. I will provide a brief summary of the clinical course of the majority of discontinued patients enrolled with a single DU and with two DUs. With the exception of placebo 240/1053 and sucralfate 108/1055 who had healed ulcers at the time of discontinuation, all other patients who had endoscopy at the time of discontinuation finished unhealed. The ulcer status of patients who did not have endoscopy at the time of discontinuation, in their majority sucralfate and carafate patients, is unknown. The manner in which these patients should be handled in the intent-to-treat analysis will be explained in section 5, page 42 which deals with four week DU healing. The following is a summary of the CRFs of patients with one DU:

Placebo arm

138/1052. Smoker, + history of DU, entered 10/11/88 with a 2 cm DU, tenderness in the abdomen, moderate abdominal pain and a urinary infection. Endoscopist wrote "pt has advanced disease with scarring". Medication was dispensed three days (10/14) after baseline endoscopy. Two weeks later the patient is discontinued "because of failure to improve" and flaring of reflux symptoms. The exit endoscopy showed decrease in ulcer size to 1.5 cm with erosive esophagitis.
Comment: Under study protocol, dispensing antiulcer medication after 48h of baseline endoscopy constitutes a protocol violation, in this case severe because this patient had advanced disease with abdominal tenderness and was in immediate need of antacids. Unclear is the rationale for termination in a patient that already entered with abdominal pain, was started on antacids and experimental medication later than other patients and had a decrease in ulcer size. There is no record in the CRF of a follow-up, e.g. medication, hospitalization.

240/1053 27y male, student, non-smoker - history of DU, had at baseline endoscopy a 0.5 cm bulbar ulcer with severe duodenitis. Two weeks later the patient is discontinued because "he thinks he is receiving a placebo and doesn't want to be in the study any longer". The adverse reaction box was crossed?. The patient had an endoscopy one week later which showed a healed ulcer. On this visit, the lab showed he had a significant decrease in the white count and increase in serum creatinine. Sponsor considered this patient as discontinued 21 days after entry in the patient listing of amendment #4, page 224, Vol. 2. Reason in CRF: voluntarily removed from the study.

107/1055 Non-smoker, + history of DU, moderate abdominal pain and 0.7 cm DU. Patient returned two days later because of increased symptoms. An endoscopy showed a 1 cm ulcer and some fluid retention in the stomach. Patient was discontinued due to treatment failure. No follow up.

185/1058 Smoker, + history of DU, with a 1 cm DU at entry. Medication dispensed 48h later. Patient came for week 2 appointment and stated her symptoms were greatly improved. Patient discontinued 1 month later. There is a last paragraph of a later written on a Tulane Medical Center physician progress note, that states patient would not be able to continue the study. It also states that a representative of was contacted and stated that the patient should continue the study since a patient could not be dropped for non-compliance. The patient was notified. Reason for discontinuation: Lost to Follow-Up (LTFU).

21/1057 Non-smoker, + history of DU, with a 0.3 cm ulcer at entry. The study medication form shows patient had appointment seven days after baseline?. This appointment was supposed to be at two weeks. An endoscopy 12 days later, showed same ulcer size. CRF reason for termination states that "pt. was in the emergency room with an episode of severe vertigo. He stopped the study medication and the symptoms cleared". This patient discontinuation was labeled as an adverse reaction to the drug. Comment: To this reviewer, other than for non-compliance, there was no reason to drop this patient from the study since vertigo is clearly not a side effect of sucralfate.

264/1060 Smoker, + history of DU, with 1 cm ulcer and severe abdominal pain at entry. CRF states that the patient was removed from the study two weeks later for "adverse reaction to study drug". It refers for explanation to page 27. Page 27 refers the adverse reaction as abdominal pain of 10 days duration. There is a comment on a follow-up endoscopy but no endoscopy report with ulcer size. The comment states that the ulcer is still present with development of esophagitis; pt. was placed on H_2 blockers. Comment: This patient may have been dropped for treatment failure, perhaps, but certainly not for an adverse reaction since the patient entered with severe abdominal pain and the investigator was aware of it. Performing an unscheduled endoscopy at 2 weeks without a reasonable justification is of concern to this reviewer.

188/1066 Non-smoker, - history of DU. Returned for week 2 visit and received medication. Reason for discontinuation: LTFU

256/1066 Smoker, + history of DU. 0.8 cm ulcer. Discontinued two weeks later because of enlargement of the ulcer and appearance of erosions in the duodenum and antrum. CRF states that patient was hospitalized.

82/1068 Non smoker, + history of DU, 0.5 cm ulcer at baseline, moderate abdominal pain. Patient had marked improvement of symptoms. Dropped at week 4 because of an increase in 0.3 cm in the ulcer size.

229/1075 Non-smoker, - history of DU, 0.5 cm ulcer at baseline with duodenitis, mild daytime pain. Dropped at week four because of appearance of a second ulcer.

213/1076 Smoker, - history of DU, 1 cm ulcer at baseline. Two weeks after entry the patien is dropped because of "ringing in head". The endoscopy showed an 80% reduction in size of the ulcer, now a 2 mm erosion. Comment: This reviewer fails to understand the removal of a patient with ringing in the head from a study with non-absorbable antiulcer medication. As in a previous case, performing an endoscopy two weeks after entry without clear justification is of concern to this reviewer.

Sucralfate arm.

128/1052 Non-smoker, + history of DU, 0.8 cm ulcer at baseline, severe day and night pain and lactose intolerance. By the two week appointment patient had used all 50 antacid tablets dispensed. Pain had some improvement during the day but continued at night. Patient was very anxious and had to be placed on xanax tablets. Patient was dropped at two weeks. Endoscopy showed an erosion; no size given. Reason for discontinuation: the patient listing of Amendment #4, page 220, Vol. 2 states "Intercurrent illness" as the reason for discontinuation.

205/1052 Smoker, - history of DU, 1.5 cm ulcer with erosion. PI wrote advanced disease, moderate abdominal pain. Dropped at week two with no f/u endoscopy. Reason for discontinuation: LTFU

62/1055 Smoker, unknown history of DU, 0.6 cm ulcer with patchy gastric erythema, severe daytime pain. Dropped 17 days later, LTFU. No f/u endoscopy.

70/1055 Page with DU risk factors and baseline endoscopy report are missing. Patient entered with a hypochromic anemia and severe abdominal pain. This patient took 2 tablets qid of antacids in two weeks. Sponsor stated she misunderstood directions. The patient discontinued on day 17. Endoscopy at the time of discontinuation showed a 0.7 cm ulcer. The final PI comment reads as follows, "Pt was admitted to the study on 11/18/88 with a 0.7 cm duodenal ulcer. Her initial and subsequen labs reflected low Hct, Hgb and RBC values. It was felt that the pt could remain on

study with careful monitoring. There was never any indication of bleeding. At the request of however, this pt was discontinued a few days after her WK 2 visit due to the low lab values. The pt said her symptoms had improved a great deal. A final endoscopy was done at termination. The ulcer was unchanged". Reason for discontinuation: page 225, Vol. 2, Amendment #4 was the following: "Pt. discontinued at request of Pharmakinetics due to contirually low lab results". Comment: This case exemplifies the close contacts of with PI's. The interference of n the PI clinical decision which led to the removal of this patient is of great concern.

108/1088 Non-smoker + history of DU, 0.5 cm ulcer with friability, moderate nighttime pain. By the week 2 appointment patient had increase in abdominal pain and stated that he was "eating antacids like candy". PI stated than an endoscopy (EGD) done on precaution revealed "a markedly improved DU"; no size given. Sponsor declared this patient healed. Comment: the PI did not specify that the ulcer was completely healed. The EGD report stated "ulcer was markedly improved" The endoscopy was included in a "Tulane Medical Center" form and not in the trial's CRF. Ulcer status at the time of discontinuation remains uncertain. This patient was declared terminated at day 29; Reason for discontinuation: LTFU.

187/1188 Non-smoker, + history of DU, 1 cm ulcer at baseline. Sponsor stated patient phoned two weeks after entry and said she had developed a rash, nausea and vertigo. There is a note on a Tulane Medical Center physician's progress report which states that the patient was examined by a GI fellow and discontinued from the study; no date given. No f/u endoscopy.

88/1088 Smoker, + history of DU, 0.5 cm ulcer at baseline, severe daytime pain. Returned for week 2 appointment. Dropped one day after week 2 appointment. However, was given week 4 appointment?, and patient returned on day 31. No f/u endoscopy. Reason for discontinuation: lack of compliance.

239/1039 Smoker, - history of DU, 0.8 cm ulcer with erosions, moderate abdominal pain. Endoscopy at week 4 showed same ulcer size and a second 0.5 cm ulcer. Reason for discontinuation: LTFU. Comment: This patient should be considered a treatment failure.

263/1060 Smoker, - history of DU, 0.5 cm at baseline, moderate nighttime pain. Patient declared LTFU 14 days after entry. No f/u endoscopy.

49/1088 Non-smoker, + history of DU, 0.6 cm ulcer at baseline, moderate nighttime pain. Entered with an SGPT of 343 and a SGOT of 182. Patient dropped from the study one week later due to abnormal liver function tests; SGPT was 311 and SGOT 182. In the endoscopy report at discontinuation the PI stated: "Endoscopy not done per

143/1074 Smoker, + history of DU, 0.5 cm ulcer at baseline, severe daytime pain. Patient declared LTFU three days after entry. No f/u endoscopy.

274/1075 Non-smoker, - history of DU, 0.7 cm ulcer, moderate abdominal pain. Patient declared LTFU one day after entry. Reason: patient refused further treatment. No f/u endoscopy.

Carafate arm

139/1052 Smoker, - history of DU, 1.5 cm ulcer with duodenitis at entry, severe nighttime pain. Patient returned for week two appointment 13 days after entry and was resupplied with medications. The diary cards indicate marked improvement of symptomatology. Patient was declared LTFU; there is no date of discontinuation. In the patient tabulation list of July 5, 1990, and in the database this patient is included with no follow-up visit. No f/u endoscopy.

208/1053 Smoker, - history of DU, 0.6 cm ulcer at baseline with duodenal and antral erosions, mild abdominal pain. Had follow-up endoscopy (day 29) which showed decrease of the ulcer size to 3 mm. The patient tabulation list includes the discontinuation date as of day 29 (day of the follow-up endoscopy); the CRF has no date of discontinuation. The final form was dated 60 days after entry. Reason for discontinuation: LTFU (Page 222, Vol. 2, Amendment #4). Comment: Discontinuing from the study, without justification, a patient on carafate tablets which, as discussed, were easily identifiable, the same day that the follow-up endoscopy showed a marked decrease of the ulcer size does not assure this reviewer that bias was minimized. If, on the other hand, this patient was discontinued on a different day, the sponsor should have been careful to record it.

16/1054 Smoker, + history of DU, 1 cm ulcer at baseline, moderate abdominal pain. Patient discontinued day 15 of the study. Reason: felt symptoms had not improved and refused further treatment. No f/u endoscopy.

64/1055 Smoker, - history of DU, 0.8 cm ulcer at baseline, severe daytime pain. LTFU after baseline. No f/u endoscopy.

69/1055 Smoker, - history of DU, 1.2 cm ulcer at baseline, mild abdominal pain. Returned for week 2 visit but didn't show up for week 4 visit. LTFU. No f/u endoscopy.

268/1059 Smoker, + history of DU, 0.5 cm ulcer at baseline, moderate daytime pain. Had scheduled week four endoscopy on day 30 which showed healing of previous ulcer with "small residual erosion", page 11 of CRF; no size provided. Patient discontinued that same day because he had stopped study medication on the third week and instead took zantac bid for four days. Comment: My review of Amendment #2 indicates that many patients were entered without a washout period after subtherapeutic doses of H_2 blockers and some took, occasionally, H_2 blockers during the trial. Again, dropping

from the trial a carafate patient who had a small erosion on endoscopy, the same day of the endoscopy, does not reassure this reviewer that bias was minimized. This patient was considered as unhealed at week four.

58L/1060 Smoker, + history of DU, 0.4 cm ulcer, moderate abdominal pain. Patient dropped the following day because of location of the ulcer, pyloric or pre-pyloric. After discontinuation, the patient was placed on carafate qid.

141/1074 Smoker, + history of DU, 0.4 cm ulcer at baseline, moderate abdominal pain. Patient called on day 21 of the trial to inform that he had been admitted to the George Washington Hospital; reason not provided. The PI believed the reason for admission may have been psychiatric. No f/u endoscopy.

33/1075 Smoker, - history of DU, 0.4 cm ulcer at baseline, moderate nighttime pain. Dropped on day 15 of the trial. Had an appointment on day 27 of the trial; the PI explained that patient's symptoms had been greatly improved by week 2 of the trial. However, the patient was late for week 2 appointment and had been off the medication for more than a week. No follow-up endoscopy. After discontinuation, patient was placed on carafate 4 g/day.

The following are summaries of the CRFs from patients who were enrolled with two DUs and were discontinued by day 25. Since all carafate patients with two DUs at baseline completed the trial, these CRFs correspond to placebo and sucralfate cases. None of the sucralfate patients with two DUs who departed prematurely had endoscopy at the time of discontinuation, while two of the four placebo patients were endoscoped before termination.

Placebo arm

164/1052 Patient discontinued two weeks after entry; sponsor stated as reason: "lack of efficacy" (page 221, Vol. 2, Amendment #4). My review of the CRF indicates that this patient was a non-smoker, with + history of DU, entered with two 1.0 cm x 1.0 cm duodenal ulcers and moderate abdominal pain. The PI wrote in the comments section of entry endoscopy: "Advanced disease". Medication was dispensed 72 hours after baseline endoscopy. The patient was endoscoped twelve days after dispensing the medication. The PI found no change in DU size and the patient was dropped from the study.

121/1051 Male, smoker with + history of DU entered with two small DU. DU #1 was 0.4 cm, DU #2 was 0.2 cm; mild abdominal day pain. Patient had also history of neck surgery with slight motion limitations. The abdominal pain assessment diary showed complete disappearance of the pain in the first five days. The sponsor's reason for the dropout was that "patient voluntarily decided to withdraw". Signed J.W. In the "investigator's global evaluation" it is stated that "patient voluntarily discontinued the medication since he found difficulty in swallowing them." The difficulty swallowing must have been due to the neck surgery already

available to the PI in the preliminary visit. Swallowing of sucralfate tablets is well known to be difficult, even for normal people. Previous neck surgery and decreased neck motion is a relative contraindication for UGI endoscopy. This reviewer considers dangerous the inclusion of a patient with mild abdominal symptomatology and decreased neck motion in a DU trial which requires repeated endoscopies. The risk of an esophageal perforation in this patient might have increased with every endoscopy.

182/1078 [illegible] year male, non-smoker, with no previous history of DU, had at baseline two small bulbar ulcers. Patient had severe abdominal pain and the preliminary laboratory evaluation form indicates a picture of hepatitis, probably viral with a serum SGPT of 118 IU/L, SGOT of 72 IU/L, elevated alkaline phosphatase (128 IU/dl) and slight leukopenia. These results made the patient ineligible for the study. Yet the patient was entered and randomized to placebo. The lab values worsened at the week two visit. Three days later, the patient had an endoscopy which showed marked improvement: DU #2 was gone and DU #1 was reduced to a 2 mm erosion. The patient was dropped due to "intercurrent illness unrelated to study medication".

142/1074 33 old male, smoker, with + history of DU enrolled to placebo with two small duodenal ulcers. Patient was dropped 15 days later for "non-compliance". No follow-up endoscopy.

Sucralfate arm

209/1052 32 year, male, smoker with + history of DU, randomized to sucralfate with two DUs: DU #1 was 1.5 cm to 2.5 cm, DU #2 was 1 cm to 2 cm in size. At entry the PI noted that the pt. had serious duodenal disease with deformities and erosions". The study medication distribution page of the week two visit shows the medication was assessed and that the patient was resupplied with medications. There is also a note: "will return meds at week 4" and crossing the note: "pt dropped". The final disposition page ("reason for concluding the study") is dated 2 days after the week two visit and states lost to follow-up as a reason for discontinuation.

150/1075 Male, smoker, with + history of DU who had a large 1 cm DU and another 0.4 cm ulcer. The patient returned for the two week visit and was resupplied with medications. Final disposition: LTFU with no follow-up endoscopy.

156/1066 Smoker, with + history of DU, two 0.6 cm bulbar ulcers, moderate daytime pain. An endoscopy 28 days later, failed because the PI was unable to reach the stomach due to lack of cooperation from the patient. This patient was dropped 28 days after entry.

221/1076 Non-smoker, - history of DU, enrolled with a 0.4 cm and 0.3 cm DUs and moderate daytime pain. The CRF has a comment on a serum aluminum level of 19 mcg/L: "has increased. However, pt now being treated for ulcer, + consistent with meds".

124/1051 Smoker, with + history of DU, enrolled with a DU #1 of 1.2 cm and a DU #2 of 0.8 cm plus severe day and night abdominal pain. The patient was seen back two weeks later. On page 8 of the CRF there are two different notes in the "comments" section with two different handwriting. On the top line it says "no cause of recent 2 week history of vomiting was found", the next line reads "Patient dropped from study due to severity of symptoms". The adverse reaction box was crossed out. Comment: This reviewer considers this case eligible as a treatment failure due to increase in GI symptomatology. On the endoscopy report page dated on the same two week visit it is written in the "comments" section: "Endoscopy not done due to inability to contact study patient by phone or mail". The statement is signed by and dated 18 days later of the last visit. The reason for not performing the endoscopy on the follow-up visit, when the patient had severe GI symptoms which appeared to suggest outlet obstruction or possible perforation, remains unexplained to this reviewer.

128/1050 Non-smoker, with + history of DU, 64 y old, with two small duodenal ulcerations, diabetic and with a UTI dropped from the trial 24 hours subsequent to entry because of a protocol violation. The protocol violation was a remote history of perforation of DU which occurred in 1944, forty-four years before entry. The patient had already been dispensed with Biocraft sucralfate.

4. Four Week Window Violations.

The study protocol pre-established days 26-30 as the window for the week four endoscopy. A rigid endoscopy window is necessary to avoid time becoming a confounding variable in the healing process. Endoscopies performed before the first day of the endoscopy window (day 26) are "early" endoscopies and preclude the DU's of the chance for healing. Endoscopies done beyond the last day (day 30) of the endoscopy window have an extra chance for healing. In the July 5, 1990 amendment the sponsor informed us in the a database that a total of thirty-three endoscopies had been performed beyond the pre-established window. The following table details the data.

Reviewer Table 13
Four Week Endoscopies Performed After
Protocol Pre-established Endoscopy Window (Day 30)

Center	Patient	Day of Endoscopy	Disposition
		Placebo	
1049	25	31	Completed
1049	25	38	Completed
1052	199	32	Completed
1052	88	31	Completed
1075	77	35	Completed
1075	195	35	Completed
1075	271	31	Discontinued (appearance of 2° DU at wk 4)
		Carafate	
1052	5	33	Completed
1052	168	31	Discontinued
1052	179	42	Discontinued
1052	184	32	Completed
1052	186	35	Completed
1059	265	36	Discontinued
1066	257	37	Completed
1075	193	32	Completed
1075	198	31	Completed
1076	210	34	Completed
		Sucralfate	
1049	27	31	Completed
1052	166	33	Completed
1052	177	32	Completed
1052	202	31	Completed
1053	236	32	Completed
1054	15	31	Completed
1055	134	37	Completed
1058	89	32	Completed
1060	43	31	Completed
1068	93	31	Completed
1074	253	33	Completed
1075	145	31	Completed
1075	194	39	Completed
1075	233	38	Completed
1075	272	37	Completed
1076	101	33	Completed

The above data allows for the following observations:

a) A total of two hundred forty-seven endoscopies were performed; 33 endoscopies or 13% of total endoscopies were done after the pre-established window.

The analysis reveals that 7/88 (8%) of the endoscopies were in the placebo arm, 10/82 (12%) were in the carafate arm, while 16/77 (21%) were in the sucralfate arm.

b) Of the thirty-three patients endoscoped after the pre-stated endoscopy window twenty-nine patients completed the study, four were discontinued. All discontinued were in the placebo arm (N=1) and the carafate arm (N=3); none in the sucralfate arm. All completed patients were healed. Placebo had 6/93 or 6%, carafate had 7/89 or 8% and sucralfate had 16/91 or 18%. The difference between s vs c p=0.7 and that of s vs p was p=0.046, two-sided.

c) Two centers, 1052 and 1075, were responsible for 55% (18/33) of all four week endoscopy violations.

5. Summary of Discontinuations and Window Violations.

The higher number of sucralfate dropouts, the differential dropout of sucralfate patients with high risks, e.g., two DU's at baseline and previous history of DU, the higher numerical difference in the number of sucralfate patients with late endoscopies, show either combined or individually, a trend that favors sucralfate over carafate. This appears not to have occurred by chance; either numerically or statistically, the analyses appear to confirm the validity of the trend.

6. DU Healing Results

The scientific validity of results which are based on doubtful protection of blinding, discrepancies, inconsistencies and uncertainties are at best questionable. This reviewer will show the four week results filed by the sponsor and the results achieved by the reviewer based on the analysis of the information provided by the sponsor. For a detailed statistical information of the adjustments required for the intent-to-treat analysis the reader is referred to Dr. Huque's review of this trial, pages 10-11 (Dr. M. Huque, Division of Biometrics).

a. Four Week Healing Rate Based on Data Filed in August 16, 1989

In all my analysis, discontinued patients with no follow-up endoscopy or unhealed ulcers at discontinuation will be included as unhealed. Exceptions are placebo and sucralfate patients 240/1053 and 108/1055 who had healed ulcers at discontinuation. This scenario is based on the marked imbalance in the number of dropouts between Biocraft sucralfate and Marion Carafate. As mentioned, by day 26 of the study there were 17 dropouts in the sucralfate arm vs 7 in the carafate arm (19% vs 8%, respectively). This marked imbalance in numbers included qualitative imbalances in high risk factors for 11 of sucralfate vs 4 of carafate were patients with previous history of DU and 6 of sucralfate vs 0 of carafate were patients with two DUs. In view of the imbalance in the enrollment and discontinuation of the higher risk 2 DU patients I will also show the 4 week healing results of patients enrolled with 2 DUs. My review of the patient tabulation list (Vol. 3, page 20, August 16, 1989 filing) revealed that the sponsor included sucralfate patient #156/1066 as healed at week four. This patient was discontinued at week

four with no follow-up endoscopy because of "inability to tolerate endoscopy". This patient was later included as unhealed in the final submitted database of July 5, 1990. This reviewer believes that the inclusion of this patient as healed may have been an oversight in the data computation and will consider him as unhealed in all my analyses. I will first summarize the data of August 16, 1989. However, statistical p values will not be included in this first analysis and will be shown in the final results of July 5, 1990.

1. The following are the healing results of all randomized patients as filed in the original ANDA of August 16, 1989.

Reviewer Table 14

Intent-to-Treat Analysis of All Randomized Patients
as Filed by Biocraft in August 16, 1991, Vol. 3, Pages 1-22

	Placebo	Sucralfate	Carafate
Total Patients	93	91	89
Healed/Total	18/93	38/91	39/89
Percent	19%	42%	44%

2. In its original ANDA, Biocraft filed 24 placebo, 7 carafate and 0 (zero) sucralfate patients as enrolled with 2 DU. The following Table shows the healing rates of patients enrolled with two DUs.

Reviewer Table 15

Four Week Healing of Patients Enrolled With Two Duodenal Ulcers, as Filed by Biocraft in August 16, 1989

	Placebo	Sucralfate	Carafate
Total Patients	24	7	0
Healed/Total	3/24	3/7	0
Percent	13%	43%	0

b. Four Week Healing as Filed by Biocraft on April 16, 1990 and July 5, 1990. The following table shows the healing data obtained from the filing of Amendment #3.

Reviewer Table 16

Intent-to-Treat of All Randomized Patients as Filed by Biocraft on April 16, 1990

	Placebo	Sucralfate	Carafate
Total Patients	93	91	89
Healed/Total	16	40	40
Percent	17%	44%	45%

In the April filing the sponsor also informed us of changes in the 4 wk. healing status of some patients. Placebo 133/1066 was changed from healed to unhealed, carafate 152/1066 from healed to unhealed while sucralfate 93/1068 from unhealed to healed. These changes favored sucralfate.

c. Four Week Healing as Filed by Biocraft on July 5, 1990

On this final filing, the sponsor declared unhealed patients who had been declared healed with endoscopies performed beyond the pre-stated window. There were 33 late endoscopies. I have comments on them in a previous section.

1. The following table shows the healing rate of all randomized patients as filed in the final amendment.

Reviewer's Table 17

Four Week Intent-to-Treat Analysis Based on Data Filed by Biocraft on July 5, 1990

	Placebo	Sucralfate	Carafate
Total Patients	93	91	89
Healed/Total as filed by Biocraft*	15	31	35
Percent	16%	34%	39%

* Healed with endoscopies beyond the pre-established window have been already included as unhealed.

2. The following Table shows the healing rate of patients enrolled with two DU, based on data filed by Biocraft on July 5, 1990.

Reviewer's Table 18

Four Week Healing of Patients Enrolled With Two DU as Filed by Biocraft on July 5, 1990

	Placebo	Sucralfate	Carafate
Total Patients	24	15	14
Discontinued	4	6	0
Healed/Total	2/24	3/15	6/14
Percent	8%	20%	43%

c. In the subsection "a" of the section on "concerns about implementation of randomization...", page 19 of this review I listed five centers which had patterns of repetitive sequences. Combined, these centers enrolled 160 patients. It is of interest to assess the possible impact that the disruption in the implementation of randomized code had on the healing rates in these centers. The following table summarizes the results.

Reviewer Table 19
Four Week Healing Rate of Centers 1052, 1055, 1059, 1066 and 1075 All Patients

Center	Number Pts	Placebo	Carafate	Sucralfate
1052	45	1/15 (7%)	3/15 (20%)	4/15 (27%)
1055	27	0/9 (0%)	2/8 (25%)	5/10 (50%)
1059	28	1/9 (10%)	4/10 (40%)	4/9 (40%)
1066	25	1/9 (10%)	3/8 (38%)	2/8 (25%)
1075	35	2/13 (15%)	6/11 (55%)	5/11 (45%)
All Five Centers	160	5/55 (9%)	18/52(35%)	18/53(34%)

Centers 1053, 1060, 1064 and 1076 enrolled 10 or more patients per center. These centers had repetitive sequences but without a definite pattern. The 4 week healing rate of these centers and the healing rate of centers with low enrollment is shown in the following table.

Reviewer Table 2c
Four Week Healing in Centers 1053, 1060, 1064, 1076 and Centers with Low Enrollment. All Patients Included

Centers	Enrollment	Placebo	Carafate	Sucralfate
1053	20	1/7(14%)	3/6(50%)	1/7(14%)
1060	12	2/4(50%)	1/4(25%)	1/4(25%)
1064	10	1/4(25%)	2/3(67%)	2/3(67%)
1076	26	4/9(44%)	6/8(75%)	6/9(67%)
1074	7	0/2(0%)	0/2(0%)	1/3(33%)
1063	7	2/3(67%)	0/2(0%)	0/2(0%)
1049	6	0/2(0%)	1/2(50%)	1/2(50%)
1058	6	0/2(0%)	1/2(50%)	0/2(0%)
1051	5	0/2(0%)	0/1(0%)	0/2(0%)
1054	4	0/1(0%)	1/2(50%)	0/1(0%)
1057	3	0/1(0%)	0/1(0%)	1/1(100%)
1068	3	0/1(0%)	0/1(0%)	0/1(0%)
1067	2		1/1(100%)	0/1(0%)
1061	1		1/1(100%)	
1050	1		0/1(0%)	
Total	**113**	**10/38(26%)**	**17/37(46%)**	**13/38(34%)**

d. Comments:

1. Inconsistencies.

a. In the database filed with the statistician reviewer, carafate patient 187/1066 was included as having a second 2 cm ulcer at week four which made this patient unhealed. This patient was included as healed at week four in the database filed to the statistician reviewer on April 16 and July 5, 1990. The second ulcer was not included in the database of July 5, 1990. No explanation was given for this apparent discrepancy.

b. Patient 188/1066 was declared healed in the database of April 16, 1990 and unhealed in the database of July 5, 1990.

c. Patient 275/1075 had one ulcer at baseline in the April 16, 1990 database and two ulcers at baseline in the July 5, 1990.

d. The study protocol required complete healing of DU to declare a patient completed at the week 4 endoscopy. Patients 133/1050 (carafate) and 303/1064 (sucralfate) completed the study at week 4 with unhealed ulcers.

2. Results

a. The week four results show equivalence between sucralfate and carafate. The 2 sided p value by Mantel Haenszel test is for sucralfate vs placebo = 0.017 and for carafate vs placebo = 0.0003. The 90% confidence interval for equivalence is between -18% to 8%. This data was taken from Dr. Huque's statistical review, Page 10, Analysis #1.

b. The results appear to be driven by healing rate of centers 1052, 1055, 1059, 1066 and 1075, the centers with patterns of repetitive sequences. The placebo rate in these 5 centers is 9% and the difference between sucralfate and placebo is 25%. In the 15 remaining centers the placebo rate is 26% and the difference between sucralfate and placebo is 8%. In the aforementioned 5 centers the healing rate of carafate is 34% and the healing rate of sucralfate is 1% lower. In the remaining centers carafate patients had a 12% better healing rate than sucralfate. Since the 5 centers had each enrollments of 25 patients or more, it is fair to compare their healing rate to centers with no zero cells and enrollment of 10 or more. Among the remaining 15 centers, centers 1053, 1060, 1064 and 1076 had each enrollments of 10 or more patients and combined for a total of 68 patients. In these centers the placebo healing rate is 8/24 (33%), the carafate rate is 12/21 (57%) and the sucralfate rate is 10/23 (43%), contrastingly different from the 5 centers healing rate and in the opinion of this reviewer closer to expected results with an approved antiulcer drug. This marked differences between groups of major centers suggest a very atypical patient population in those 5 centers and appear to indicate that the patterns of repetitive sequences found in these centers may have impacted on the final healing results.

c. Of concern to this reviewer is the very poor response of the study population to the approved carafate tablets. If we draw an historical comparison between the four week carafate healing rate of this trial and the four week healing rate of the two trials which served as the basis for the carafate approval, we find that this trial's 39% healing rate is markedly lower than the 75% healing rate shown in the McHardy trial and 92% healing rate achieved in the Hollander trial (see this MO review of NDA 19,723, Page 3, Jan. 12, 1990). This unusual response to an approved and marketed antiulcer drug further questions the type of population used in this study.

d. In the subset of patients entered with two duodenal ulcers, sucralfate was not equivalent to carafate in the comparison to placebo. Two sided, the difference between sucralfate vs placebo

is p=0.354 or not significant while the difference between carafate vs placebo is p=0.034. The 90% confidence interval in the difference sucralfate from carafate is between -60% to 17% (this latter analysis was taken from Dr. M. Huque's review, page 8).

7. Summary and Comments of Week Eight Discontinuations, Endoscopy Violations and DU Healing Results

Though not the first analysis in this equivalence trial, the eight week results should solidify and confirm the four week results. The eight week healing results are of more relevance in this case because the four week results showed a rather unusual low healing rate. The results shown, however, indicate a very poor healing rate for the eight weeks endoscopy as well.

a. Discontinuations: Contrary to the forty-three patients discontinued between days 1-30 there were ten patients discontinued between day 31 and the end of the trial. Similarly, in contrast to the eighteen sucralfate patients discontinued between days 1-30, only one sucralfate patient was discontinued between day 31 to the end of the trial. The following is the list of patients and the reasons for the dropouts.

Placebo Arm:

54/1066. The sponsor stated as the reason for discontinuation "intercurrent illness, possibly related to study med. which required hospitalization" (July 5, 1990 tabulation list, Vo. 2, page 232). The ulcer status at termination was healed. My review of the CRF indicates this 41y male was entered with a 0.6 cm DU and severe day and nighttime abdominal pain. At week four the patient had a 3 mm erosion and no adverse reaction. The patient weeks 2 and 4 diaries show no abdominal pain until either the previous or the same day of the endoscopy. Six days later the patient showed LLQ and epigastric tenderness and a high white count. Page 30, Vol. 1 of the original filing had the diagnosis after hospitalization: acute enteritis with vomiting and diarrhea. Apparently, this patient developed an infectious condition, but not related to the study medication.

234/1075. The sponsor stated as the reason for discontinuation "adverse reaction to study medication" (July 5 tabulation list, page 236). The patient was included as unhealed. My review of the CRF indicates this 38y male was entered with a 0.8 cm DU; at week 4 had same ulcer size. Dropped at week 6. The patient had heme + stools; the PI did a rectal digital exam and considered as differential diagnosis fissure vs hemorrhoids. An endoscopy done at the time of discontinuation showed that the DU was healed with remaining erosive duodenitis. As in the previous case, this patient did not have a reaction to the study medication. It is unclear to this reviewer the reason for dropping this patient from the study.

271/1075. Treatment failure. DU increased in size with the appearance of a second ulcer.

301/1064. Lost to follow-up.

Sucralfate Arm:

151/1068. Entered with a 6 mm DU. At week four the size of the DU was 2 mm. Had serum aluminum levels of 82 mcg/L. Pharmakinetics dropped the patient at day 43 because of high serum aluminum levels. The final endoscopy showed residual duodenitis. Included as healed in the tabulation list.

Carafate Arm:

117/1052. Lost to follow-up.

186/1052. Lost to follow-up.

179/1052. 38y male, entered with a 1 cm DU. At the week four endoscopy, done 41 days later, the DU was reduced to an erosion. The patient was considered as lost to follow-up. Included as unhealed.

265/1059 Entered with a 0.7 cm DU. At week four the PI wrote that the patient took the study medication for only five days and had taken 6 1/2 Advil per day for ten consecutive days prior to the week two appointment. The patient was continued in the study. The follow-up endoscopy, done 36 days after baseline, showed healing of DU with no ulcer but 'erosions". The final PI evaluation stated she was dropped because she was not compliant. The PI considered the ulcer "healed with two erosions". The sponsor stated as the reason for the drop out that she was "unable to keep appointments". It is obvious to this reviewer that the intake of Advil may have hampered the time of this patient's ulcer healing. As with previous patients, it is unclear the location of the erosions, but the fact that the PI considered the ulcer healed makes me believe they were not located at the site of the original ulcer. Her status was considered as unhealed by the sponsor.

286/1959. Entered with a 0.9 cm DU and erosions. Week four endoscopy showed "moderate duodenitis with erosions; healing of ulcer". Patient was dropped 45 days later by not returning to the appointment. The PI wrote in the final global evaluation the following: "Ulcer had healed at four weeks with only residual erosions". Included as unhealed.

Comments:

My observations are the following:

1. Of the total 53 discontinuations, only 19% occurred in the last four weeks.

2. Only 1 sucralfate patient was discontinued after the four week endoscopy compared to 18 sucralfate patients dropped before that period.

3. Three of the five carafate patients who were discontinued were discontinued with erosions.

b. Endoscopy Window Violations. As in the four week analysis, I will consider violations all endoscopies done beyond the 58 day. There were twenty-nine violations. The list is shown in the following table.

Reviewer Table 21

Eight Week Endoscopy Window Violations

INV	PATIENT	ENDOSCOPY DAY	DISPOSITION
		Placebo	
1048	25	59	Healed
1048	28	66	Healed
1052	199	62	Unhealed
1053	60	59	Healed
1055	68	59	Unhealed
1055	71	60	Unhealed
1068	190	62	Healed
1075	149	60	Unhealed
1075	195	67	Unhealed
1075	197	63	Unhealed
1076	102	62	Unhealed
1076	292	61	Unhealed
		Carafate	
1051	122	61	Unhealed
1052	101	66	Healed
1052	176	61	Healed
1052	182	72	Healed
1052	186	62	Unhealed
1053	58	61	Unhealed
1063	11	63	Unhealed
1075	198	62	Unhealed
		Sucralfate	
1052	118	62	Healed
1052	130	73	Healed
1052	168	61	Healed
1052	177	60	Healed
1052	184	64	Healed
1060	43	62	Healed
1075	38	60	Unhealed
1075	145	61	Unhealed
1075	233	60	Unhealed

c. Comments:

1. Of the total twenty-nine week eight endoscopy violations, 41% (12/29) were in the placebo arm, 28% (8/29) were in the carafate arm and 31% (9/29) were in the sucralfate arm.

2. The placebo arm had 33% (4/12), healed carafate had 38% (3/8) healed and sucralfate had 67% (6/9) healed.

3. Following the same criteria used in the four week window violations, the eight week window violations will be declared unhealed.

d. Primary Efficacy Results. I will follow the same sequence as in the four week analysis but I will show the final data as filed in July 5, 1990. There were two patients in each arm, enrolled with two DU who healed at week eight. Due to these small number of patients healed with two DU, I will present the healing rate of the total number of patients.

Reviewer Table 22

Eight Week Healing Rate of Total Patients Enrolled

	Placebo	Sucralfate	Carafate
Number of Patients	93	91	89
Number Healed	37	52	52
Healed with window violations; >58 days (unhealed by reviewer)	2	6	3
Healed after corrections	35	46	49
Percent Healed	38%	51%	55%

Comments:

1. The difference between sucralfate and placebo, 13%, is not significant: p=0.102.

2. The difference between carafate and placebo, 17%, is significant: p=0.026.

3. As regard to an eight healing superiority over a placebo control, Biocraft sucralfate and Marion's sucralfate are not equivalent.

4. Compared to each other, the eight week healing rate show no difference.

VII. Summary of the Medical Officer Review:

The following is a brief descriptive list of my comments and analyses.

1. Conduct of the Trial

a. Randomization

1. The sponsor had a prospective randomization code numbered from 1-360. The randomization code had blocks with the three assignments A=placebo, B=carafate and C=sucralfate in six different random sequences. Centers were numbered from 49-68 and from 74-76. Biocraft informed that it shipped to most centers packages containing six consecutively numbered assignments or two consecutive blocks per package. The study protocol requested to enter between 8 and 24 patients per center (page 4 of this review).

2. Consecutively numbered assignments were not matched with consecutively numbered centers. Instead, centers received arbitrarily selected blocks, incomplete blocks combined with complete blocks, disrupted and incomplete blocks shipped by the sponsor or another center plus consecutive numbered assignments were reversed or disrupted either prior to shipment or at the centers. In centers 1052, 1055, 1059, 1066 and 1075 the arrangements of selected blocks resulted in a pattern of repetitive sequences. These 5 centers enrolled from 25-45 patients per center for a total of 160 patients. In center 1052 the first block of the three packages started with the sequence ACB. As a consequence of reversal of two consecutive numbers, the first block of three other packages started with the sequence ABC and as a consequence 7/8 packages started with the same initial assignment A=placebo. Center 1055 received two consecutive packages with the same sequence - CAB, a package combining complete and incomplete blocks and a block from another PI. The PI of this center disrupted the order of several packages. In center 1059 3/5 consecutive packages had two identical sequences/package, e.g., CBA-CBA or BAC-BAC. In this center, the first assignment of two consecutive blocks was always repeated, e.g., C..-C... Center 1066 received 3/4 completed packages with the same initial sequence-CBA. Center 1075 received three consecutive packages with the same initial sequence=ACB and another three started with the same initial sequence=CAB. In one package the initial sequence-CAB was obtained by disrupting the randomized sequence of the block.

b. Blinding

1. Carafate tablets are pink and are stamped in one of the surfaces. The color and stamp are distinguishable features from the smooth yellow colored sucralfate and placebo tablets.

2. The sucralfate tablets are composed of sucralfate 1 G.
The placebo tablets are composed of almost
This composition makes
the placebo tablets more distinguishable by their sweeter taste if splitting of the tablet occurs before swallowing.

3. The randomization code used in the trial was unblinded. Page one of the code specifies the treatment arms by letters: A=placebo, B=carafate, C=sucralfate. There were several coordinators and monitors who had access to this unblinded code.

4. Randomization was in blocks of three assuring enrollment of all treatment arms in a block. A block may have been vulnerable because one of the treatment arms, carafate, had tablets with an easily distinguishable stamp and pink color and because a second treatment arm, placebo, had tablets which may have been sweeter by taste than sucralfate tablets. The vulnerability of the blind increased if the blind is broken for placebo or sucralfate for an adverse reaction. Center 1054 enrolled a total of four patients. The first patient in the block was placebo patient 13 and the blind of this patient was broken due to an adverse reaction. Next in the block was carafate patient 14; carafate tablets were distinguishable. It could have been easily guessed that the third patient in the block was sucralfate.

5. There was frequent communication between observers and PIs for decisions on patient discontinuation, endoscopies on discontinued patients and testing of serum aluminum levels. Sucralfate patient 70/1055 was discontinued at the request of Sucralfate patient 49/1066 was discontinued and the endoscopy at discontinuation was canceled per Biocraft arbitrarily selected patients for serum aluminum level. The large majority selected were patients in the blinded placebo and sucralfate arms. This reviewer counted 71% (66/93) of placebo tested, 62% (56/91) of sucralfate tested and only 16% (18/89) of carafate tested. The difference between s vs c and p vs c has a p value of less than 0.001. Between scheduled and unscheduled this reviewer counted for placebo 146 visits, for sucralfate 153 visits and for carafate only 48 visits. Patient 151/1056 was discontinued by because of an aluminum level of 82 mcg/L. There were several sucralfate patients with high aluminum levels; one carafate patient had levels above 100 mcg and 200 mcg. These patients were not discontinued from the trial.

6. The sponsor changed, post-study, post-FDA filing, after the blind had been broken, the healing status of a number of patients.

c. Discontinuations; Week Four.

1. Number and Chronology of Discontinuations. There were a total of 53 patients discontinued from the trial or 19% of the total enrollment (53/273). A total of 43 patients or 16% (43/273) were discontinued during the first 30 days of the trial. A total of 38

patients were discontinued before the endoscopy window (day 1-25) and that accounted for 14% (38/273) or the majority of discontinuations. There were significantly, p=0.047, more sucralfate, 17/91 (19%) than carafate, 7/89 (8%) patients dropped early from the trial (day 1-25).

2. Endoscopy in Discontinued Patients. None of the 7 carafate patients discontinued between day 1-25 had a follow-up endoscopy More sucralfate, 14/17 (82%), than placebo patients, 5/14 (36%), were dropped from the trial without a follow-up endoscopy. This difference is significant at a p value of 0.012.

3. Discontinuation of Patients With Previous History of DU. There were 56% (52/93) placebo, 60% (53/89) carafate and 51% (46/91) sucralfate patients enrolled with a positive history of DU. During day 1-30 more sucralfate patients with this risk factor, N=11, than carafate, N=4, were dropped from the trial, increasing the difference between the two active arms from 9% at baseline to 16%. This difference, unfavorable to the carafate arm had a p value of 0.034.

4. Discontinuation of Patients With Two DU at Baseline. From the first filing in 1989 until amendment #4 in 1990, Biocraft filed four different numbers for enrollment of patients with two DUs; August 16, 1989 = 31 (P=24, C=7, S=0). March 5, 1990 = 62 (P=27, C=15, S=20). April 30, 1990 = 52 (P=23, C=14, S=15). August 9, 1990 = 53 (P=24, C=14, S=15). This trial had 19% of patients enrolled with two DUs (53/273). Placebo had 26% (24/93), carafate had 16% (14/89) and sucralfate had 16% (15/91). By day 25 of the trial 4 placebo, 0 carafate and 6 sucralfate patients with two DUs had been discontinued from the trial. Two of the four placebo vs 0/6 sucralfate patients dropped had f/u endoscopy. By day 30 there were 22 placebo, 14 carafate and 9 sucralfate patients with two DUs. The difference between p vs s has a p value of 0.042.

5. Review of CRFs From Discontinued Patients. The CRFs examined are, in their majority, incomplete. The baseline endoscopy report and risk factors of sucralfate patient 70/1055 are missing from the CRF. Several progress report notes from PIs are incomplete. Discontinued placebo patients 132/1052 and 164/1052 had medications dispensed 72 hours after the baseline endoscopy. The study protocol pre-stated 48 hours as the maximum allotted time limit to start patients on study medications.

d. Window Violations. A total of 247 four week endoscopies were performed. Thirty-three endoscopies were performed after day 30 of the trial; 8% (7/88) in the placebo, 12% (10/89) in the carafate and 21% (16/77) in the sucralfate arm. Twenty-nine of these patients completed the trial: 6 placebo, 7 carafate and 16 sucralfate. All finished healed. Including all patients, the difference between sucralfate (16/91) vs placebo (6/93) is significant (p=0.046).

e. Week Eight Discontinuations. Between days 30-58 there were 10 patients or 4% (10/273) dropped from the study: 4 placebo, 5 carafate and 1 sucralfate.

f. Week Eight Endoscopy Window Violations. Twenty-nine patients had endoscopies after day 58: 12 placebo, 8 carafate and 9 sucralfate. Placebo had 4 healed, carafate 3 and sucralfate 6.

C. Results

These results include all randomized patients. Discontinued patients with no follow-up endoscopy were declared unhealed. Healed patients with endoscopies performed after 4 wk and 8 wk pre-established endoscopies windows were declared unhealed.

a. Week Four

At week 4 endoscopy placebo healed in 15/93 (16%), carafate healed in 35/89 (39%) and sucralfate healed in 31/91 (34%). The difference between s vs p (18%) has a p=0.017 and c vs p (23%) has a p=0.0003.

The above results appear to be driven by the healing rates of the five centers (1052, 1055, 1059, 1066 and 1075) with a pattern of repetitive sequences. In these centers (N=160) the 4 week healing rate for placebo = 5/55 (9%), for carafate = 18/52 (35%) and for sucralfate = 18/53 (34%). The difference between s vs p is 25% and carafate is 1% superior than sucralfate. In the remaining 15 centers (N=113) the 4 week healing rate for placebo = 10/38 (26%), for carafate = 17/37 (46%) and for sucralfate = 13/38 (34%). In these 15 centers the difference s vs p = 8% and carafate is 12% superior than sucralfate. The difference is more contrasting if a comparison is made between the five centers and centers with no zero cells and enrollment of 10 or more patients each. Centers 1053, 1060, 1064 and 1076 combined for a total of 68 patients. In these centers the healing rate for placebo = 8/24 (33%) for carafate = 12/21 (57%) and for sucralfate = 10/23 (43%).

b. Week Eight

At week eight endoscopy placebo healed in 35/93 (38%), carafate healed in 49/89 (55%) and sucralfate healed in 46/91 (51%) of endoscoped patients. The difference between s vs p is not significant (p=0.102); the difference between c vs p is significant (0.026).

VIII. Recommendation for Regulatory Action

This reviewer will follow the medical review guidelines included in the FDA Staff Manual Guide, BD 4831.1, August 14, 1980.

The four week results of this single trial show equivalence between the sponsor's sucralfate and the marketed carafate. However, there are two important reasons which hamper a recommendation of approvable, at this time. These reasons are the following:

1. Conduct of the Trial. The conduct of this trial was such that it does not allow to conclude that bias was minimized. Although there was a prospective randomization code, the sponsor did not implement the randomization code in an orderly fashion. Centers received arbitrarily selected blocks, incomplete blocks mixed with complete blocks, disrupted sequences of blocks inserted with complete blocks plus the fact that in many occasions consecutive numbered assignments were reversed or disrupted by the sponsor or centers. This allowed for the creation of patterns with repetitive sequences in the five centers with higher enrollment. The blinding was not properly protected for the following reasons: a. The randomization code was unblinded and several coordinators, monitors and observers had access to the code. b. Monitors were in frequent contact with PI's for aluminum levels and for clinical decisions which led to the discontinuation of patients, interference in performing endoscopies and treatments. c. Carafate tablets are stamped and have a distinguishable pink color which do not allow for blinding. d. The randomization in blocks of three which included the three assignments/block was a poor choice because it allowed for permeating the code if either placebo or sucralfate became unblinded, e.g. by an adverse reaction. e. This feeble blocking was compounded by the use of almost [redacted] the placebo tablets which may have made them distinguishable by their sweeter taste. The inadequate implementation of the randomization code and the lack of blinding protection may have led to different healing rates between the five centers with defined patterns of sequences and other centers, to imbalances in the proportion of discontinuations, to a higher number of discontinuations at week four, to imbalances in the discontinuation of poor risk factors for DU healing, to endoscopy window violations and to imbalances in these window violations. My review indicates that these apparent irregularities favored the sponsor's drug. At this time and based on my information, I cannot conclude that this was an adequate and well controlled trial.

This reviewer is requesting to the Director of the Division of Gastrointestinal and Coagulation Drug Products and to the Division of Scientific Investigations to initiate an in-depth investigation on this trial's conduct. This reviewer requests to Scientific Investigations to inquire those individuals responsible for the coordination and implementation of shipment of packages with patient assignments so to assess who was in charge of selecting blocks for shipments and what was the rationale used in the selections; to inquire from coordinators, monitors and statistician who had access to the unblinded randomization code or to the code breaker about their knowledge of patient assignments and frequency of contact with PIs. It is of particular relevance to inquire the PI's of the five centers which had patterns of repetitive sequences as well as other PIs, e.g., from centers 1074, 1066, 1054, 1051 about their knowledge of patient sequences, about the instructions given to them by the sponsor prior or during the trial, about the protocol and randomization code and about the requirement to contact monitors from [redacted] or Biocraft regarding decisions on discontinuations, endoscopies and serum aluminum levels. The PI's should be questioned as of how often were these contacts and who were the monitors they were supposed to contact. It is of further relevance to inquire the PI's about patient responses to ingestion of the yellow tablets and to possible differences in taste between tablets. It would

also be advisable to review the CRF's of a few completed patients enrolled with two DUs, e.g. patients 0145, 0230 from center 1975, patient 059 from center 1053, patient 241 from center 1059 and 293 from center 1076; this in view of the discrepancies in the number of patients with two DU encountered during my review.

It is the recommendation of this reviewer that any decision about approvability be pending on the results and analysis of this in-depth investigation conducted by the Office of Compliance.

2. Clinical Significance. The results of this trial show an unusually low efficacy which is not in accordance with healing rates by an active antiulcer medication. Based on the results of this single trial, a patient receiving a full therapeutic dose of Biocraft's sucralfate plus a few antacids tablets would be expected to have a 34% chance of having the DU healed after one month of treatment and a 51% chance of having it healed after two months of treatment. Similarly, this trial's very low healing rate shown with the approved and marketed carafate does not compare to the high efficacy achieved in the McHardy and Hollander trials (75% and 92%) and U.S. trials which were the basis for the approval of this antiulcer medication. It is possible that the low healing rates obtained in the carafate arm might have been in part due to the rigorour intent-to-treat analysis used by us, the reviewers. However, the four week dropout in the carafate arm, 10% was the lowest of the three treatment arms. The inclusion of the evaluable subset increases the healing rate to only 44% (35/80), still markedly lower than 4 week healing rates achieved in previous trials with the use of carafate tablets. For instance, the inclusion of all randomized patients in the McHardy and Hollander trials results in healing rates of 71% (82/116) and 77% (27/35), respectively. The table shown below represents a review of the english literature and lists healing rates of most of DU trials conducted with carafate tablets up to 1989. This Table 1 is part of the report by Lam S.K., Implications of sucralfate-induced ulcer healing and relapse. The American J. of Medicine, 86(Suppl.6A):122-126, 1989. The table's DU healing rates as pertains to carafate tablets correspond to references 2-10. Reference 11 represent healing rates with carafate suspension, which is a different preparation of carafate. Reference 11 alludes to the report by Martin F. Multicenter study group. Sucralfate suspension 1 g four times per day in the short treatment of active duodenal ulcer, The American J. of Medicine, 86(suppl. 64):104-107, 1989. References 6 and 8 allude to the U.S. McHardy and Hollander trials. The percentages of the table represent four week results with the exception of reference 3 which alludes to six week DU results in a South African population (Moshal M.G., Sucralfate in the treatment of of duodenal ulcers: a double-blind endoscopically controlled trial. South African Med J., 57:742-744, 1980).

TABLE I
Efficacy Studies of Sucralfate in Duodenal Ulcer

	Sucralfate		Placebo		H_2-Receptor Antagonists		
Reference	Number of Patients	Percent Healed	Number of Patients	Percent Healed	Number of Patients	Percent Healed	p Value
[7]	16	69	17	41			<0.02
[8]	30	80	29	24			<0.01
[9]	16	93	16	31			<0.01
[10]	69	80	55	60			<0.05
[11]	109	75	107	64			<0.04
[12]	18	80	17	41			<0.05
[13]	24	92	31	58			<0.0.
[14]	33	72	32	25			<0.02
[15]	17	82	18	39			<0.01
[16]	114	51	112	34			<0.02
[17]	39	83			28 C	71	
[18]	30	86			29 C	76	
[19]	15	67			15 C	73	
[20]	35	91			37 C	84	
[21]	31	71			32 C	75	
[22]	20	55			20 C	80	
[23]	177	77			194 C	77	
[24]	141	79			142 C	76	
[25]	42	74			35 R	74	
[26]	246	80			234 C	80	
All studies	1210	79			766	77	

C = cimetidine, R = ranitidine.

This reviewer recommends to assess the low healing rates achieved in this trial and its questionable clinical significance in any future decision of approvability of this generic sucralfate.

Robert Prizont, M.D.

cc:
ANDA 70-848
HFD-180/Consult File
HFD-180/SFredd
HFD-180/RPrizont
r/d 3/14/91, 8/8/91 9/3/91
9/16/91 jgw
f/t 9/18/91
MED\C\70848103.0R

APPENDIX 1

November 3, 1989

NOV 6 1989

Dr. Bette Barton
Clinical Investigation Branch
HFD-344, Room 125
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

SUBJECT: ANDA 70-848
Sucralfate Tablets, 1 gram
Biocraft Laboratories

Dear Dr. Barton,

Reference is made to your telephone call on October 20, 1989, requesting additional data concerning the order of patient entry into study #8619, "A Comparison of the Effectiveness and Safety of Generic Sucralfate in the Treatment of Duodenal Ulcer Disease."

Due to the initially limited supply of active ingredient, Biocraft was able to manufacture and package enough study medication for 303 patients. The medication was packaged in individual patient packs which were numbered consecutively. Because of the limited number of patient packs and because the packs were randomized in blocks of three, each investigator's initial drug shipment contained enough drug for six patients (six patient packs). Therefore, as shown in Attachment 1, patient numbers run in groups of six across the first drug shipment to most of the investigators. Attachment 1 also lists the patient packs each investigator was shipped, where they were shipped from and which ones were used.

When an investigator needed more study drug, an additional block of six patient packs was shipped from Biocraft. If a site did not use all of the patients packs it was shipped, the remainder was sent back to Biocraft for redistribution or sent directly to another site that required additional drug. The unused patient packs from an original block of six were redistributed as a unit, e.g. if two packs were used out of six, the remaining four packs were redistributed as a block. This method of redistribution was reviewed and approved by the study statistician who determined that the procedure would not affect the overall study randomization scheme.

RECEIVED

Attachment 2 shows the chronological order of patient enrollment for each investigator. Attachment 2 should be used to match your request for Case Report Forms to the order of patient enrollment. site consisted of two centers, one at the Veteran's Administration Medical Center and one at the Tulane Medical Center. was initially shipped 12 patient packs, six for each center. His overall order of patient enrollment reflects the simultaneous enrollment at both sites.

Attachments 3 and 4 are included for your convenience. Attachment 3 is a numerical listing of all patients enrolled in the study. Attachment 4 lists all patient packs which were not used in the study.

If you have any questions please call me at

Sincerely,

ATTACHMENT 1

ATTACHMENT 2

ATTACHMENT 3

ATTACHMENT 1

Listed below is the sequence of patient numbers for PRS-011 per investigative site:

INVESTIGATOR	STUDY MEDICATION SHIPPED FROM	PT. #	PTS. ENROLLED	DATE SHIPPED
	Biocraft	001-006	001-006	04/28/88
	Biocraft	115-120	115-120	07/06/88
	Biocraft	127-132	127-132	07/21/88
	Biocraft	163-168	163-168	10/12/88
	Biocraft	175-180	175-180	10/18/88
	Biocraft	181-186	181-186	10/20/88
	Biocraft	199-204	199-204	10/25/88
	Biocraft	205-216	205-207	10/27/88
	to Biocraft	208-216	--	01/19/89
	Biocraft	007-012	007-012	05/03/88
	Biocraft	103-108	105	06/29/88
		103-104	--	03/14/89
	to Biocraft	106-108	--	02/09/89
	Biocraft to	106-108	--	02/23/89
	Biocraft	013-018	013-016	05/03/88
		017-018	--	03/28/89
	Biocraft	019-024	--	05/03/88
	to Biocraft	019-024	--	05/12/88
	Biocraft	025-030	025-030	05/03/88
	Biocraft	031-036	031-036	05/03/88
	Biocraft	241-246	241-246	11/21/88
	Biocraft	265-270	265-270	12/30/88
	Biocraft	208-216	--	01/19/89
	to Biocraft	286-288	--	02/07/89
	Biocraft	298-300	298-300	02/17/89
	Biocraft	286-288	286-288	03/03/89
	Biocraft	211-213	211-213	03/09/89
		103-104	103	03/14/89
		284-285	--	03/23/89

ATTACHMENT 2

ATTACHMENT 2

INVESTIGATOR	STUDY MEDICATION SHIPPED FROM	PT. #	PTS. ENROLLED	DATE SHIPPED
	Biocraft	037-042	--	05/06/88
	to Biocraft	037-042	--	10/26/88
	Biocraft to	037-042	--	01/30/89
).				
	Biocraft	043-048	043-048	05/11/88
		259-264	259-264	02/03/89
		017-018	--	03/29/89
	Biocraft	049-054	049-054	05/18/88
	Biocraft	151-156	151-156	08/30/88
	Biocraft	187-192	187-192	10/25/88
	Biocraft	253-258	253-258	12/08/88
	to Biocraft	208-216	--	01/19/89
	Biocraft	214-216	214	04/19/89
	Biocraft	055-060	055-060	05/18/88
	Biocraft	169-174	169-174	10/18/88
	Biocraft	235-240	235-240	11/08/88
	to Biocraft	079-084	--	12/12/88
	Biocraft	079-084	079-080	02/06/89
	Biocraft	061-072	061-072	05/19/88
		277-282	277-282	02/03/89
	to Biocraft	106-108	--	02/09/89
	to Biocraft	134-138	--	02/09/89
	Biocraft	106-108	106-108	02/23/89
		157-159	157	03/09/89
		134-138	134-138	03/10/89
	Biocraft	073-078	073-074	05/24/88
	to Biocraft	075-078	--	02/09/89
	Biocraft to	075-078	--	02/23/89
	Biocraft	079-084	--	05/24/88
	to Biocraft	079-084	--	12/12/88
	Biocraft to	079-084	--	02/06/89

STUDY MEDICATION OBTAINED FROM	PT. #	PTS. ENROLLED	DATE SHIPPED
Biocraft	085-090	085-090	05/25/88
Biocraft	157-162	--	09/19/88
	157-159	--	03/09/89
	160-162	--	02/27/89
to Biocraft	019-024	--	05/12/88
Biocraft	019-024	019-021	05/26/88
to Biocraft	022-024	--	03/10/89
Biocraft	091-096	091-093	06/08/88
to Biocraft	094-096	--	04/07/89
Biocraft	097-102	097	06/13/88
to Biocraft	098-102	--	02/22/89
Biocraft to	098-100	--	03/21/89
Biocraft to	101-102	--	04/14/89
Biocraft	109-114	109-114	06/29/88
Biocraft	301-303	301-303	02/17/89
to Biocraft	098-102	--	02/22/89
Biocraft	098-100	098	03/21/89
Biocraft	121-126	121-125	07/20/88
Biocraft	259-264	--	12/15/88
Biocraft	277-282	--	01/12/89
	259-264	--	02/03/89
	277-282	--	02/03/89
Biocraft	133 138	133	08/18/88
to Biocraft	134-138	--	03/09/89
Biocraft to	134-138	--	03/10/89
Biocraft	139-144	139-144	08/23/88
Biocraft	283-288	283	01/26/89
to Biocraft	286-288	--	02/07/89
to	284-285	--	03/23/89

INVESTIGATOR	STUDY MEDICATION SHIPPED FROM	PT. #	PTS. ENROLLED	DATE SHIPPED
	Biocraft	145-150	145-150	08/29/88
	Biocraft	193-198	193-198	10/25/88
	to Biocraft	037-042	--	10/26/88
	Biocraft	229-234	229-234	11/08/88
	Biocraft	271-276	271-276	01/12/89
	Biocraft	037-042	037-042	01/30/89
	to Biocraft	075-078	--	02/09/89
	Biocraft	295-297	295-297	02/14/89
	Biocraft	075-078	075-076	02/23/89
	Biocraft	217-222	217-222	11/07/88
	Biocraft	247-252	247-252	12/02/88
	to Biocraft	208-216	--	01/19/89
	Biocraft	289-294	289-294	01/26/89
	Biocraft	098-102	--	02/22/89
	to	160-162	160-162	02/27/89
	Biocraft	208-210	208-210	03/03/89
	Biocraft	101-102	101-102	04/14/89

ATTACHMENT 2

October 30, 1989

8619 INVESTIGATORS WITH PATIENTS BY START DATE

I AME	INVID	PATID	START DATE
	001976	000217	20-NOV-88
		000218	20-NOV-88
		000219	25-NOV-88
		000220	28-NOV-88
		000221	30-NOV-88
		000222	02-DEC-88
		000247	04-JAN-89
		000248	04-JAN-89
		000249	16-JAN-89
		000250	18-JAN-89
		000251	24-JAN-89
		000252	25-JAN-89
		000289	25-JAN-89
		000290	03-FEB-89
		000292	09-FEB-89
		000291	10-FEB-89
		000293	17-FEB-89
		000294	24-FEB-89
		000160	02-MAR-89
		000161	06-MAR-89
		000162	10-APR-89
		000208	12-APR-89
		000209	14-APR-89
		000210	18-APR-89
		000101	19-APR-89
		000102	25-APR-89

8519 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001049	000025	15-JUN-88
		000026	10-OCT-88
		000027	21-OCT-88
		000028	04-NOV-88
		000029	27-JAN-89
		000030	27-FEB-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001050	000133	25-JAN-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001051	000121	17-OCT-88
		000122	21-NOV-88
		000123	28-NOV-88
		000124	08-DEC-88
		000125	30-JAN-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001052	000001	15-JUN-88
		000002	17-JUN-88
		000003	21-JUN-88
		000004	27-JUN-88
		000005	30-JUN-88
		000006	01-JUL-88
		000115	12-JUL-88
		000116	18-JUL-88
		000117	18-JUL-88
		000118	26-JUL-88
		000119	01-AUG-88
		000120	12-AUG-88
		000127	17-AUG-88
		000128	07-OCT-88
		000129	10-OCT-88
		000130	10-OCT-88
		000131	10-OCT-88
		000132	11-OCT-88
		000164	11-OCT-88
		000163	13-OCT-88
		000165	18-OCT-88
		000166	18-OCT-88
		000167	18-OCT-88
		000168	19-OCT-88
		000175	19-OCT-88
		000176	19-OCT-88
		000177	20-OCT-88
		000178	21-OCT-88
		000179	21-OCT-88
		000180	24-OCT-88
		000181	24-OCT-88
		000182	24-OCT-88
		000183	25-OCT-88
		000184	25-OCT-88
		000185	26-OCT-88
		000186	26-OCT-88
		000199	27-OCT-88
		000200	27-OCT-88
		000201	27-OCT-88
		000202	28-OCT-88
		000203	31-OCT-88
		000204	31-OCT-88
		000205	31-OCT-88
		000206	02-NOV-88
		000207	02-NOV-88

October 30, 1989 8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001053	000055	08-JUN-88
		000056	16-AUG-88
		000057	27-SEP-88
		000058	15-OCT-88
		000059	17-OCT-88
		000060	17-OCT-88
		000169	20-OCT-88
		000170	29-OCT-88
		000171	01-NOV-88
		000172	26-NOV-88
		000173	03-DEC-88
		000174	06-DEC-88
		000235	10-DEC-88
		000236	27-DEC-88
		000237	07-JAN-89
		000238	02-FEB-89
		000239	14-FEB-89
		000240	18-FEB-89
		000079	25-MAR-89
		000080	08-APR-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001054	000013	17-AUG-88
		000014	25-AUG-88
		000015	09-SEP-88
		000016	05-JAN-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001055	000067	12-OCT-88
		000068	09-NOV-88
		000069	14-NOV-88
		000070	18-NOV-88
		000071	04-FEB-89
		000072	12-FEB-89
		000277	12-FEB-89
		000278	12-FEB-89
		000279	12-FEB-89
		000061	13-FEB-89
		000062	18-FEB-89
		000063	22-FEB-89
		000064	25-FEB-89
		000065	25-FEB-89
		000066	04-MAR-89
		000280	04-MAR-89
		000281	08-MAR-89
		000282	11-MAR-89
		000106	13-MAR-89
		000107	27-MAR-89
		000108	29-MAR-89
		000134	05-APR-89
		000135	06-APR-89
		000136	17-APR-89
		000137	24-APR-89
		000138	24-APR-89
		000157	26-APR-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001057	000020	10-NOV-88
		000019	06-DEC-88
		000021	23-DEC-88

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001058	000085	11-JUL-88
		000086	04-AUG-88
		000087	30-AUG-88
		000088	31-AUG-88
		000089	06-OCT-88
		000090	24-JAN-89

October 30, 1989

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001059	000031	23-JUN-88
		000032	09-SEP-88
		000033	12-OCT-88
		000034	21-OCT-88
		000035	31-OCT-88
		000036	18-NOV-88
		000241	22-NOV-88
		000242	23-NOV-88
		000243	02-DEC-88
		000244	21-DEC-88
		000245	30-JAN-89
		000246	03-FEB-89
		000265	07-FEB-89
		000266	13-FEB-89
		000267	14-FEB-89
		000268	15-FEB-89
		000269	16-FEB-89
		000270	17-FEB-89
		000298	17-FEB-89
		000299	02-MAR-89
		000300	03-MAR-89
		000286	06-MAR-89
		000287	08-MAR-89
		000288	10-MAR-89
		000211	13-MAR-89
		000212	14-MAR-89
		000103	19-APR-89
		000213	24-APR-89

October 30, 1989

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001060	000043	28-JUN-88
		000044	07-JUL-88
		000045	20-SEP-88
		000046	27-JAN-89
		000047	14-FEB-89
		000048	15-FEB-89
		000259	21-FEB-89
		000260	21-FEB-89
		000261	22-FEB-89
		000262	28-FEB-89
		000263	23-MAR-89
		000264	30-MAR-89

[redacted] 30, 1989

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001061	000097	27-JUL-88

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
...	001063	000007	13-MAY-88
		000008	27-MAY-88
		000009	14-JUN-88
		000010	28-JUN-88
		000011	27-SEP-88
		000012	01-FEB-89
		000105	22-FEB-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001064	000109	16-NOV-88
		000110	19-DEC-88
		000111	21-DEC-88
		000112	15-FEB-89
		000113	16-FEB-89
		000114	17-FEB-89
		000301	02-MAR-89
		000302	20-MAR-89
		000098	24-MAR-89
		000303	24-MAR-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001066	000049	23-MAY-88
		000050	15-JUN-88
		000051	14-JUL-88
		000052	02-AUG-88
		000053	02-SEP-88
		000054	07-SEP-88
		000151	09-SEP-88
		000152	26-SEP-88
		000153	12-OCT-88
		000154	20-OCT-88
		000155	20-OCT-88
		000156	01-NOV-88
		000187	03-NOV-88
		000188	08-NOV-88
		000189	15-NOV-88
		000190	30-NOV-88
		000191	21-DEC-88
		000192	05-JAN-89
		000253	16-FEB-89
		000254	22-FEB-89
		000255	28-FEB-89
		000256	09-MAR-89
		000257	18-APR-89
		000258	21-APR-89
		000214	26-APR-89

ATTACHMENT 3

ATTACHMENT 4

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001067	000073	18-NOV-88
		000074	12-DEC-88

October 30, 1989

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001068	000091	25-NOV-88
		000092	11-JAN-89
		000093	27-JAN-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001074	000139	13-SEP-88
		000140	26-OCT-88
		000141	17-NOV-88
		000142	08-DEC-88
		000143	12-JAN-89
		000144	06-FEB-89
		000283	15-FEB-89

8619 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	INVID	PATID	START DATE
	001075	000145	13-OCT-88
		000146	14-OCT-88
		000147	19-OCT-88
		000148	22-OCT-88
		000149	01-NOV-88
		000150	01-NOV-88
		000194	03-NOV-88
		000195	03-NOV-88
		000193	05-NOV-88
		000196	05-NOV-88
		000197	10-NOV-88
		000198	12-NOV-88
		000229	17-NOV-88
		000230	22-NOV-88
		000231	29-NOV-88
		000232	05-JAN-89
		000233	13-JAN-89
		000234	21-JAN-89
		000271	21-JAN-89
		000272	21-JAN-89
		000273	24-JAN-89
		000274	27-JAN-89
		000275	28-JAN-89
		000276	04-FEB-89
		000037	07-FEB-89
		000038	11-FEB-89
		000039	11-FEB-89
		000040	14-FEB-89
		000041	16-FEB-89
		000042	18-FEB-89
		000295	22-FEB-89
		000296	25-FEB-89
		000297	25-FEB-89
		000075	25-MAR-89
		000076	13-APR-89

APPENDIX 2

Response 6

The randomization list for the drug codes were produced by who packaged and labeled the clinical supplies for this study.

The envelope containing the blinded code was maintained in a secure Document Control area at upon receipt from Almedica on May 7, 1988. had access to the blinded code in case it was necessary to break the blind for a patient with a serious adverse event. However, the blind was never broken at for any patient during the conduct of the study.

On July 10, 1989 upon completion of the study and after ensuring that the database had been locked with a timed and dated diskette, the sealed, tamper-evident envelope containing the blinded randomization list for Protocol 8619 was opened in the presence of two directors. Biocraft sent a facsimile to on July 10, 1989 to verify the code sent from

Biocraft also retained a copy of the randomization code. Nicholas Maselli, Assistant Director of Regulatory Affairs at Biocraft, approved the randomization code on March 1, 1988. This approval was returned to Biocraft received the blinded code breaker from Almedica on May 5, 1988. Biocraft sent the randomization code to statistical consultant, on April 6, 1988. The randomization code and code breaker were kept locked in Nicholas Maselli's office throughout the conduct of the analysis. All 273 patients completed the study before the blind was broken.

A complete list of persons who had access to the treatment codes is listed below:

At the time of enrollment:

Biocraft Laboratories, Inc.:
Nicholas Maselli, Assistant Director of Regulatory Affairs
Debi Parker, Regulatory Submissions Coordinator

During the study:

Biocraft Laboratories, Inc.:
Nicholas Maselli, Assistant Director of Regulatory Affairs
Debi Parker, Regulatory Submissions Coordinator

After last patient completed the trial:

Biocraft Laboratories, Inc.:
Nicholas Maselli, Assistant Director of Regulatory Affairs
Debi Parker, Regulatory Submissions Coordinator

ll investigators were notified September 11, 1989 of each patient's treatment roup.

f you have any questions concerning this submission, please contact me at 01-703-0400.

hank you.

Sincerely,

BIOCRAFT LABORATORIES, INC.

Nicholas Maselli
Assistant Director of
Regulatory Affairs

biocraft
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Fairfield, NJ 07004
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Fax: 201-575-8089

17 Industrial Park
Waldwick, NJ 07463
Phone: 201-445-3141
Fax: 201-445-8564

5000 Christopher Drive
Mexico, MO 65265
Phone: 314-581-8080
Fax: 314-581-8085

July 15, 1991

FEDERAL EXPRESS
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North #2
Document Control Room #150
HFD-600
7500 Standish Place
Rockville, Maryland 20855

Our Reference
ANDA 70-848

Dear Staff:

Reference is made to my telephone conversation of July 1, 1991 with Mr. Harvey Greenberg of the Office of Generic Drugs regarding submission of the following information and samples to our Abbreviated New Drug Application for Sucralfate Tablets, 1 Gram. Enclosed please find the following:

1. Formula card for Lot 12715 which is the test product used in our clinical bioequivalence study.

2. Samples of two patient packs utilized in the clinical bioequivalence study as follows:

   a. Patient pack #18 which was shipped to to from Biocraft on May 3, 1988 and then shipped from on March 28, 1989.

   b. Patient pack #284 which was shipped to from Biocraft on February 7, 1989 and then shipped from to on March 23, 1989.

(continued)

TO: Staff

RE: ANDA 70-848

We chose to send these patient packs which were not dispensed to a patient so that you will be able to see the double-blind two part tear-off label as described on Page 7 Section B of our clinical protocol number 8619. If we were to send a patient pack which was dispensed to a patient who consequently discontinued from the study, the tear-off portion of the label (which includes the blinding information) would have been detached and affixed to the patient's case report form as per our protocol.

Patient pack 284 has never been opened as evidenced by the tamper evident seal which is still intact. Patient pack 18 has a broken tamper evident seal (which may have occurred during shipment). However the study drugs were unused as ascertained by the CRA who reconciled this patient pack. Upon reconciliation, this patient pack was sealed (taped), initialed, and dated by the CRA, at the study site, prior to shipment back to Biocraft.

3. The following patient packs in question were randomized and shipped to investigators to be dispensed to the patients. However, the investigators that received these patient packs never enrolled enough patients, thus these patient packs were never used. They are as relayed by Harvey Greenberg:

Patient	ARM
#22	Sucralfate Tablets, 1 gram Lot #12715
#23	Carafate Tablets, 1 gram Lot N7257
#24	Placebo Tablets, 1 gram Lot X1715
#81	Carafate Tablets, 1 gram Lot N7257
#82	Placebo Tablets, 1 gram Lot X1715
#83	Carafate Tablets, 1 gram Lot X7257
#84	Sucralfate Tablets, 1 gram Lot 12715
#99	Sucralfate Tablets, 1 gram Lot 12715
#100	Carafate Tablets, 1 gram Lot N7257
#104	Sucralfate Tablets, 1 gram Lot 12715
#215	Sucralfate Tablets, 1 gram Lot 12715
#216	Carafate Tablets, 1 gram Lot N7257

A copy of the relevant pages of our "code breaker" is also attached, identifying the drugs in each patient pack in question. Additionally, we have also enclosed a copy of our randomization code which allows you to view the complete randomization of the study.

Please note that our patient numbers were determined according to which patient pack the patient received, and thus were not always assigned a consecutive patient number.

(continued)

Biocraft Laboratories, Inc.

TO: Staff

RE: ANDA 70-848

In addition, our submission of November 3, 1989 to Dr. Bette Barton, of the Clinical Investigation Branch explains in detail, the shipment of study medication to each investigator, where they were shipped from and which ones were used. It also contained a numerical listing of all patients enrolled in the study and a list of all patient packs which were not used in the study (Attachment 4 of Nov. 3, 1989 correspondence). We would like to point out that this list of patient packs not used in the study differs from the list relayed to us over the telephone by Harvey Greenberg. We have enclosed a copy of our November 3, 1989 submission for your review.

If you have any questions or require additional information, please do not hesitate to contact me.

Thank you.

Sincerely,

BIOCRAFT LABORATORIES, INC.

Debi Parker

Debi Parker
Regulatory Submissions Coordinator

DP/ag

Enclosure

biocraft

LABORATORIES, INC.

Corporate Headquarters
18-01 [illegible]
P.O. Box 848
Fair Lawn, NJ 07410
Phone: 201-796-0400
Fax: 201-797-0421
Fax: 201-797-0018

92 Route 46
P.O. Box [illegible]
Elmwood Park, NJ 07407
Phone: 201-796-3436
Fax: 201-796-1434

202 McLean Blvd
Paterson, NJ 07504
Phone: 201-749-7494
Fax: 201-677-8180

6-10 Slater Lane
Fairfield, NJ 07004
Phone: 201-575-2775
Fax: 201-575-6086

12 Industrial Park
Waldwick, NJ 07463
Phone: 201-445-3141
Fax: 201-445-8564

5000 Christopher Drive
Mexico, MO 65265
Phone: 314-581-8080
Fax: 314-581-8086

July 31, 1991

FEDERAL EXPRESS

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North #2
Document Control Room #150
HFD-600
7500 Standish Place
Rockville, Maryland 20855

Our Reference:
ANDA 70-848

Dear Staff:

In response to Harvey Greenberg's questions during our telephone conversation of today regarding our Sucralfate Tablets, 1 Gram Clinical Bioequivalence Study, please be informed of the following:

1. There was only <u>one</u> randomization of the study drug. The randomization code was submitted in our correspondence dated July 15, 1991. The pages of the "codebreaker" which accompanied our previously submitted samples, are the same randomization.

2. We did not conduct an interim analysis of the data. The randomization code was not broken until the last patient had completed the study. Therefore, an interim analysis of the data, whether for statistical, safety or administrative purposes, could not be conducted.

Thank you.

Sincerely,

BIOCRAFT LABORATORIES, INC.

Nicholas Masalli

Nicholas Masalli
Assistant Director of
Regulatory Affairs

NM/lah

- RIUCRAFT -

MDS 143987

FILE
DATE [illegible]
TIME 10:54:51

PAGE NO. 1

CENTER 1

BLOCK SIZE 3

TREATMENT GROUP(S)
A B C

T G DESCRIPTION

A PLACEBO
B CARAFATE(MARION)
C SUCRALFATE(RIUCRAFT)

TREATMENT GROUPS SEED #: 59566422

A	B	C
1	3	2
4	5	6
8	9	7
12	11	10
13	14	15
18	16	17
21	19	20
24	23	22
25	26	27
28	30	29
31	32	33
34	36	35
37	39	38
42	41	40
44	45	43
46	47	48
51	50	49
54	52	53
56	55	57
60	58	59
[illegible]	63	62
66	64	65
68	69	67
71	72	70
75	73	74
76	77	78
79	81	80
82	83	84
85	87	86
88	90	89
92	91	93
95	94	96
98	97	99
102	100	101
105	103	104
107	106	108
111	109	110
113	114	112
115	117	116
119	120	118
121	122	123
125	126	124
127	129	128
132	131	130
135	133	134
137	138	136
139	141	140
142	144	143
146	147	145
149	148	150
153	152	151
155	154	156
158	159	157
162	161	160
164	163	165
167	166	168
171	169	170
[illegible]	[illegible]	[illegible]

ACCEPTANCE COPY

BY:.........................

DATE:.........................

STUDY

PATIENT TREATMENT GROUP ASSIGNMENT REPORT

RANDOMIZATION

FILE

DATE 12/08/88

PAGE NO. 2

TIME 10:55:26

CENTER 1

TREATMENT GROUP(S)
A B C ..... BLOCK SIZE
3

TREATMENT GROUPS SEED #: 585661122

A	B	C
175	176	177
178	179	180
181	182	183
185	186	184
188	187	189
190	191	192
195	193	194
197	198	196
199	201	200
204	203	202
207	206	205
209	210	208
215	211	212
214	216	213
217	218	219
220	222	221
224	223	225
	226	228
	231	230
	232	227
	237	235
	239	238
243	242	241
246	245	244
248	249	247
252	251	250
255	254	253
256	257	258
260	259	261
264	262	263
266	265	267
269	268	270
271	273	272
275	276	274
278	279	277
281	282	280
285	284	283
288	286	287
289	291	290
292	294	293
296	297	295
300	298	299
301	302	303
306	305	304
307	309	308
311	310	312
313	315	314
316	318	317
321	320	319
323	324	322
325	326	327
328	330	329
	332	333
	334	335
339	338	337

APPENDIX 3

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALBUMINUM B 0.0-6.0 MG/ML
1052/1	Female	1							
		2							
		3							
		3 T							
1052/4	Female	1							
		2							
		4							
1063/8	Male	1							
		2							
		3							
		4							
1063/12	Male	2							
		4							
1054/13	Male	1							
		1 T							
1057/21	Male	1							
		1 T							
1049/25	Female	1							
		2							
		2 U							
		4							
1049/28	Female	1							
		2							
		4							
1059/31	Female	2							
		3							
		4							
1059/34	Female	1							
		2							
		4							
1075/37	Female	1							
		2							

M = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 33-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALBUMINUM B 0.0-6.0 MG/ML
1075/37	Female	3							
1075/42	Female	1 U							
		4							
1060/44	Female	1							
		2							
		4							
1060/46	Female	1 U							
		2							
		3							
1066/51	Male	1							
		2 T							
		1							
1066/54	Male	2							
		2 T							
		1							
1053/56	Male	2							
		4							
		1							
1053/60	Male	4							
		1							
1055/61	Male	1 T							
		1							
1055/66	Male	1 T							
		1							
1055/68	Male	2							
		3							
		4							
		1							
1055/71	Male	2							
		2 T							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

300263

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1075/75	Male	1							
		3							
1075/76	Male	1							
		3							
1053/79	Male	1							
		4							
1058/85	Male	1							
		2							
		4							
1058/88	Male	1							
		2							
		4							
1068/92	Female	1							
		1 T							
		2							
1064/98	Male	1							
		3							
1076/102	Male	1							
		4							
1063/105	Male	1							
		1 T							
1055/107	Male	1							
1064/111	Male	1							
		2							
		4							
1064/113	Male	1							
		1 U							
		2							
		4							
1052/115	Female	1							
		2							
		4							
1052/119	Male	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 MG/ML
1052/119	Male	2							
		4							
1051/121	Male	1							
1051/125	Male	4							
		1							
1052/127	Male	2							
		4							
		1							
1052/132	Male	1 T							
		1							
1055/135	Female	1							
1055/137	Male	1 T							
		1							
1074/139	Male	2							
		3							
		4							
		1							
1074/142	Male	1							
1075/146	Female	2							
		3							
		4							
		1							
1075/149	Male	2							
		4							
		1							
1066/153	Male	2							
		2 U							
		3							
		4							
		1							
1066/155	Male	2							
		4							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALBUMINUM B 0.0-6.0 MG/ML
1076/162	Male	1							
		U							
		T							
1052/164	Male	1							
		T							
1052/167	Female	2							
		4							
1053/171	Male	1							
		2							
		4							
1053/174	Male	2							
		4							
1052/175	Male	1							
		2							
		4							
1052/178	Male	1							
		2							
		4							
1052/181	Male	1							
		2							
		4							
1052/185	Male	1							
		U							
		4							
1066/188	Male	1							
		2							
1066/190	Female	1							
		2							
		4							
1075/195	Male	1							
		2							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 MG/ML
1075/195	Male	4							
1075/197	Male	1							
		2							
		4							
1052/199	Female	1							
		1 U							
		2							
		2 T							
1052/204	Female	1							
		2							
		2 U							
		2 T							
1052/207	Male	1							
		1 U							
		1 T							
1076/208	Male	1							
		3							
1059/212	Female	1							
		4							
1066/214	Female	1							
		4							
1076/218	Female	1							
		1 T							
1076/220	Female	1							
		2							
		3							
1075/229	Female	1							
		2							
		2 T							
1075/234	Male	1							
		2							
		2 T							
1053/236	Male	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1053/236	Male	2							
		4							
1053/240	Male	1							
		1 T							
1059/243	Male	1							
		2							
		4							
1059/246	Male	1							
		2							
		4							
1076/248	Male	2							
		3							
		1							
1076/252	Male	2							
		3							
		1							
1066/255	Male	4							
		1							
1066/256	Male	1 T							
		1							
1060/260	Female	3							
		1							
1060/264	Female	1 T							
		1							
1059/266	Male	4 U							
		4							
		1							
1059/269	Female	4 T							
		1							
1075/271	Male	2							
		3							
		1							
1075/275	Male								

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

300268

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: PLACEBO

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1075/275	Male	2							
		4							
1055/278	Male	1							
		2							
		2 T							
1055/281	Female	1							
		4							
1059/288	Male	1							
		4							
1076/289	Female	1							
		2							
		4							
1076/292	Female	1							
		2							
1075/296	Female	1							
		4							
1059/300	Male	1							
		3							
1064/301	Male	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: CARAFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1052/3	Male	1							
		3 U							
1052/5	Male	1							
		3							
1063/9	Male	1							
		2 T							
1063/11	Male	1							
		2 U							
1054/14	Female	1							
		3							
1054/16	Male	1							
		2 U							
1057/19	Female	1							
		1 U							
		2							
		3							
		4							
1049/26	Male	1							
		2							
		3							
		3 U							
1049/30	Female	1							
		4							
1059/32	Female	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

300270

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: CARAFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1059/32	Female	3							
1059/36	Female	1							
		2							
		4							
1075/39	Male	1							
1075/41	Male	1							
		3							
1060/45	Female	1							
		2 U							
		4							
1060/47	Male	1							
		4							
1066/50	Female	1							
		4							
1066/52	Female	1							
		2							
		4							
1053/55	Male	1							
		2							
		2 T							
1053/58	Male	1							
		2							
		4							
1055/63	Male	1							
		3							
1055/64	Female	1							
1055/69	Female	1							
1055/72	Male	1							
		2							
		2 T							
1067/73	Female	1							
		2 U							
		2 T							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: SUCRALFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1052/2	Male	1							
		2							
		3							
1052/6	Male	1							
		2							
		3							
1063/7	Female	1							
		2							
		3							
1053/10	Male	1							
		2							
		4							
1054/15	Male	1							
		2							
		2 U							
		3							
1057/20	Female	1							
		2							
		3							
1049/27	Female	1							
		2							
		2 U							
		3							
1049/29	Male	1							
		2							
		3							
1059/33	Male	1							
		2							
		8							
1059/35	Male	1							
		2							
		4							
1075/33	Male	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: SUCRALFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1075/38	Male	2							
		4							
1075/40	Male	1 U							
		3							
1060/43	Male	1							
		4							
1060/48	Male	1							
		3							
1066/49	Male	1							
		1 U							
		1 T							
1066/53	Male	1							
		2							
		4							
		4 U							
1053/57	Male	1							
		4							
1053/59	Female	1							
		2							
		4							
1055/62	Male	1							
1055/65	Female	1							
		3							
1055/67	Male	1							
		2							
		2 U							
		2 T							
1055/70	Female	1							
		1 T							
1067/74	Male	1							
		2							
		4							
1053/80	Male	1							

H = MORE THAN 15% ABOVE NORMAL RANGE.
I = MORE THAN 15% INCREASE FROM BASELINE.
D = MORE THAN 15% DECREASE FROM BASELINE.
L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

SPONSOR. BIOCRAFT LABORATORIES, INC.

TABLE A10B

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GRP: ...RALFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1053/80	Male	4							
1058/86	Male	1							
		2							
1058/89	Male	1							
		2							
		4							
1068/93	Male	1							
		2							
		2 U							
1076/101	Male	3							
1055/108	Male	1							
1064/110	Male	1							
		2							
		3							
1064/112	Male	1							
		2							
		3							
1052/116	Female	1							
		2							
		4							
1052/118	Male	1							
		2							
		4							
1051/123	Male	1							
1051/124	Female	1							
		1 T							
1052/128	Male	1							
		1 T							
1052/130	Female	1							
		2							
		3							
		3 T							

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T = TERMINATION VISIT

SPONSOR: BIOCRAFT LABORATORIES, INC.

TREATMENT GROUP: SUCRALFATE

SERUM CHEMISTRY PATIENT LISTING

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 MG/ML
1055/134	Male	1							
		4							
1055/136	Male	1							
		1 T							
1074/140	Male	1							
		1 U							
		3							
1074/143	Male	1							
1075/145	Male	1							
		2							
		4							
1075/150	Male	1							
		2							
1066/151	Male	1							
		2							
		2 U							
		2 T							
1066/156	Male	1							
		2							
		2 T							
1055/157	Female	1							
		1 T							
1076/160	Male	1							
		4							
1052/165	Male	1							
		2							
		3							
1052/168	Female	1							
		2							
		4							
1053/170	Female	1							
		2							
		4							

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SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: SUCRALFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 MG/ML
1053/172	Male	1							
		2							
		3							
1052/177	Male	1							
		2 U							
		2 T							
		1							
1052/180	Male	4							
		1							
1052/183	Male	2							
		2 U							
		2 T							
		1							
1052/184	Female	3							
		1							
1066/189	Male	2							
		2 T							
		1							
1066/192	Male	2							
		3							
		1							
1075/194	Female	2							
		3							
		1							
1075/196	Female	2							
		3							
		1							
1052/200	Male	2							
		1							
1052/202	Male	1 U							
		3							
		1							
1052/205	Male								

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I = MORE THAN 15% INCREASE FROM BASELINE.
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SPONSOR: BIOCRAFT LABORATORIES, INC.

SERUM CHEMISTRY PATIENT LISTING

TREATMENT GROUP: SUCRALFATE

INV/PAT	SEX	VISIT	CHOLESTEROL 0-49 / >49 M 142-183/149-286 F 140-261/156-300 MG/DL	ALKALINE PHOSPHATASE B 31-110 U/L	TOTAL PROTEIN B 6.1-8.4 G/DL	ALBUMIN B 3.3-4.9 G/DL	CALCIUM B 8.4-10.3 MG/DL	INORGANIC PHOSPHORUS B 2.2-5.1 MG/DL	SERUM ALUMINUM B 0.0-6.0 NG/ML
1076/250	Male	1 U							
		2							
		3							
		3 U							
1066/253	Male	1							
		2							
		4							
1066/258	Male	1							
		4							
1060/261	Female	1							
		4							
1060/263	Female	1							
1059/267	Male	1							
		3							
1059/270	Male	1							
		4							
1075/272	Female	1							
		2							
		3							
1075/274	Female	1							
1055/277	Male	1							
		2							
		2 T							
1055/280	Female	1							
		3							
1074/283	Male	1							
		2							
		3							
1059/287	Male	1							
		4							
1076/290	Female	1							
		2							
		3							

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L = MORE THAN 15% BELOW NORMAL RANGE.
U = UNSCHEDULED VISIT
T = TERMINATION VISIT

APPENDIX 4

biocraft

LABORATORIES, INC.

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Fax: 314-581-8085

June 17, 1991

FEDERAL EXPRESS

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North #2
Document Control Room #150
HFD-600
7500 Standish Place
Rockville, Maryland 20855

Our Reference:
ANDA 70-848

Dear Staff:

Reference is made to my telephone conversation of June 12, 1991 with Mr. Harvey Greenberg of the Office of Generic Drugs regarding submission of the following information and samples to our Abbreviated New Drug Application for Sucralfate Tablets, 1 Gram. Enclosed please find the following:

1. Formula Card for Lot X1715 which is the placebo used in our clinical bioequivalence study.

   The lot numbers of the three inactive ingredients which comprise the placebo tablets are indicated in the last column of the formula card.

2. Samples of the Biocraft active and placebo tablets utilized in the clinical bioequivalence study as follows:

   a) Sucralfate Tablets, 1 Gram, Lot 12715 are contained in Patient Pack #22 which contains a two week supply of Sucralfate Tablets (2 blister cards of 36 tablets per card).

(continued)

June 17, 1991

To: Office of Generic Drugs

Re: ANDA 70-848

b) Placebo Tablets, Lot X1715 are contained in Patient Pack #24 which contains a two week supply of Placebo Tablets (2 blister cards of 36 tablets per card).

Both of the above blister cards were sealed (taped), initialed and dated by the CRA who reconciled these study drugs. A copy of the relevant page of our "Codebreaker" is also attached, identifying the drugs in each patient pack.

3. Please be advised that an interim analysis of the clinical data was not conducted.

If you have any questions or require additional information, please do not hesitate to contact me.

Thank you.

Sincerely,

BIOCRAFT LABORATORIES, INC.

Nicholas Maselli
Assistant Director of
Regulatory Affairs

NM/lah
Enc.

,NTMENT
'OWDER
'ABLET
:APSULE

BIOCRAFT LABORATORIES, Inc.

DATE MIXED: 3/27/89 FORMULA CARD

SUCRALFATE TABLETS

FORMULA			Weighed by		Supervised By:	Added to Pot By:		Control
INGREDIENTS	EACH UNIT	% BATCH	Init.	Init.				
Sucralfate	1000 mg		HA	DJ	H Brown	HA	DJ	B402
			HA	DJ	H Brown		DJ	B316
			HA	DJ	H Brown		DJ	B271
			GA	DJ	H Brown		DJ	B213
			PM	JK	P Mullen	PM	JK	B213
Final Standard wt.								

ard Running wt. mg Size Color White Punch See below Type

ctic

ient

Formulated by: Herman Brown 3/27/89

Checked by: [illegible] 3/27/89

t"

Issued by: H. Brown

Date issued: 3/27/89

060

☐ OINTMENT
☐ POWDER
☒ TABLET
☐ CAPSULE

BIOCRAFT LABORATORIES, Inc.

LOT NO. X 1715

DATE MIXED: 2/9/88

FORMULA CARD

QUANTITY Tablets

PLACEBO FOR SUCRALFATE TABLETS

FORMULA			Weighed by	Supervised	Added to	
INGREDIENTS	EACH UNIT	Kg BATCH Gm	Init. Init.	By:	Pot By:	Control
			MG DS	MG	DS MG	A-10485
			MG DS	MG	DS MG	A-10800
			MG DS	[illegible]	DS CG	A-11001
Final Standard wt.						

Standard Running wt.: 1070mg. Size Color white Punch Capsule shaped 0.75" x 0.35" Type

Instructions:

Comments:

Formulated by: H. Aronson 1/22/88

Checked by: Amin HR 1/22/88

Issued by: H Aronson

Date issued: 2/8/88

Attachment 4

The following patient packs were not assigned:

Patient #

17- 18
22- 24
77- 78
81- 84
94- 96
99-100
104
126
158-159
215-216
223-228
284-285
304-322 not shipped

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 27, 1995

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Recommendation Re: Biocraft's Sucralfate, ANDA 70-848

TO: Mr. Jason Gross, HFD-612, MPN 2 113

THROUGH: Director, Office of Drug Evaluation III

Paula Rotstein MD 12/8/95

I agree with Dr Fredd's recommendation - the study is acceptable and the results support bioequivalence.

This application for a generic sucralfate from Biocraft, ANDA 70-848, has been under review since August 25, 1989, and has been the subject of multiple reviews, inspections, amendments and memoranda. A listing of the major documents I have consulted in this overview is as follows:

Sta istical Reviews: July 12, 1991; October 22, 1991; March 17, 1992; February 10, 1994; March 15, 1994; March 30, 1995.

Medical Reviews: September 18, 1991; March 10, 1994; March 23, 1995.

Division Director Memo: October 29, 1991.

DS. Inspections & Memos:

Inspection: March 11, 1993 - April 6, 1993.
Response: July 23, 1993.

De Woskin Memo: August 18, 1993.

Ruff-Lloyd Memo: May 19, 1993.

Lloyd Memo: July 22, 1993.

Barton Memo: May 10, 1993.

Investigator: 1/3-5/90.

Inspections: 6/11-14/90.
11/14-16/89; July 14, 1993.
6/15-18/90.
2/8/90.
7/22-31/91.

Biocraft Letter: August 23, 1995 re databases.

I have assembled these in a review file which is attached. I will address some major concerns raised by this application and provide my perspective and recommendation.

I. Results

The study was a three arm study comparing Biocraft's sucralfate, Marion's Carafate and placebo.

The primary purpose of the study was to demonstrate the bioequivalence of Biocraft's sucralfate to Marion's Carafate. The Orange book now identifies Blue Ridge Laboratories Inc. as the sponsor for Carafate. Blue Ridge is a company formed by Marion, and Marion is now Hoechst Marion Roussel. The Carafate used in Biocraft's study is the same drug under any of these sponsor names.

Since the rate and extent of sucralfate at the site of action could not be determined by PK or PD studies, systemically or locally, a clinical endpoint, i.e. duodenal ulcer (DU) healing at 4 weeks, was chosen as the primary point of comparison for the active drugs. A difference of ± 20% in a 90% CI was thought to be an acceptable difference to establish bioequivalence. Placebo was also included to assure that if the active drugs were bioequivalent in this study, they were also effective. Biocraft submitted the results in 1989. Problems with the case report form listings led to a revised database presentation to the agency in July 1990, which included an independent blinded re-evaluation of all case report forms to classify ulcer healing status. Following a 1993 inspection, an audit of the data entry errors was made where a less than 0.5% rate of errors was claimed by the sponsor. The sponsor has stated to us recently that whatever database is used, all statistical analyses demonstrated that there was no significant difference between Carafate and Sucralfate. However, they have not provided post 1993 results.

The July 1990 revised database was contrasted to the original 1989 database in our statistician's July 12, 1991 review.

Focusing on the 4 week healing results the 1989 results were:

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	83	18	22%	S - P: 29%	<.001
Carafate	82	41	50%	C - P: 28%	<.001
Sucralfate	76	39	51%	S - C. 1%	.885
Total	241 patients	98 patients		90% Confidence Interval (S - C)**: (-16%, 18%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval is calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

The July 1990 amended results demonstrated the following:

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	93	15	16%	S - P: 18%	.017
Carafate	89	35	39%	C - P: 23%	.0003
Sucralfate	91	31	34%	S - C: -5%	.701
Total	273 patients	81 patients		90% Confidence Interval (S - C)**: (-18%, 8%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

These results would lead us to conclude that Biocraft's sucralfate is bioequivalent to Marion's Carafate in this study that also demonstrated the active drugs were better than placebo. After consideration of imbalances between treatment groups (e.g. patients entering with 2 ulcers, patients with only baseline endoscopy, patients with late endoscopy) the statistician in this review concluded that "Biocraft generic sucralfate is more effective than placebo, and is bioequivalent to Carafate in patients with duodenal ulcer."

Table - Week 4 results with adjustments as in Analysis #1
(All randomized patients with 1 baseline ulcer included)

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	69	13	19%	S - P: 18%	.018
Carafate	75	29	39%	C - P: 20%	.010
Sucralfate	76	28	34%	S - C: -2%	.868
Total	220	70		90% Confidence Interval (S - C)**: (-16%, 13%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

This analysis with adjustment for imbalances 1), 2) and 3) discussed above also indicates that, in patients with one baseline ulcer, the generic sucralfate was effective and bioequivalent to Carafate.

II. Audits of the Conduct of the Study

Acceptance of results of this study depends on whether it can be accepted as adequate and well-controlled. One critical feature of an adequate and well-controlled study is randomization.

In the September 18, 1991 medical officer review a discussion of the randomization method is provided. A pattern of repetitive sequences was found for centers 1052, 1055, 1059, 1066 and 1075. The repetitive sequence (for blocks of 6) in a number of cases caused a recurrence of the first drug to be assigned. Not the same recurrent pattern in every center, but a repetition of some assignment sequence nonetheless. This can be appreciated by a chart from the February 10, 1994 statistical review outlining assignments at 3 centers.

Reviewer Table 1

Centers with Repetitive Treatment Assignments

Center 1052		Center 1055		Center 1059	
Patient #s	Assignments	Patient #s	Assignments	Patient #s	Assignments
(1, 2, 3)	A _ _	(67, 68, 69)	C A B	(31, 32, 33)	A B C
(4, 5, 6)	A B C	(70, 71, 72)	C A B	(34, 35, 36)	A C B
(115, 116, 117)	A C B	(277, 278, 279)	C A B	(241, 242, 243)	C B A
(118, 119, 120)	C A B	(61, 62, 63)	A C B	(244, 245, 246)	C B A
(127, 128, 129)	A C B	(64, 65, 66)	B C A	(265, 266, 267)	B A C
(130, 131, 132)	C B A	(280, 281, 282)	C A B	(268, 269, 270)	B A C
(164, 163, 165) switching of patient order	A B C	(106, 107, 108)	B A C	(298, 299, 300)	B C A
(166, 167, 168)	B A C	(134, 135) did not ship the B of BCA	C A	(286, 287, 288)	B C A
(175, 176, 177)	A B C	(136, 137, 138)	C A B	(211, 212)	B A
(178, 179, 180)	A B C	(157) 1st assignment of Block # 53 (CAB)	C	(103, 213)	B C
(181, 182, 183)	A B C				
(184, 185, 186)	C A B				
(199, 200, 201)	A C B				
(202, 203, 204)	C B A				
(205, 206, 207)	C B A				

Questions that arose out of this observation were whether a prospective randomized sequence was used and followed. While we determined that there was a prospective, computer generated randomization sequence, it appeared from run tests not always random. I commented on this in my October 29, 1991 memorandum and suggested that repetitive assignments within some centers may have been the result of the repetitive pre-established sequences going to center activity enrolling patients at a time when those sequences were to be dispensed.

Another major concern was blinding. We knew at the outset that we could not absolutely blind Marion's Carafate which was elongated beyond that which would fit into a 000 gelatin capsule, pink, and stamped "Carafate". That is so for all comparative sucralfate to Carafate studies. Biocraft tried to deal with this by sealing Carafate in white opaque covered blister packs. They also instructed patients not to discuss the drug they were taking with others conducting the study. The pink tinge of the Carafate tablets was noted as a concern re blinding on a May 10, 1993 memorandum from Dr. Bette Barton of DSI which also noted inadequate randomization procedures, particularly related to documentation of and procedures for control of shipments of drug to study sites, direct shipment of drug between investigators, and concerns about "Clinical Supply Requisition" forms. She also commented on inadequate aluminum analyses procedures which made the safety data re aluminum levels not verifiable.

It should also be noted according to an August 18, 1993 memorandum from Inspector De Woskin of the Baltimore District Office, the randomization list was prepared by who packaged and labeled the clinical supplies for the study. It was given to Biocraft where Ms. Parker and Mr. Maselli who were not blinded, and to where the code breaker was kept in an unopened tamper evident envelope.

The inspection 3/11/93-4/6/93 stated that "there was no randomization plan prior to the start of the study," the center investigators did not always schedule 4 and 8 week evaluations at the specified timepoints, there were problems with aluminum collections, and patients with the same birthday were enrolled at center (#1052). An audit of center was recommended. On page 15 of that report it is noted that there was no evidence that the monitors were discussing "test article characteristics" at sites. Indeed there was documentation that stressed the importance of non-communication on this subject between patient and investigator. However, they noted that the person approving shipments of drug from Biocraft to the study centers was unblinded.

On 7/23/93 responded to the inspection findings. At the inspection personnel available for the

inspection were not those who conducted the studies, and required shipping documentation was not available at the inspection. They claim this documentation was made available to Dr. Barton on 6/3/93. The explanation for the reshipment of unused sucralfate was limited supply of that drug. They claimed that shipments were made "in numerical order" on an as-needed basis. Shipping from one site to another was due to very limited supply and occurred at the very end of the study to complete enrollment where time was critical.

Inspections of (center 1052), (center 1075), (center 1055), (center 1059), (center 1066), and (center 1076) were carried out.

No objectionable conditions were noted for and The replicate birthdays for participating patients in center was explained at least in one case by the participation of twins.

For use of an incomplete consent form. reshipping of drug from to Biocraft to (patient number 160-162 study drugs), and in another case from to (patient number 083-084 study drugs) were noted in the inspection.

For 17 out of 35 patients failed to adhere to specified endoscopy times at 4 and 8 weeks.

At center it was noted that records were incomplete, and endoscopies were not scheduled at protocol specified times.

Rather than having the same endoscopist perform all endoscopies on a patient, many co-investigators including fellows participated at center. A list of sub-investigators participating in this center was provided (page 100092) in the ANDA as follows:

Principal Investigator	Sub-Investigators

As has been noted, on May 10, 1993 Dr. Barton issued a memorandum citing the most egregious problem areas for this study as follows:

"I. Inadequate Blinding:

The blisters on the study medication packages were formed of a "white opaque-PVC material" (see page 2 of exhibit 9). The placebo and the Biocraft sucralfate tablets were white in color (see page 4 of exhibit 9); however, the Carafate tablets were pink. The blisters containing the Carafate tablets had a noticeable "pink tinge". Both Biocraft and were aware of this pink tinge (see page 4 of exhibit 9). Due to the pink tinge of the Carafate blisters, issued a memo to the study monitors advising them not to look at the blisters (see "Guideline for Counting of Study Medication at the Investigative Site" dated 20 July 88).

II. Inadequate Randomization Procedures:

1. The "Procedure for Shipping of Study Medication" (see page 2 of exhibit 11) specifies that a "Request for study medication shipment will be received at from testing centers. This information will be documented in memo form. The required memos were not available during the FDA inspection.

2. During the inspection, FDA was unable to document a standard procedure that controlled the sequence of the study drug shipments to the study sites. Although the "Procedure for Shipping of Study Medication" (see page 2 of exhibit 11) specifies that a memo should document a request for drug shipment to a study site, such memo were not available. The CRO suggested that telephone calls and/or monitoring reports may have been used in place of memos but, to date, these alternate methods have neither been documented nor been shown equivalent to a memo for controlling the shipping sequence. Since a consistent procedure for determining the shipping sequence could not be documented, true randomization could not be verified.

"Contract reports" (i.e., memos, telephone calls, monitor memos, etc.) have been requested from (i.e., from on 10 May 93 by CIB).

3. Study drug was shipped directly from one clinical investigator to another. During the inspection no documentation was available that specified a consistent

shipments. The study drugs involved in these shipments from study site to study site (e.g., study drug #103-104, 17-18, 157-9, 259-64, 277-282, etc.) never re-entered the PharmaKinetics inventory for control (see exhibits 12-15).

4. The "Clinical Supply Requisition" forms (see exhibit 12) listed the subject numbers of the study drugs to be shipped to study sites. Many of the subject numbers were hand written (e.g., regulations #18-41), drugs were issued out of numerical sequence (e.g., requisitions #16, 51-65), the study numbers of the drugs to be shipped failed to agree with the study numbers reported as shipped (e.g., requisitions #26, 27), the shipping dates were not reported (e.g., requisitions #35, 38), and unusual quantities of drug packs were sent to study sites (e.g., requisitions #62-64).

III. Inadequate Aluminum Analysis Procedures:

Problems were noted during the inspection with (a) the sensitivity of the method used for the aluminum analysis (see pages 1 and 7 of exhibit 34), (b) the use of incorrect vials (see page 5 of exhibit 34), (c) the contamination of specimens (see pages 1, 7, 9 and 10 of exhibit 34), and (d) the confusion with accession numbers (see page 10 of exhibit 34). Due to significant problems with the aluminum analysis procedures, the aluminum data are not verifiable.

Due to the above observations, DSI is concerned about the blinding, the randomization and the aluminum analyses for this study."

On May 19, 1993 Compliance recommended disqualification of the study as they stated:

"Based upon the inspectional findings, Newark District recommends that the study be disqualified. Newark District has assigned a temporary classification of "AA" and is forwarding the EIR to CDER for final classification.

Specifically, inspectional Observations were cited concerning: Test article accountability; Test article distribution; discrepancies in Case Report forms compared with the Final Report; Validation and Clinical Batch stability analyses; and Tamper evident seals."

Considering the inspection findings, the medical officer in the memorandum dated 3/10/94 provides a summary conclusions and recommendations for regulatory action. The questions raised by the medical officer and statistician were transmitted to Biocraft by OGD in their letter of July 27, 1994. Biocraft's response and the medical officer's evaluation of that response are summarized

in section III of this report.

III. Further Medical and Statistical Reviews

In response to a July 27, 1994 deficiency letter, Biocraft provided a 9/28/94 amendment.

One requested analysis was a comparison of 4 week DU healing rates and equivalence at Center 1052-1055-1059 versus all other centers. Another requested analysis was of the 5 centers with repetitive sequences versus the other centers, and an assessment of treatment by center interaction. Other questions re the randomization plan, and results in large versus small centers was requested.

Biocraft in responding noted that in "none of these subsets was there a larger enough sample size to have sufficient power to have a fair test of inequivalence."

The reported results for the sucralfate-Carafate comparison in various subgroupings were presented by the medical officer as follows:

Equivalence of 4 Week Healing Rates Between Sucralfate-Carafate In Subsets of Centers

Centers Total = 20	Sample Size	Sucralfate	Carafate	90% C.I.[A]	Diff. S-C
1052;1055; 1059;1066; 1075 *	*105*	*18/53 (34%)*	*18/52 (35%)*	*- 16% + 15%*	*- 1%*
1052;1055; 1059	*67*	*12/34 (35%)*	*9/33 (27%)*	*- 11% + 27%*	*+ 8%*
1052;1055	*48*	*9/25 (36%)*	*5/23 (22%)*	*-7% +36%*	*+ 14%*
19 Centers (minus 1052)	150	27/76 (36%)	32/74 (43%)	-20.8% +5%	- 7%
19 Centers (minus 1055)	162	26/81 (32%)	33/81 (41%)	-21% +4%	- 9%
18 Centers (minus 1052;1055)	132	22/66 (33%)	30/66 (45%)	-26% +2%	- 12%
17 Centers (minus 1052;1055; 1059)	113	19/57 (33%)	26/56 (46%)	- 28% +2%	- 13%
15 Centers (minus 1052;1055; 1059;1066; 1075)	75	13/38 (34%)	17/37 (46%)	- 30% +7%	- 12%
All	180	31/91 (34%)	35/89 (39%)	- 17% +7%	- 5%

* Refers to Centers with Repetitive Sequences or First Assignments.
[A] Calculated by M. Huque, Division of Biometrics, CDER/FDA.

For the question of placebo to sucralfate healing rates in various center subgroupings, Biocraft provided the following analysis.

Proportion Healed

Centers	Sucralfate	Carafate®	Confidence Interval
1052-1055-1059	12/34=0.35	9/33=0.27	[-0.11;0.27]
Other Centers	19/57=0.33	26/56=0.46	[-0.28;0.02]

Centers	Sucralfate	Carafate®	Confidence Interval
1052-1055-1059-1066-1075	18/53=0.34	18/52=0.35	[-0.16;0.15]
Other Centers	13/38=0.34	17/37=0.46	[-0.30;0.07]

While Biocraft reported no treatment by center interaction for the placebo-sucralfate comparison, our medical officer and statistician provided a more detailed assessment.

Treatment by Center Interaction; Sucralfate vs. Placebo

Center Groupings	Sucralfate Rate	Placebo Rate	(Sucralfate - Placebo) Difference	2-sided p (Breslow Interaction) *
1052	4/15 (27%)	1/15 (7%)	+20%	0.56
Other 19 Centers	27/76 (36%)	14/78 (18%)	+18%	
1055	5/10 (50%)	0/9 (0%)	+50%	0.077
Other 19 Centers	26/81 (32%)	15/84 (18%)	+14%	
1052-1055	9/25 (36%)	1/24 (4%)	+32%	0.084
Other 18 Centers	22/66 (33%)	14/69 (20%)	+13%	
1052-1055-1059	12/34 (35%)	2/33 (6%)	+29%	0.081
Other 17 Centers	19/57 (33%)	13/60 (22%)	+11%	
1052-1055-1059-1066-1075	18/53 (34%)	5/55 (9%)	+25%	0.087
Other 15 Centers	13/38 (34%)	10/38 (26%)	+8%	

* Calculated by M. Huque, Division of Biometrics, CDER/FDA.

Biocraft provided a table with center by center results for the large centers, i.e. those with six or more patients, and all centers with less than six patients combined as center 2000.

ULCER HEALING RATES FOR SUCRALFATE VS. CARAFATE - CENTER-BY-CENTER

VISIT-WEEK 4 (DAYS ON MED.<31)

CENTER	TOTAL NUMBER OF SUBJECTS	NUMBER HEALED ON SUCRALFATE	PROPORTION HEALED ON SUCRALFATE	NUMBER HEALED ON CARAFATE	PROPORTION HEALED ON CARAFATE	DIFFERENCE IN PROPORTIONS	STANDARD ERROR OF DIFFERENCE
1052	30	4/15	0.26667	3/15	0.20000	0.06667	0.15396
1053	13	1/7	0.14286	3/6	0.50000	-0.35714	0.24323
1055	18	5/10	0.50000	2/8	0.25000	0.25000	0.22009
1059	19	3/9	0.33333	4/10	0.40000	-0.06667	0.22066
1060	8	1/4	0.25000	1/4	0.25000	0.00000	0.30619
1064	6	2/3	0.66667	2/3	0.66667	0.00000	0.38490
1066	16	2/8	0.25000	3/8	0.37500	-0.12500	0.22964
1075	22	4/11	0.36364	6/11	0.54545	-0.18182	0.20875
1076	17	6/9	0.66667	6/8	0.75000	-0.08333	0.21938
2000*	31	3/15	0.20000	5/16	0.31250	-0.11250	0.15522

They found no significant treatment by center interaction.

The medical officer noted considerable differences in some large centers (1052 and 1055) favorable to sucralfate, and different directionality in a grouping of 5 large and 13 small centers.

Other questions addressed by Biocraft included the rationale for supplying "16 days" of extra test article. The reason given was that 16 tablets (4 days) extra were provided to allow for difficulties in scheduling return visits.

Re cancellation of center, they noted that he was not cancelled while actively enrolling patients, but later with limited drug supply and "slow pace" of enrollment at that center that center's participation was cancelled. The medical officer suggests inconsistent application of the "slow pace" reason given to cancel this center's participation.

Biocraft was asked why the ascending random sequences center were not shipped in the next requisition to another center. Biocraft responded that the shipment for the next requisition was ready for shipment prior to cancelling center.

Pursuing the issue of whether Biocraft sent out drug as per the order of the randomized sequence, the question of order of shipments to was questioned. Biocraft's response was that had 9 scheduled endoscopies and only 2 remaining packs, while with slow enrollment shipped unused drug to The medical officer notes that only 1 patient was enrolled on February 4, 1989, not 9. However, Biocraft used the word "scheduled" not enrolled. The medical officer in follow-up comments that he does not agree with Biocraft's response, stating that the record shows they had sufficient time to make appropriate shipments, and the shortage of the article was self-created.

The next question related to a timing discrepancy re an assignment shipped to center. Biocraft explained the dates involved and the process. The medical officer commented on blinding, not timing, in considering this response.

The last question related to mismatches of chronology at center (1055) which according to Biocraft was due to intention to operate two distinct sites (VAMC and Tulane). Apparently enrollment at Tulane was rapid, and use of the VAMC drug supply for Tulane was permitted. The medical officer notes that the monitor who made these switches to Tulane was unblinded (at least to packs 66, 68, and 69). The potential for unblinding by directed assignment from the sponsor or CRO is a major concern of the medical officer.

The medical officer concludes that the randomization, blinding and conduct of the study are inadequate, particularly as related to center (1052) and center (1055) whose results drive the study.

However, the statistical review dated March 27, 1995 finds that the randomization method was adequate, and that, while the magnitude of effect (sucralfate-placebo difference) was 3-4 fold greater in centers 1052, 1055, 1059, 1066 and 1075 pooled versus other centers, both magnitudes are in the right direction and the "other centers" magnitude of effect is heavily influenced by a 25% difference in favor of placebo at center 1060.

IV. Discussion and Recommendation

Since I believe the medical officer and field inspector consider the application not approvable, primarily because the study was not adequate and well-controlled as it was conducted, and, since I reach a different judgment, I must explain.

In my memorandum of October 29, 1991 I discussed many aspects of the study. Since the July 1990 study results provide the

evidence we said we would accept to approve a generic sucralfate, I favor approval of the ANDA.

Of course such results must come from an acceptably conducted study.

This was a prospectively randomized study using a computer generated randomization list. There was reshipment and some out of sequence assignments, but these do not appear to involve any particular centers such as those with "repetitive assignments". In general, the pre-established sequence was followed. The reshipments interrupted the order in no particular direction as far as I can tell, and there is no evidence that patients did not enter the study in the order that they qualified for the study.

While "repetitive sequences" were found at 5 centers, as noted in my October 29, 1991 memorandum this could have been due to recruiting activities at particular centers at particular times. Biocraft did have access to the codes, but I wonder why they would "signal" individuals at certain sites by repeating sequences, rather than simply telling those individuals. Also while 4 centers are identified as having repetitive sequences initially, center interactions, as noted later by the medical officer, involved 2 centers, i.e. 1052· 1055 , in an interaction with the remaining center results. Both of these centers were inspected. had "no objectionable conditions". There were deficiencies at center, but it should be noted that in addition tc as P.I. there were 10 sub-investigators listed at this center, making impractical the use of "repetitive sequences" to alert the endoscopist.

As to treatment by center interactions which certainly are of concern, this was suggested for the placebo comparison (strongly influenced by a high placebo rate at center 1060) to active drug, not the active-active drug comparisons which is the primary test of bioequivalence. One cannot expect confidence intervals of point estimates for healing at 4 weeks for sucralfate to fall with a ± 20% delta at any single center, since the trial was sized for the overall result.

In a three arm study such as this, it is hard to see how one could influence the overall result of a study of bioequivalence by signaling treatment assignments to some centers through "repetitive sequences."

As to blinding, it was known to all pursuing a generic sucralfate that Carafate could not be blinded. Biocraft took some measures to blind Carafate from monitors at the site and the investigators, e.g. the white opaque blister packing and instructing patients, who would undoubtedly know if they were on

Carafate, not to discuss that with the investigator. There do not seem to be concerns that as far as identification of placebo and sucralfate which were blinded to each other, and no evidence was found that the investigator knew the patient's assignment.

Biocraft had access to the code breaker, but whether those sending out the treatment sequences actually consulted the code breaker is not known. However, this was not a stratified study where those sending out treatment assignments know the characteristics of the patient before sending the next sequence. Following the order of the prespecified randomization sequence also protects against the introduction of bias. Neither the sponsor's access to the code breaker nor the recirculation of previously allocated drug are good clinical research practices. While I do not think these are fatal flaws in the conduct of this study, I can understand how others may have a different judgment.

In summary then, I believe the July 1990 results support approval of Biocraft's sucralfate as bioequivalent to Carafate. My judgment that the conduct of the study is acceptable rests on prospective randomization, blinding at the investigator level, a three arm study where equivalence of the two active drugs is the primary comparison, and acceptable inspection at numerous individual centers, but particularly center 1052 center.

Because there is not agreement on the acceptability of this study, I am referring this consultation to the Acting Director, ODE 3, for her opinion. I would also recommend that Biocraft provide the results of the study after all corrections to the database have been made.

Stephen Fredd M.D.
Stephen Fredd, M.D.

cc: ANDA 70-848
HFD-180
HFD-110/Dr. Ganley
HFD-180/RPrizont
HFD-713/MHuque
HFD-344/Dr. Pierce
HFD-181/CSO/BStrongin
HFD-180/SFredd: 11/14/95
f/t deg: 11/14/95/11/28/95
MEMO\ANDA70848.OSF

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

DATE: October 29, 1991

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Response to Consultation on Biocraft Sucralfate ANDA 70-848.

TO: Mr. Robert Pollack, Office of Generic Drugs, HFD-230

THROUGH: Director, Office of Drug Evaluation I, HFD-100

In response to the request for our evaluation of the bioequivalence clinical study of Biocraft's sucralfate tablets and the listed drug, Carafate, the following is offered.

Since sucralfate acts locally to heal duodenal ulcer, a bioequivalence study comparing the healing rates of Biocraft's sucralfate tablets and Marion's Carafate was performed. The design included placebo to assure that the demonstration of bioequivalence of the two sucralfate products also permitted the conclusion that they were active in the particular study performed. Biocraft's study results support the conclusion that Biocraft's sucralfate is bioequivalent to Marion's Carafate as documented in Dr. Huque's statistical review as attached and this medical overview. The four week duodenal ulcer healing rate was prespecified as the primary endpoint and that result for all randomized patients was as follows (per Dr. Huque's review):

Treatment Group	No. of pts.	No. of pts Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	93	15	16%	S - P: 18%	.017
Carafate	89	35	39%	C - P: 23%	.0003
Sucralfate	91	31	34%	S - C: -5%	.701
Total	273 patients	81 patients		90% Confidence Interval (S - C)**: (-18%, 8%)	

P=placebo, C=Carafate, S=Sucralfate
*2-sided p by the Mantel-Haenszel test provided by the sponsor.
**Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

The center by center results as presented by Dr. Huque show a reasonably consistent result for active drugs compared to placebo and to each other.

Table 1

Summaries of Endoscopic Outcomes During Week 4* For All Randomized Patients For the NEW ("Revised") Data Base, July 5th Amendment)

Center # (Size)	No. Healed/Total Randomized, Healing Rate, NH(.)= Number Not Healed During Week 4, M(.)= Number Without Endoscopy During Week 4		
	Placebo	Carafate	Sucrafate
1052 (45)	1/15 (7%), NH(14), M(0)	3/15 (20%), NH(8), M(4)	4/15 (27%), NH(8), M(3)
1075 (35)	2/13 (15%), NH(9), M(2)	6/11 (55%), NH(3), M(2)	4/11 (36%), NH(3), M(4)
1059 (28)	1/9 (11%), NH(8), M(0)	4/10 (40%), NH(5), M(1)	3/9 (33%), NH(6), M(0)
1055 (27)	0/9 (0%), NH(8), M(1)	2/8 (25%), NH(4), M(2)	5/10 (50%), NH(3), M(2)
1076 (26)	4/9 (44%), NH(5), M(0)	6/8 (75%), NH(1), M(1)	6/9 (67%), NH(1), M(2)
1066 (25)	1/9 (11%), NH(7), M(1)	3/8 (38%), NH(5), M(0)	2/8 (25%), NH(4), M(2)
1053 (20)	1/7 (14%), NH(6), M(0)	3/6 (50%), NH(3), M(0)	1/7 (14%), NH(5), M(1)
1060 (12)	2/4 (50%), NH(2), M(0)	1/4 (25%), NH(2), M(1)	1/4 (25%), NH(2), M(1)
1064 (10)	1/4 (25%), NH(3), M(0)	2/3 (67%), NH(1), M(0)	2/3 (75%), NH(1), M(0)
1074 (7)	0/2 (0%), NH(1), M(1)	0/2 (0%), NH(1), M(1)	1/3 (33%), NH(0), M(2)
1063 (7)	2/3 (75%), NH(1), M(0)	0/2 (0%), NH(2), M(0)	0/2 (0%), NH(2), M(0)
1049 (6)	0/2 (0%), NH(2), M(0)	1/2 (50%), NH(1), M(0)	1/2 (5%), NH(0), M(1)
1058 (6)	0/2 (0%), NH(2), M(0)	1/2 (50%), NH(1), M(0)	0/2 (0%), NH(1), M(1)
1051 (5)	0/2 (0%), NH(1), M(1)	0/1 (0%), NH(1), M(0)	0/2 (0%), NH(0), M(2)
1054 (4)	0/1 NH(0), M(1)	1/2 NH(0), M(1)	0/1 NH(0), M(1)
1057 (3)	0/1 NH(1), M(0)	0/1 NH(1), M(0)	1/1 NH(0), M(0)
1068 (3)	0/1 NH(1), M(0)	0/1 NH(1), M(0)	0/1 NH(0), M(1)
1067 (2)	-	1/1 NH(0), M(0)	0/1 NH(1), M(0)
1061 (1)	-	1/1 NH(0), M(0)	-
1050 (1)	-	0/1 NH(1), M(0)	-
Total # of Patients (273)	15/93, (16%) NH(71), M(7)	35/89 (39%) NH(41), M(13)	31/91, (34%), NH(37), M(23)

*In the new data base any endoscopy beyond 30 days was not counted as the Week 4 endoscopy.

Dr. Huque has considered the impact of sponsor revisions of the data, the distribution of two duodenal ulcers among the three treatment groups, patients with only baseline endoscopy, and endoscopies outside of the preset window, and has provided reanalyses that permit the conclusion that the result is still acceptable.

While absolute duodenal ulcer healing rates of sucralfate in other clinical studies are not reliable comparators for the rates found in this trial and the decision on bioequivalence must rest on the results of the submitted study, it may be appropriate to point out that the therapeutic gain (i.e. active drug healing rate minus placebo healing rate) for sucralfate is 18% and for Carafate 23% and the studies of Carafate tablets in the approved labeling indicate a therapeutic gain of approximately 11% in one study and 34% in the other. Duodenal ulcer healing rates can vary considerably in different studies, and the therapeutic gain found in the current trial would be acceptable if those results are the product of an adequate and well-controlled study.

However, questions have been raised in the medical officer's review about the conduct of the trial that deserve careful consideration. While there was a pre-established computer generated randomized sequence, the code breaker was apparently available to Biocraft and staff, although they claimed that the code was not broken during the conduct of the study.

It must be emphasized that the investigators and patients did not have access to the code, and the medication was numbered (1---303), not lettered (A, B, or C). The code breaker was for the letters, not the numbers. Additionally, the protocol did not provide details of the randomization procedure (e.g. that it was blocked by three), and therefore, investigators did not have access to the unblinded assignment order, and they quite consistently followed the numerical order provided to them.

Not only were the drugs identified only by number, but the sponsor made special provision to maintain blinding on site as follows:

"There was a difference in the color of Biocraft Sucralfate and Carafate® tablets that necessitated special blister packaging with white opaque-PVC material. The placebo tablets matched Biocraft Sucralfate tablets. The opaque-PVC material prevented identification of the test substance by the person dispensing the study medication.

In order to ensure the integrity of the blind, a third-party was utilized to dispense test substances to be patients. Patients were instructed not to discuss the tablets they ingested with anyone other than the person who dispensed the test substance to them."

In the rare instances where the pre-established randomized order was not followed, no result suggesting bias could be decerned. For example, in Center 1055 assignments 67-72 preceded assignments 61-66, but the result from each sequence was the same: 1 Carafate and 1 sucralfate healed at 4 weeks. In Center 1059 where assignment 103 (Carafate) preceded assignment 213 (sucralfate), the Carafate patient healed at 4 weeks, the sucralfate patient did not. Since the study result must establish equivalence of the two active drugs and a benefit over placebo, it would be difficult to "game" the system in a simple way, and the few reversals of assignment that occurred suggest error, not bias.

The finding that within certain centers there were repetitive assignment sequences is interesting. Since the assignments were numbered, not lettered, and the investigators did not know the blocking patterns, it is not clear what effect the repetitive assignment patterns had, whether they were purposely selected or happened by chance. For example, it is noted in the medical officer report that Center 1052 had the same sequence ACB for the first three packages of 6 sent. Is this chance, or some sort of method to make it possible to discern the drug assignment and bias the results? If the code breaker was consulted and communicated to the investigator, no such indirect signals would be needed, but on first glance it does appear unlikely that such repetition could have occurred by chance. However there were 24 ACB sequences in the pre-established randomization sequence where 18 would have been expected. Also, the distribution of ACB sequences was uneven throughout the sequence. For assignments 115-150 (when Center 1052 was being resupplied) the ACB pattern began 4 sequences out of 9, where 1.3 ACB sequences would have been expected. Chance alone may be a reasonable explanation for what occurred, but it would be prudent to determine the procedure by which sequences were sent to the centers, particularly whether the responsible party had access to the code breaker, and whether selections sequences were chosen for specific centers.

The medical officer is concerned that, although the centers were numbered 1049-1068 and 1074-1076, drug assignment numbers were not made in order, i.e. 1049 received 1-6, 1050 received 7-12 etc. Rather, Center 1052 received 1-6. This concern must relate to the first shipment and not to subsequent shipments which had to be based on the timing of patient enrollment. It would not be necessary to ship additional drug to Centers 1049, 1050, 1051, 1054, 1057, 1058, 1061, 1067, 1068 since they did not enroll more than 6 patients each. The implementation of the pre-established randomization schedule depended more on the time of patient enrollment at the centers than arbitrarily assigned center numbers. I cannot ascribe any importance to the fact that Center 1052 received 1-6 rather than Center 1049.

Those centers that did not use drug disposed of the unused supply by either sending it back to Biocraft or to another investigator (probably under instructions from Biocraft). Although the drug was identified only by number, some selection of investigator who would receive the allocation rather than the next allocation in the order might have occurred, but this seems immaterial if the blind was maintained. There is no evidence that the healing results of patients receiving the reshipped drug were "better" than for those receiving initial shipments (e.g. Center 1067 sent numbers 75-78 to Biocraft who shipped them to Center 1075. Only drug numbers 75 and 76 were used, both were placebo, both healed).

For safety the medical officer review provides table 6 on page 25 suggesting that significantly fewer patients on Carafate had serum aluminum determinations, and since there was interaction between the monitors and investigators on serum aluminum findings there may have been more opportunity to interact about placebo or sucralfate patients, and if unblinded bias might have been introduced. Noting that the basis for table 6 may have been incomplete, I received information from Biocraft in a report of October 11, 1991 that 66 Placebo patients, 63 Carafate patients, and 65 Sucralfate patients had serum aluminum tests. Even without a difference, the issue of communication of monitor and investigator is important if the blind was not maintained. That seems to be the central question for further scientific investigation of this study, and, therefore, although the result of this study does support the finding that Biocraft's Sucralfate tablet is bioequivalent to Marion's Carafate tablet, I would recommend that DSI investigate Biocraft and particularly to determine whether the blind was maintained. This can be done by interviewing all who had access to the code, procedures of shipping and assigning drug, and assessing interactions during the conduct of the study. We will be happy to review the DSI report, and make a final recommendation at that time.

Stephen Fredd, M.D.

cc:
HFD-180/Consult File
HFD-180/Prizont
HFD-181/Hassall/Budabin
HFD-632/PRickman
HFD-713/MHuque
HFD-344/BBarton
HFD-180/SFredd
f/t dcg: 10/29/91/11/6/91
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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date July 2, 1987

From Acting Deputy Director
Division of Gastrointestinal and Coagulation Drug Products, HFN-180

Subject Biocraft Protocol for Sucralfate ANDA 70-848

To Director, Division of Generic Drugs, HFN-230
Through: Director, Office of Drug Research and Review, HFN-100

Robert Temple 7/15/87

Biocraft's proposed protocol to obtain an ANDA for their sucralfate would not be acceptable as an ANDA and could not lead to an AB rating. To file an ANDA for the listed drug sucralfate a sponsor must propose a controlled clinical trial which would compare the generic version to the originator's product and placebo. If such a basic design is submitted, we will be glad to review the details of such studies to assure that appropriate endpoints and safety parameters are included.

Other designs that do not include a comparison to the originator's sucralfate, such as Biocraft's proposed comparison of their generic version to placebo, would not qualify as an ANDA submission, but rather as a 505(b)2 submission and should be referred to this division as an NDA.

Should there be questions concerning this procedure, we will be happy to respond.

Stephen L. Kredd MD
Stephen L. Kredd

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

DATE: September 18, 1989

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Conducting an In-Vivo Bioavailability Study for Biocraft's Sucralfate.

TO: Harvey A. Greenberg, HFD-232

On September 14, 1989 you requested that we review Biocraft's request for a waiver of an in vivo bioequivalence study for a new supplier of the sucralfate drug substance. Biocraft has a pending ANDA for their sucralfate in which they used as the supplier for the bioequivalence trial. In their ANDA they are requesting an equivalence rating to Marion's Carafate for their sucralfate. They now request to have as an alternative supplier for the drug substance, and propose that chemical and physical testing of active ingredients and finished products should be adequate to permit a waiver of in vivo bioavailability.

Since sucralfate does not exert its therapeutic action by systemic absorption, and we do not know which chemical and physical features of sucralfate are essential to provide ulcer healing, we cannot recommend that Biocraft's request be granted. It would be useful to know if this drug substance has ever been used clinically to heal duodenal ulcer, and, if so, what results were obtained.

Stephen Fredd M.D.

Stephen Fredd, M.D.

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

DATE: May 2, 1988

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Response to Consultation re Biocraft Submission of April 27, 1988.

TO: Mr. Robert Pollock, Division of Generic Drugs, HFD-230

On April 27, 1988, Biocraft submitted a document which provides chemistry information and a clinical safety protocol. The sponsor requests a waiver from conducting any clinical trial to gain approval for the product based on the chemistry information submitted. In response to your request of May 10, 1988, for our consultation on the protocol and waiver portions of Biocraft's document, the following is offered.

There is no discussion or data presented as to how the chemistry information is correlated with Carafate's therapeutic effect other than in its ability to form in an acid environment an ulcer adherent complex. Other postulated mechanisms of action for Carafate in the treatment of acute duodenal ulcer were discussed at the meeting of January 25, 1988 with Biocraft, and in brief are the following:

1. Binding and protecting the ulcer site.
2. Stimulating the endogenous release of prostaglandins.
3. Binding bile acids.
4. Binding pepsin and/or decreasing pepsin activity.
5. Stimulating mucus production.
6. Stimulating bicarbonate production.
7. Increasing potential difference.
8. Binding and increasing residence time of Epidermal Growth Factor at ulcer site.
9. Stimulating DNA and protein synthesis ("Regereration").

Given the number and complexity of Carafate's postulated modes of action and in the absence of data that demonstrates equivalence of formulations in producing each of these effects, we continue to believe that a clinical safety and efficacy trial is needed, and consequently that a waiver of clinical studies is not justified by this submission.

Biocraft actually provides the protocol for a placebo controlled clinical study of their Sucralfate tablet. It is remarkable that they propose endoscopy at baseline, 4 and 8 weeks but plan no efficacy evaluation. That wastes clinical data that is relevant to the evaluation of their product. Such efficacy evaluation will be needed for any Sucralfate approval at this time, but even if included in the present protocol, the design would not provide sufficient information for Biocraft's Sucralfate to receive an AB rating, since there would be no clinical comparison to Marion's Carafate. An amended design which involved only comparison to placebo could lead to approval of Biocraft's product without an AB rating.

Should Biocraft desire to obtain an AB rating for their Sucralfate, we suggest a blinded randomized parallel eight week study with three test arms-- placebo, Biocraft's Sucralfate and Marion's Carafate in patients with acute duodenal ulcer. To reduce the number of patients needed for the trial, an unbalanced randomization for placebo and a one tailed test may be employed, and a difference of 20% between the active arms which could be detected with 80% power would be acceptable for efficacy. The safety evaluations should include serum aluminum determination, and, although it is preferable to use a non-aluminum containing antacid, it is understandable that this may not be feasible clinically.

We will be glad to provide further reviews as needed.

Stephen Fredd M.D

Stephen Fredd, M.D.

STATISTICAL REVIEW & EVALUATION

JUL 12 1991

ANDA #: 70-848

APPLICANT: Biocraft

DRUG NAME: Biocraft's Sucralfate 1 gm tablet
(Generic Drug)

INDICATION: Duodenal Ulcer

DOCUMENTS REVIEWED:

Volumes I to III, dated August 15, 89
Volumes I to IV, dated February 15, 1990

Amendments April 16, 1990
Some data on floppy diskettes filed with this amendment.

Volumes I to VIII: Amendment July 5, 1990
New "Revised" duodenal ulcer healing data base on floppy diskette filed with this amendment.

The issues addressed in this review have been discussed with Dr. Robert Prizont, M.D., the Medical Officer, and with Dr. Stephen Fredd, the Director of the Division of Gastrointestinal and Coagulation Drug Products.

I. INTRODUCTION

The sponsor has conducted a randomized three-arm placebo-controlled trial to establish bioequivalence between the two formulations of sucralfate (a generic sucralfate formulation vs the standard Crafate formulation). The primary clinical endpoint studied for this purpose is the week 4 healing rate of duodenal ulcer. The choice of this clinical endpoint is consistent with the fact that the original Carafate studies were 4 week studies.

This review will consider two questions: 1) Is the trial valid to determine the equivalence of two sucralfate formulations? That is, is there evidence that the formulation(s) are effective compared to placebo? 2) Are the two active agents bioequivalent?

The validity issue of this trial has been reviewed by making sure that at least one of the two active treatment groups was statistically superior to placebo with respect to week 4 healing rate at the .05 level of significance using a two-sided test. The bioequivalence question has been reviewed on using a 90 percent confidence interval criterion: If for the given clinical endpoint the 90 percent confidence interval of the treatment difference, (i.e., the response rate of the test drug minus the response rate of the reference drug), falls strictly within the plus/minus 20 percent limits around zero then the test drug is accept as clinically equivalent to the reference drug.

II. STUDY DESCRIPTION

2.1. Design

The study was designed as a randomized, double-blind, multi-center, three-arm placebo-controlled trial to establish bioequivalence between the generic sucralfate 1 gm tablet and the Carafate 1 gm tablet. This bioequivalence between the two non-absorbable products was to be determined on using the clinical endpoint which was the healing rate of duodenal ulcer after 4 weeks of treatment as prespecified in the protocol. Patients were treated in this trial for eight weeks. Endoscopies were taken at baseline, at weeks 4 and 8. Antacids were allowed but discouraged during the trial; 'Philips' Milk of Magnesia tablets were originally dispensed, but later, through protocol amendments, Maalox No. 2 tablets were dispensed. The patient-visits to clinics were to occur at baseline, and at weeks 2, 4, 6, and 8. The visit days for these scheduled visits were structured as: Week 2 (days 13 -15), Week 4 (days 26 -30), Week 6 (days 40 -44), Week 8 (days 54 -58). The attached chart "Study Schedule" lists the information recorded at various visits.

The patients at entry were to have an endoscopically verified duodenal ulcer of at least 0.3 cm in diameter and not exceeding 2.5 cm. Patients with 2 baseline ulcers were also allowed in the trial.

The protocol criteria for efficacy evaluation were as follows:

"1. Patients must be complaint for at least seven days on study medication and have at least one on-therapy clinical evaluation beyond the preliminary evaluation.

2. Valid endoscopic examinations require that the patients be between 75% and 125% compliant in the assessment period preceding the procedure.

3. An intent-to-treat analysis will be conducted on all patients who participate in the study regardless of treatment compliance. This will include a comparison of baseline evaluations to all on-therapy clinical evaluations. "

The protocol defined the primary measure of effectiveness as:

> "The primary efficacy parameter will be the percent of patients whose ulcers have healed at week 4. A positive response requires endoscopic evidence of complete healing. All other patients who are evaluable based on the criteria above will be considered non-responders at Week 4 and at the final evaluation. The final evaluation will be also tested however since spontaneous healing frequently occurs with time, the difference between the active and placebo response rates may not be as great as at the earlier time point (Week 4) and thus, not statistically significant. "

The protocol indicated that a patient healed at week 4 will be discontinued from the study, and a patient not healed at week 4 will continue taking study medication until week 8 at which time another endoscopic examination will be performed.

The protocol defined the ulcer healing as normal or hyperemic mucosa and failure to heal as erosion or ulcer. The following grading scale was to be used to describe the duodenum:

1. Normal or Hyperemic

2. Erosion - defined as a discontinuity of epithelium without any definite crater formation.

3. Ulcer - defined as discontinuity of epithelium without any definite crater formation.

2.2 Randomization & Blinding

The randomization chart filed with the ANDA indicated that the patients were randomly allocated to the three treatment group using sequence(s) of random numbers generated by the computer. The randomization was done in blocks of three patients. These treatment assignments were done before the trial started. As the treatment assignments were not displayed by center it was not possible to say that these randomization were blocked by center. The sponsor stated that:

> " A patient number and a medication kit will be assigned at the time the patient receives study medication. The medication kit number will be randomly assigned using a computer generated sequence to contain either generic sucralfate, 1 gm tablets, Carafate 1 gm tablets, or placebo matched tablets."

The study medication was supplied for each patient in a large outer container (Patient Pack), four inner containers (Dispenser Packs) and Blister Cards (two blister cards per Dispenser Pack). Dispenser Packs and Blister Cards identified the study number, patient number, patient initials, and dosage instructions. Tablets packed were: Biocraft Sucralfate 1 gram tablets (white); Carafate 1 gram tablets (pink) and placebo 1 gram tablets (white). The Patient Pack was to be labeled in a double-blind manner using a two-part tear-off label. The part of the label attached to the medication container was printed with the patient number, study number, and dosage instructions.

Comment: This procedure would not blind the Carafate tablet because its color was pink and the sucralfate and the placebo tablet color was white. However, the protocol stated:

> "All test substance will be supplied as tablets, blister sealed in foil packets to ensure the integrity of blind."

> "In order to ensure the integrity of blind, a third-party will dispense the test substance to the patients. Patients will be instructed not to discuss the tablets they are ingesting with any one other than the person who dispensed the test substance to them."

Thus, the protocol contained some precautions for minimizing the unblinding of the Carafate tablet.

III. SPONSOR'S ANALYSES & RESULTS

A total of 273 patients were randomized to this trial, 93 patients to the placebo group, 89 to the Carafate group and 91 to the Biocraft sucralfate group. Twenty (20) centers contributed patients to this trial. Seven of the 20 participating centers contributed 20 or more patients per center. The

remaining 13 centers had small number of patients per center; 3 centers had no patients in one or two treatment arms. The number of patients included by the sponsor in the "primary efficacy analysis" were: 1) 241 patients (83 placebo, 82 Carafate, 76 sucralfate) in the original submission, August 15, 1989; 2) 238 patients (81 placebo, 82 Carafate, 75 sucralfate) in the Amendment of April 16, 1990; 3) all 273 randomized patients - ITT (intention-to-treat) analysis with adjustments for late week 4 endoscopies (93 placebo, 89 Carafate, 91 sucralfate) in the Amendment of July 5, 1990).

3.1. Chronology of Data Bases Reported By The Sponsor

The chronology of the various data bases analyzed and submitted for review is as follows:

August 15, 89 & February 15, 1990: Included the original submission data base.

Amendment April 16, 1990: This amendment included the "revised" data base after some inconsistencies, found with the original submission data base, were resolved by the sponsor.

Amendment July 5, 1990: This data base included in this amendment is basically the same as the data base of the April 16 Amendment; however, minor inconsistencies were noted which are listed in this review. The sponsor analyzed this data base according to the ITT (intention-to-treat) principle on including all randomized patients, on using unhealed result at week 4 to all patient whose week 4 endoscopies were done after 30 days from the start of the prescribed study medication; the prespecified endoscopy window for week 4 was 26-30 days.

A preliminary review of this ANDA, completed May 1990, had indicated some inconsistencies with the original data base. Consequently, the sponsor was asked to check the data base against the patient case report forms and provide a revised data base incorporating the data actually recorded on the patient case report forms. The sponsor was also asked to revise the statistical results.

This review is based on the "revised" data base (Amendments April 16, July 5, 1990). The sponsor's results for the week 4 healing rate vary numerically for the 3 data bases in terms of the magnitude of the healing rate, but the results of the statistical tests of significance and conclusions for week 4 are not significantly different for these data bases. The sponsor's results for the 3 data bases are presented in the following:

3.2. Sponsor's Week 4 Results (August 15, 1989: The Original Submission Data Base)

A total of 241 patients (83 placebo, 82 Carafate, 76 sucralfate), of the 273 randomized, were included in the sponsor's "primary efficacy" (PE) analysis. According to this data base, 32 patients had no week 4 endoscopy, and were, therefore, not included in the analysis. These 32 patients excluded from the analysis are listed in Table 9 (attached). The overall results by this analysis were as follows:

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	83	18	22%	S - P: 29%	<.001
Carafate	82	41	50%	C - P: 28%	<.001
Sucralfate	76	39	51%	S - C: 1%	.885
Total	241 patients	98 patients		90% Confidence Interval (S - C)**: (-16%, 18%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval is calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

3.2. Sponsor's Week 4 Results (Amendment: April 16, 1990)

A total of 238 patients (81 placebo, 82 Carafte, 75 sucralfate), of the 273 randomized, were included in the PE analysis. According to this data base, 35 patients did not have week 4 endoscopy, and were, therefore, not included in this analysis. The additional 3 patients excluded (32 for the original data base to 35 for this data base) were: sucralfate patient #70 (week endoscopy taken at week 3, unhealed), placebo patient #240 (week 4 endoscopy taken at week 3, healed), placebo patient #264 (week 4 endoscopy taken at week 2, unhealed). The overall results based on this data base were as follows:

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	81	16	20%	S - P: 33%	<.001
Carafate	82	40	49%	C - P: 29%	<.001
Sucralfate	75	40	53%	S - C: 4%	.577
Total	238 patients	96 patients		90% Confidence Interval (S - C)**: (-10%, 18%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval is calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

Thus, the sponsor's results for this data base were not significantly different from the results for the original submission data base.

3.2. Sponsor's Week 4 Results (Amendment: July 5, 1990)

In this analysis the sponsor included all randomized patients, but patients whose endoscopies were were late and were taken after 30 days from the start of the medication were set to unhealed status for week 4. The results were as follows:

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	93	15	16%	S - P: 18%	.017
Carafate	89	35	39%	C - P: 23%	.0003
Sucralfate	91	31	34%	S - C: -5%	.701
Total	273 patients	81 patients		90% Confidence Interval (S - C)**: (-18%, 8%)	

P = placebo, C = Carafate, S = Sucralfate

* 2-sided p by the Mantel-Haenszel test provided by the sponsor.

** Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

3.4. Summary Tables for the Sponsor's "Revised" Data

Table 1 gives the summary of week 4 endoscopic outcomes by center and pooled over centers for the revised data base (July 5th Amendment). This table gives, by center, the frequencies of patients who healed, patients who did not heal, and patients who did not have week 4 endoscopy. In this July 5th data base, patients with late endoscopies (after day 30 from baseline) were counted as having no endoscopy at week 4.

Table 2 displays the comparative demographic information for all randomized patients. The data indicated balance with respect to the demographic characteristics listed in this table.

Table 3 displays the week 4 endoscopy outcomes by one and two ulcers at baseline. The data indicated imbalance with respect to patients with 2 ulcers at baseline. This imbalance occurred despite the fact that the study was a randomized trial.

Table 4, in the upper part, lists patients without endoscopy after baseline. Numerically, there are more patients of this type in the sucralfate group than in the Carafate or the placebo group.

Table 5 lists patients whose endoscopies were taken above the week 4 window (days 26-30). Numerically, there are more patients of this type in the sucralfate group than in the Carafate and the Sucralfate group.

Table 4 includes patients whose endoscopies were taken before the week 4 window (days 26-30). Numerically, there are more patients of this type in the placebo group than in the other 2 treatment groups.

Table 6 lists patients with 2 baseline ulcers. Numerically, there are more patients of this type in the placebo group than in the other two treatment groups.

Table 7 lists dropouts during the week 4 treatment period. This table indicates more dropouts for the sucralfate and the placebo groups than for the Carafate group.

Table 8 shows the frequency distribution of drug compliance; less than 75% and greater than 125% medication intake defined as cut-off points for noncompliance. This data indicate that, at week 4, the compliance rate is somewhat less in the sucralfate group than in the placebo group: (placebo, 94%) vs (sucralfate, 81%).

IV. REVIEWER'S EVALUATION & COMMENTS

4.1. Imbalances ("Revised" Data)

Imbalances between treatment groups were noted for the July 5 Amendment data base with respect to the following variables:

1). The number of patients enrolled with 2 baseline ulcers

2). The number of patients with only baseline endoscopy.

3). The number of patients with late week 4 endoscopies (endoscopies taken above the week 4 window (days 26-30)).

The details regarding these imbalances are discussed in the rest of this section #4.1.

The following table shows the distribution of the number of patients with 2 baseline ulcers and the observed week 4 healing rates for these patients.

Table: Distribution of the number of patients with 2 baseline ulcers

Treatment Group	No. of pts. 2 BUs	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	24	2	8%	S - P: 12%	.354
Carafate	14	6	43%	C - P: 35%	.034
Sucralfate	15	3	20%	S - C: -13%	.245
Total	53	11		90% Confidence Interval (S - C): (-62%, 17%)	

P = placebo, C= Carafate, S = Sucralfate
* 2-sided p by the Fisher's exact test

As seen in the above table, and Table 6, for patients with 2 baseline ulcers, the observed imbalance, 24/93 vs. 14/89 vs. 14/91, was not statistically significant at the .05 level; 2-sided p=.157 on using a chi-square test with 2 degrees of freedom. Still such an imbalance is likely to cause some bias in the comparisons against placebo. This observed imbalance was mainly because of centers #1059 and #1074. Center #1059 enrolled 6 such patients in the placebo arm, none in the Carafate arm, and only 1 in the sucralfate arm. Center #1074 enrolled 2 such patients, both in the placebo arm.

However, there is no imbalance with respect to 2 baseline ulcer for the sucralfate vs Carafate comparison; 14 patients in the Carafte group as compare to 15 patients in the Carafte group had 2 baseline ulcers. Therefore, this reviewer is not concerned about the effect of imbalance with respect to 2 baseline ulcers for the equivalence evaluation of the two active formulations.

For the subgroup of patients with 2 baseline ulcers, the observed week 4 healing rate for the Carafate group is significantly greater than the corresponding healing rate for the placebo group, indicating the validity of the trial in patients with 2 baseline ulcers. The sucralfate vs. placebo comparison for this subgroup is not statistically significant. However, because, of small group sizes, these comparison results for sucralfate can not be used to conclude that sucralfate was not better than placebo or sucralfate was inferior to Carafate in patients with multiple duodenal ulcers.

The total numbers of patients with only baseline endoscopy was 14 in the sucralfate group as compared to 7 in the Carafate and 5 in the placebo group (see, Table 4). This imbalance was statistically significant as seen in the following table:

Table: Distribution of the number of patients with only baseline endoscopy

	Placebo	Carafate	Sucralfate
# of patients randomized	93	89	91
# with only baseline endoscopy	5/93 (5%)	7/89 (8%)	14/91 (15%)
Comparisons: Overall (Sucralfate Vs. Carafate Vs. placebo): 2-Sided p=.056 (Chi-square = 5.8, df=2) Sucralfate Vs. placebo: 2-sided p= .030 (Fisher's exact test) Carafate Vs. Placebo: 2-sided p =.561 (Fisher's exact test)			

Thus, the number of patients without any post-baseline endoscopy is greater in the Sucralfate group than either in the placebo group or the Carafate group. This imbalance is likely to bias the results for comparisons against placebo and Carafate. One way to protect against this bias is to analyze the data on including all randomized patients on assuming unhealed status for these 26 patients.

A total of 34 patients had late endoscopies; endoscopies were taken after day 30 on study (see, Table 5). These patients had no endoscopy for the 0^+ - 30 day treatment period. The following table shows the comparison results for the late endoscopy patients:

Table - Results For the Late Endoscopy Patients (endoscopies done after 30 days on study)

Treatment Group	No. of pts.	No. of pts. Healed	Observed Rate	Statistical Comparisons	2-Sided p*
Placebo	8	2	25%	S vs. P	.109
Carafate	10	3	30%	S vs. C	.248
Sucralfate	16	9	56%	S vs. (C + P)	.163
Total	34	14			

P = placebo, C= Carafate, S = Sucralfate
* 2-sided p by the Fisher's exact test

The above imbalance, although statistically not significant, could still bias the week 4 results in favor of sucralfate when compared to placebo and Carafate. One way to protect against such a bias is to analyze the data on assuming unhealed status for these 34 patients during the 4 week treatment period. Given the data in the above table, such an adjustment would make the

statistical tests conservative in comparing sucralfate against placebo or against Carafate.

4.2 Analyses For Effectiveness And Bioequivalence (Using Conservative Approaches)

The observed imbalances in the aforementioned 3 areas could inflate and bias the sucralfate week 4 healing rate in favor of sucralfate. Therefore, the following analyses were undertaken. The Analysis #1 is a conservative analysis for protecting against the two types of imbalances, 2) and 3) mentioned above. Then Analysis #2 were done for protecting against all 3 types of imbalances, 1), 2), and 3).

Analysis #1

In this week 4 analysis, patients who had only baseline endoscopies are assumed unhealed. Also, patients whose post-baseline endoscopies were done after 30 days on study are assumed unhealed, even though some of these sucralfate patients were reported healed on day 31. These adjustments in the analysis penalizes the sucralfate group, but corrects for bias resulting from imbalances due to no post-baseline and late week 4 endoscopies - these imbalancing events occurred more frequently in the sucralfate group than in the other two treatment groups. The results for this analysis are as follows:

Trial Validity Results (With respect to Week 4 healing):
Sucralfate 31% (31/91) vs placebo 16% (15/93), 2-sided p =.017 (Mantel-Haenszel test)
Carafate 34% (35/89) vs placebo 16% (15/93), 2-sided p =.0003 (Mantel-Haenszel test)

Bioequivalence Result (With respect to Week 4 healing):
90% confidence interval for the sucralfate minus Carafate difference in the healing rates: (-18%, 8%)

However, for this analysis, one may still question the validity of the result in the presence of more early endoscopy patients in the placebo group than in the sucralfate group (see, Table 4). But this imbalance does not seem to bias the result. This conclusion is based after examining the data with respect to the 'either-or' event of either early endoscopy or no endoscopy after baseline. The placebo and the sucralfate treatment groups are comparable with respect to this 'either-or' event, 15% rate for placebo vs. 19% for sucralfate (2-sided p= .558). Except for one placebo patient #240/center=1053 (see, Table 4), all early or no-endoscopy patients (13 in placebo and 17 in sucralfate) are set to unhealed status in the Analysis #1.

Thus, the Analysis #1 indicates that the trial was valid and the generic sucralfate is bioequivalent to Carafate with respect to week 4 healing of duodenal ulcer.

Analysis # 2

The Analysis #1 may still have some bias against placebo because it includes patients with 1 as well as with 2 baseline ulcers, when given that, there are more patients with 2 baseline ulcers in the placebo group than in the Carafate and the placebo group. Therefore, Analysis #2 was done on excluding all together patients with 2 baseline ulcers. This analysis is then just the analysis for patients with 1 baseline ulcer with adjustments as applied in Analysis #1. The results were as

shown in the following table:

Table - Week 4 results with adjustments as in Analysis #1
(All randomized patients with 1 baseline ulcer included)

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	69	13	19%	S - P: 18%	.018
Carafate	75	29	39%	C - P: 20%	.010
Sucralfate	76	28	34%	S - C: -2%	.868
Total	220	70		90% Confidence Interval (S - C)**: (-16%, 13%)	

P = placebo, C = Carafate, S = Sucralfate
* 2-sided p by the Mantel-Haenszel test provided by the sponsor.
** Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

This analysis with adjustment for imbalances 1), 2) and 3) discussed above also indicates that, in patients with one baseline ulcer, the generic sucralfate was effective and bioequivalent to Carafate.

4.3 Cumulative Healing Rates Weeks 4 to 8 (Kaplan-Meier Method)

In order to evaluate the overall results for the trial, cumulative healing rates with respect to time (days on study) were estimated by the Kaplan-Meier method from week 4 to week 8 (see, Figure 1), and the treatment groups were compared by the log-rank test. In this analysis all randomized patients were included. Also, patients with only baseline endoscopy were assumed unhealed in the trial (i.e., assumed censored end of the day 58, the upper time limit for the 8 week endoscopy) to get some protection against bias. The results are shown in Figure 1 (attached). The log-rank comparison tests showed the following p-values:

Log-rank comparison tests:
Sucralfate vs. placebo, 2-sided p =.033
Sucralfate vs. Carafate, 2-sided p =.929

The fact that the 2-sided p-value for the Sucralfate vs. Carafte is greater than .9 for this analysis provides supportive evidence in favor of bioequivalence between sucralfate and Carafate.

4.4. Comments for the April 16, 1990 Amendment Data Base

The sponsor filed a data base on diskette with the April 16, 1990 Amendment. A review of this earlier data showed a few inconsistencies. But, these inconsistencies, in this reviewer's assessment, did not impact or change the above results. The inconsistencies noted by this reviewer for this data base vs the July 5, 1990 Amendment data base were as follows:

Patient #188/Center=1066

April 16 Amendment: This patient is marked healed at week 4

July 5 Amendment: This patient is shown without endoscopy after baseline.

Patient #187/Center=1066

April 16 Amendment: This patient is marked healed at week 4, but the size of the second ulcer at week 4 is coded to be of 2 cm long.

July 5 Amendment: This patient is marked healed at week 4, but ulcer sizes are shown as zeros at this week.

Patient #275/Center=1075

April 16 Amendment: This patient is coded with only 1 baseline ulcer.

July 5 Amendment: This patient is coded with 2 baseline ulcers.

4.5. Comments for the Original Submission Data Base

The review of this original data base showed serious imbalance with regard to patients with 2 baseline ulcers: 23 patients for placebo, 7 patients for Carafate, and no patient for sucralfate. It is possible that in the original submission the patient information with respect to 2 baseline ulcers was not carefully coded and verified by the sponsor's staff.

However, this reviewer has compared the case report forms for some 50 dropout patients and for patients from centers listed below against the July 5 Amendment data base (comparison checks only with regard to endoscopy outcomes).

Center 1052 - (30 patients checked),
Center 1075 - (24 patients checked),
Center 1076 - (18 patients checked),
Center 1059 - (18 patients checked)

Copies of the the patient case report forms for some patients from these centers and for dropout patients were provided by the sponsor upon request by this reviewer. These comparison checks, based upon a sample from the population of 273 patients, found the July 5 Amendment data base to be satisfactory with regard to the endoscopy outcomes. Therefore, in drawing the conclusion for this trial, this reviewer has relied on the most recent revised data base which is the July 5 Amendment data base.

V. OVERALL CONCLUSION

Despite some observed imbalances in the data, filed with the April 16 and July 5 Amendments, the statistical review of this revised efficacy data by conservative approaches indicates that, for this trial, the Biocraft generic sucralfate is more effective than placebo, and is bioequivalent to Carafate in patients with duodenal ulcer.

M F Huque

Reviewer: M. F. Huque, Ph. D.
Supervisory Mathematical Statistician

This review consists of 12 pages of text and 13 pages of tables and figures.

Concur: Dr. Dubey 7-11-91

cc: Orig. ANDA 70-848
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Mr. Hassall
HFD-713/Dr. Dubey [File: DRU 1.3.2], generics
HFD-713/Dr. Huque
Chron.
Dr. Huque/X7580/mfh/06/27/91

STUDY SCHEDULE

	VISITS				
	PREL.	2	4	6	8
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Hx of Duodenal Ulcer Disease	X				
Demographic Information	X				
Medical History	X				
Medication History	X				
Physical Examination	****X	X	X	X	X
Hemoccult Testing	X		X		X
Laboratory Evaluations	X	**X	*X		X
Vital Signs	X	X	X	X	X
EKG	X		*X		X
Endoscopy	X		X		X
Study Medication Distribution	X	X	X	X	
Previous/Concomitant Medication	X	X	X	X	X
Adverse Reaction Assessment		X	X	X	X
Study Medication Compl. Assess.		X	X	X	X
Study Conclusion Explanation					**X*
Investigator Global Evaluation					**X*
Pregnancy Test	X		X		X

* Conducted only if ulcer(s) have healed and patients will not continue in the study.
** Serum aluminum measurements only.
*** Conducted at any point at which the patient discontinues from the study.
**** Included a rectal examination at the preliminary visit.

APPEARS THIS WAY
ON ORIGINAL

Table 1
Summaries of Endoscopic Outcomes During Week 4* For All Randomized Patients
For the NEW ("Revised") Data Base, July 5th Amendment)

Center # (Size)	No. Healed/Total Randomized, Healing Rate, NH(.)= Number Not Healed During Week 4, M(.)= Number Without Endoscopy During Week 4		
	Placebo	Carafate	Sucralfate
1052 (45)	1/15 (7%), NH(14), M(0)	3/15 (20%), NH(8), M(4)	4/15 (27%), NH(8), M(3)
1075 (35)	2/13 (15%), NH(9), M(2)	6/11 (55%), NH(3), M(2)	4/11 (36%), NH(3), M(4)
1059 (28)	1/9 (11%), NH(8), M(0)	4/10 (40%), NH(5), M(1)	3/9 (33%), NH(6), M(0)
1055 (27)	0/9 (0%), NH(8), M(1)	2/8 (25%), NH(4), M(2)	5/10 (50%), NH(3), M(2)
1076 (26)	4/9 (44%), NH(5), M(0)	6/8 (75%), NH(1), M(1)	6/9 (67%), NH(1), M(2)
1066 (25)	1/9 (11%), NH(7), M(1)	3/8 (38%), NH(5), M(0)	2/8 (25%), NH(4), M(2)
1053 (20)	1/7 (14%), NH(6), M(0)	3/6 (50%), NH(3), M(0)	1/7 (14%), NH(5), M(1)
1060 (12)	2/4 (50%), NH(2), M(0)	1/4 (25%), NH(2), M(1)	1/4 (25%), NH(2), M(1)
1064 (10)	1/4 (25%), NH(3), M(0)	2/3 (67%), NH(1), M(0)	2/3 (75%), NH(1), M(0)
1074 (7)	0/2 (0%), NH(1), M(1)	0/2 (0%), NH(1), M(1)	1/3 (33%), NH(0), M(2)
1063 (7)	2/3 (75%), NH(1), M(0)	0/2 (0%), NH(2), M(0)	0/2 (0%), NH(2), M(0)
1049 (6)	0/2 (0%), NH(2), M(0)	1/2 (50%), NH(1), M(0)	1/2 (5%), NH(0), M(1)
1058 (6)	0/2 (0%), NH(2), M(0)	1/2 (50%), NH(1), M(0)	0/2 (0%), NH(1), M(1)
1051 (5)	0/2 (0%), NH(1), M(1)	0/1 (0%), NH(1), M(0)	0/2 (0%), NH(0), M(2)
1054 (4)	0/1 NH(0), M(1)	1/2 NH(0), M(1)	0/1 NH(0), M(1)
1057 (3)	0/1 NH(1), M(0)	0/1 NH(1), M(0)	1/1 NH(0), M(0)
1068 (3)	0/1 NH(1), M(0)	0/1 NH(1), M(0)	0/1 NH(0), M(1)
1067 (2)	-	1/1 NH(0), M(0)	0/1 NH(1), M(0)
1061 (1)	-	1/1 NH(0), M(0)	-
1050 (1)	-	0/1 NH(1), M(0)	-
Total # of Patients (273)	15/93, (16%), M(71) , M(7)	35/89 (39%), M(41), M(13)	31/91, (34%), M(37), M(23)

*In the new data base any endoscopy beyond 30 days was not counted as the Week 4 endoscopy.

Table 2

Demographic Information
(All Randomized Patients)

DEMOGRAPHIC VARIABLE		PLACEBO	CARAFATE	SUCRALFATE	OVERALL
Age (years)					
	N	76	82	83	241
	MEAN	40.7	43.6	42.5	42.3
	STD.	12.5	12.5	11.5	12.2
	MIN.	20.0	19.0	20.0	19.0
	MAX.	68.0	70.0	69.0	70.0
Height (in.)					
	N	76	82	83	241
	MEAN	68.1	67.8	68.0	68.13
	STD.	3.6	3.7	4.0	3.6
	MIN.	59.0	59.0	56.7	56.7
	MAX.	77.0	76.0	78.0	78.0
Weight (lbs.)					
	N	76	82	83	241
	MEAN	164.0	173.1	174.6	164.3
	STD.	36.7	31.0	40.5	36.6
	MIN.	97.0	115.0	95.0	95.0
	MAX.	265.0	250.0	365.0	365.0
Duration of Duodenal Ulcer Disease (years)					
	N	35	47	45	127
	MEAN	10.0	12.0	9.3	10.5
	STD.	8.8	9.3	7.9	8.7
	MIN.	0.4	0.4	0.2	0.2
	MAX.	38.1	33.5	30.3	38.1

(Table continued to the next page .....)

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Table 2

Demographic Information
(All Randomized Patients)

DEMOGRAPHIC VARIABLE		PLACEBO	CARAFATE	SUCRALFATE	OVERALL
Sex					
	Male	55	58	57	170
	Female	28	24	18	70
Race					
	Caucasian	51	53	44	148
	Black	27	24	26	77
	Oriental	2	1	0	3
	Hispanic	1	4	3	8
	Other	2	0	2	4
Occupation					
	Housewife	9	6	2	17
	Student	4	4	3	11
	Managerial	8	3	4	15
	Retired	7	3	6	16
	Unskilled	11	9	11	31
	Skilled	25	36	32	93
	Professional	15	15	13	43
	Unemployed	4	5	5	14
	Other	0	1	0	1
Smoker					
	YES	39	35	43	117
	NO	44	47	33	124
Alcohol Consumption					
	Never	33	45	38	116
	Occasional	42	29	33	104
	Moderate	7	8	4	19
	Often	1	0	1	2
History of Duodenal Ulcer Disease					
	YES	45	50	36	131
	NO	36	30	39	105
	UNKNOWN	2	2	1	5
Episodes of Ulcer Attacks					
	YES	36	38	24	98
	NO	13	11	13	37
	DO NOT KNOW	23	21	28	72
Frequency of Ulcer Attacks					
	Less than or Equal to 6 Months	16	21	15	52
	7-11 months	2	4	1	7
	Every 12 months	5	1	2	8
	Greater than 12 months	13	13	8	34

Table 3
Summaries of Endoscopic Outcomes During Week 4*
For All Randomized Patients
(One Baseline Ulcer VS Two Baseline Ulcers)

July 5th Data Base

Center # (Size)	Outcomes for Patients With 1 Baseline Ulcer: Healing Rate, Number Not Healed, Number Without Endoscopies			Outcomes for patients With 2 Baseline Ulcers: Healing Rate, Number Not Healed, Number Without Endoscopies		
	Placebo	Carafate	Sucralfate	Placebo	Carafate	Sucralfate
1052 (45)	1/12 N(11) 8% M(0)	3/13 N(6) 23% M(4)	4/13 N(7) 31% M(2)	0/3 N(3) M(0)	0/2 N(2) M(0)	0/2 N(1) M(1)
1075 (35)	0/9 N(7) 0% M(2)	3/6 N(1) 50% M(2)	3/8 N(2) 38% M(3)	2/4 N(2) M(0)	3/5 N(2) M(0)	1/3 N(1) M(1)
1059 (28)	1/3 N(2) 33% M(0)	4/10 N(5) 40% M(1)	3/8 N(5) 38% M(0)	0/6 N(6) M(0)		0/1 N(1) M(0)
1055 (27)	0/8 N(7) 0% M(1)	2/8 N(4) 25% M(2)	5/10 N(3) 50% M(2)	0/1 N(1) M(0)		
1076 (26)	4/7 N(3) 57% M(0)	6/8 N(1) 75% M(1)	4/5 N(1) 80% M(0)	0/2 N(2) M(0)		2/4 N(0) M(2)
1066 (25)	1/7 N(5) 14% M(1)	3/6 N(3) 50% M(0)	2/7 N(4) 29% M(1)	0/2 N(2) M(0)	0/2 N(2) M(0)	0/1 N(0) M(1)
1053 (20)	1/5 N(4) 20% M(0)	1/3 N(2) 33% M(0)	1/6 N(4) 17% M(1)	0/2 N(2) M(0)	2/3 N(1) M(0)	0/1 N(1) M(0)
1060 (12)	2/4 N(2) 50% M(0)	1/4 N(2) 25% M(1)	1/4 N(2) 25% M(1)			
1064 (10)	1/4 N(3) 25% M(0)	2/3 N(1) 67% M(0)	2/3 N(1) 67% M(0)			
1074 (7)		0/2 N(1) 0% M(1)	1/3 N(0) 33% M(2)	0/2 N(1) M(1)		
1063 (7)	2/3 N(1) 67% M(0)	0/1 N(1) 0% M(0)	0/2 N(2) 0% M(0)		0/1 N(1) M(0)	
1049 (6)	0/2 N(2) 0% M(0)	1/2 N(1) 50% M(0)	1/2 N(0) 50% M(1)			
1058 (6)	0/2 N(2) 0% M(0)	0/1 N(1) 0% M(0)	0/2 N(1) 0% M(1)		1/1 N(0) M(0)	
1051 (5)		0/1 N(1) 0% M(0)		0/2 N(1) M(1)		0/2 N(0) M(2)

*In the new data base any endoscopy after 30 days was not counted as the Week 4 endoscopy.

M(.) = # of patients without endoscopy during the 4 Week treatment period.
N(.) = Number of patients found not healed by endoscopy.

(Table continued to the next page)

(Table continued from the previous page)

Table 3
Summaries of Endoscopic Outcomes During Week 4* For All Randomized Patients
(One Baseline Ulcer Vs Two Baseline Ulcers)

Center # (Size)	Outcomes for Patients With 1 Baseline Ulcer: Healing Rate, Number Not Healed, Number Without Endoscopies						Outcomes for patients With 2 Baseline Ulcers: Healing Rate, Number Not Healed, Number Without Endoscopies		
	Placebo		Carafate		Sucralfate		Placebo	Carafate	Sucralfate
1054 (4)	0/1	N(0) M(*)	1/2	N(0) M(1)	0/1	N(0) M(1)			
1057 (3)	0/1	N(1) M(0)	0/1	N(1) M(0)	1/1	N(0) M(0)			
1068 (3)	0/1	N(1) M(0)	0/1	N(1) M(0)	0/1	N(0) M(1)			
1067 (2)			1/1	N(0) M(0)					0/1 N(1) M(0)
1061 (1)			1/1	N(0) M(0)					
1050 (1)			0/1	N(1) M(0)					
Total # of Patients (273)	13/69 (19%) N(51) M(5)		29/75 (39%) N(33) M(13)		28/76 (37%) N(32) M(28)		2/24 (8%) N(20) M(2)	6/14 (43%) N(8) M(0)	3/15 (20%) N(5) M(7)

*In the new data base any endoscopy after 30 days was not counted as the Week 4 endoscopy.

M(.) = # of patients without endoscopy during the 4 Week treatment period.
N(.) = Number of patients found not healed by endoscopy.

TABLE 4
Patients Without Endoscopies After Baseline/ Or Patients With Endoscopies Taken Before the Week 4 Window (Days 26 -30)

Placebo			Carafate			Sucralfate		
Patient No.	Days on Study	Status, /#Basel. Ulcers	Patient No.	Days on Study	Status, /#Basl Ulcers	Patient No.	Days on Study	Status, /#Basel Ulcers
13/1054	0	-, 1	16/1054	0	-, 1	49/1066	0	-, 1
121/1057	0	-, 2	39/1075	0	-, 1	62/1055	0	-, 1
135/1055	0	-, 1	64/1055	0	-, 1	86/1058	0	-, 1
142/1074	0	-, 2	69/1055	0	-, 1	123/1051	0	-, 2
188/1066	0	-, 1	129/1052	0	-, 1	124/1051	0	-, 2
21/1057	12	NH, 1	141/1052	0	-, 1			
107/1055	2	NH, 1	262/1060	0	-, 1	143/1074	0	-, 1
132/1052	15	NH, 1				150/1075	0	-, 2
162/1076	17	NH, 2				156/1066	0	-, 2
164/1052	15	NH, 2				157/1055	0	-, 1
218/1076	15	NH, 1				200/1052	0	-, 2
256/1066	18	NH, 1				205/1052	0	-, 1
240/1053	21	H, 1				221/1076	0	-, 2
264/1060	13	NH, 1				263/1060	0	-, 1
						274/1075	0	-, 1
						70/1055	17	NH,1
						108/1055	14	NH,1
						128/1052	14	NH,1

H= Patient healed
NH= Patient not healed

TABLE 5

Patients Whose Endoscopies Were Taken Above the Week 4 Window: Days 26 -30
(Endoscopies Taken After 30 Days From Baseline)

Placebo			Carafate			Sucralfate		
Patient No.	Days on Study	Status, /#Basel Ulcers	Patient No.	Days on Study	Status, /#Basl Ulcers	Patient No.	Days on Study	Status, /#Basel Ulcers
25/1049	31	NH, 1	5/1052	33	H, 1	15/1054	31	H, 1
28/1049	38	NH, 1	166/1052	31	NH, 1	27/1049	31	H, 1
66/1055	31	NH, 1	179/1052	42	NH, 1	43/1060	31	NH, 1
75/1075	35	H, 1	182/1052	32	NH, 1	89/1058	32	NH, 1
188/1066	36??	H??, 1	186/1052	35	NH, 1	101/1076	33	H, 2
195/1075	35	NH, 1	193/1075	32	H, 1	93/1068	31	H, 1
199/1052	32	NH, 2	198/1075	31	NH??, 1	134/1055	37	NH, 1
271/1075	31	NH, 1	210/1076	34	H, 1	145/1075	31	NH, 2
			257/1066	37	NH, 1	168/1052	33	NH, 1
			265/1059	36	NH, 1	177/1052	32	NH, 1
						194/1075	39	H, 1
						202/1052	31	H, 1
						233/1075	38	NH, 1
						238/1053	32	H, 1
						272/1075	37	H, 1
						283/1074	33	H, 1

??

Placebo patient 188/1066:

Had no endoscopy after baseline according to the July 5th data base

Had week 4 endoscopy on day 36 with healed status, according to the April 16 data base

Carafate patient 198/1075:

Was not healed according to the July 5th data base

Was healed according to the April 16th data base

Table 6
Patients With 2 Baseline Ulcers And Their Week 4 Healing Status
(July 5th Data Base)

Placebo			Carafate			Sucralfate		
Patient No.	Days on study	Status	Patient No.	Days on study	Status	Patient No.	Days on Study	Status
31/1059	27	NH	11/1063	28	NH	59/1053	30	NH
37/1075	28	H	52/1066	27	NH	74/1067	28	NH
42/1075	28	NH	55/1053	29	H	101/1076	33	H
76/1075	28	H	87/1058	27	H	123/1051	0	-
121/1051	0	-	147/1075	27	H	124/1051	0	-
125/1051	28	NH	148/1075	29	H	145/1075	31	NH
139/1074	30	NH	152/1066	30	NH	156/1066	28	H
142/1074	0	-	173/1053	28	NH	180/1052	29	NH
162/1076	17	NH	182/1052	32	NH	200/1052	0	-
164/1052	15	NH	186/1052	35	NH	209/1076	28	NH
174/1053	28	NH	198/1075	31	H	221/1076	0	-
185/1052	28	NH	232/1075	28	H	230/1075	27	H
199/1052	32	NH	239/1053	28	NH	241/1059	28	NH
214/1066	28	NH	276/1075	28	NH	127/293	28	NH
236/1053	28	NH				150/1075	0	-
243/1059	28	NH						
246/1059	28	NH						
255/1066	28	NH						
266/1059	28	NH						
269/1059	28	NH						
278/1055	29	NH						
288/1059	28	NH						
289/1076	29	NH						
275/1075	28	NH						

Table 7
Dropouts During the 4 Week Treatment Period
(Start of the Medication to 30 Days on Study)

Placebo			Carafate			Sucralfate		
Center No.	Pat No.	Days on Study (Status)	Center No.	Pat No.	Days on Study (Status)	Center No.	Pat No.	Days on Study (Status)
1051	121	0	1052	129	0	1051	123	0
1052	132	15 (NH)	1052	203	29 (NH)	1051	124	0
1052	164	15 (NH)	1054	16	0	1052	128	14 (NH)
1053	240	21 (H)	1055	64	0	1052	200	0
1054	13	0	1055	69	0	1052	205	0
1055	107	2 (NH)	1059	268	28 (NH)	1055	62	0
1055	135	0	1060	262	0	1055	70	17 (NH)
1057	21	12 (NH)	1074	141	0	1055	108	14 (NH)
1060	264	13 (NH)	1075	39	0	1055	157	0
1066	188	0	Total: 9 Patients Dropout Rate 9/89 (10%)			1058	86	0
1066	256	18 (NH)				1059	299	28 (NH)
1068	92	28 (NH)				1060	263	0
1074	142	0				1066	49	0
1075	229	26 (NH)				1066	156	0
1076	162	17 (NH)				1074	143	0
1076	218	15 (NH)				1075	150	0
Total: 16 Patients Dropout Rate 16/93 (17%)						1075	274	0
						1076	221	0
						Total: 18 Patients Dropout Rate 18/91 (20%)		

Table 8

Frequency Distribution of Drug Compliance

Treatment	Week	Less than 75%	75% to 125%	Greater than 125%	Total # of Patients
Placebo	2	8 (9%0	80 (91%)	0	88
	4	4 (5%)	74 (94%)	1 (1%)	79
	6	5 (8%)	56 (92%)	0	61
	8	7 (11%)	57 (88%)	1 (1%)	65
Carafate	2	9 (11%)	75 (87%)	2 (2%)	86
	4	11 (13%)	71 (87%)	0	82
	6	3 (8%)	36 (90%)	1 (2%)	40
	8	6 (15%)	32 (82%)	1 (3%)	39
Sucralfate	2	8 (9%)	77 (91%)	0	85
	4	14 (18%)	62 (81%)	1 (1%)	77
	6	1 (3%)	31 (97%)	0	32
	8	5 (14%)	28 (80%)	2 (6%)	35

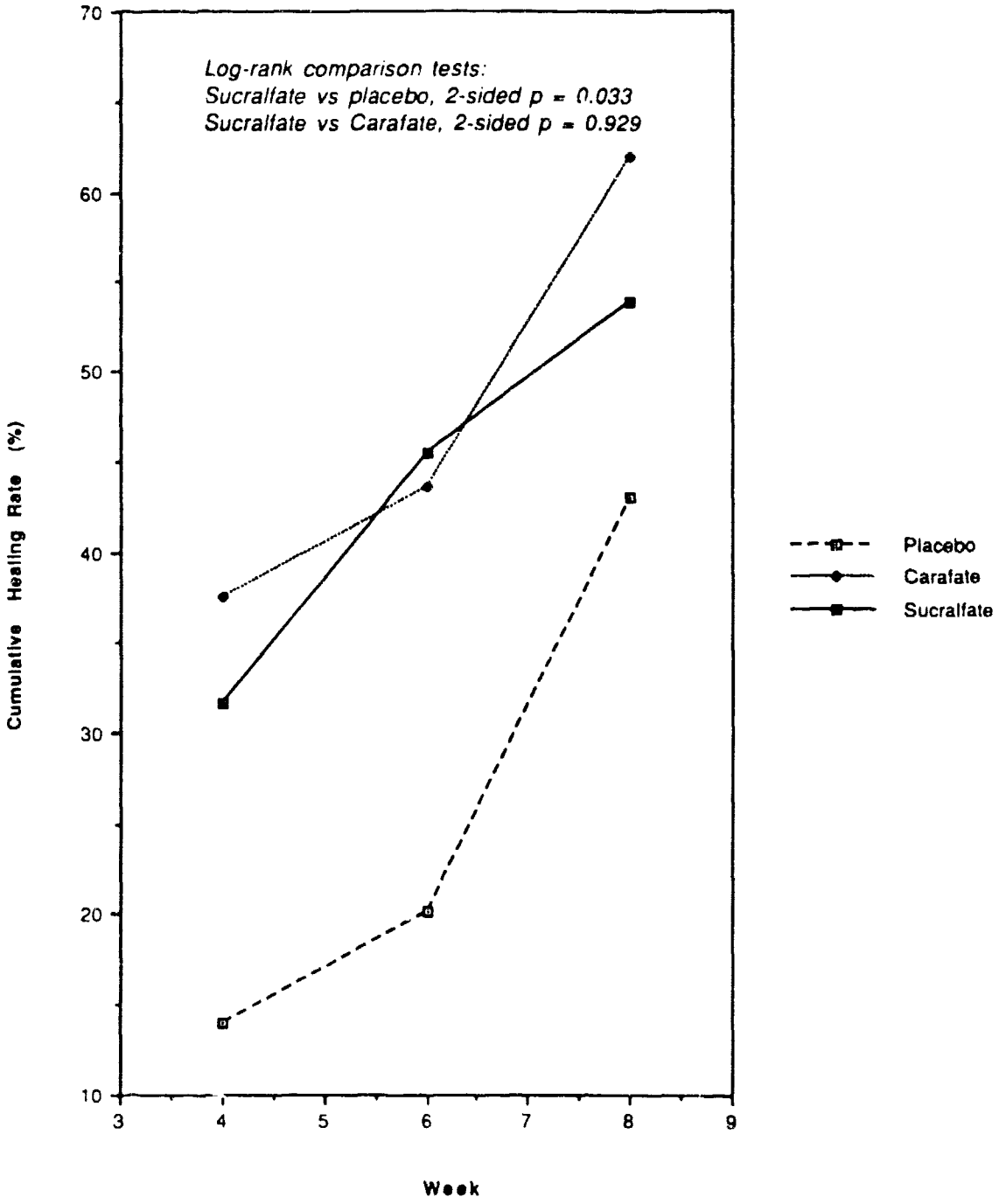
APPEARS THIS WAY
ON ORIGINAL

Table 9
Patients Excluded from the Efficacy Analysis
(Original Submission Data)

PLACEBO	CARAFATE	SUCRALFATE
1051/121	1052/129	1051/123
1052/132	1054/16	1051/124
1052/164	1055/64	1052/128
1054/13	1055/69	1052/200
1055/135	1060/262	1052/205
1057/21	1074/141	1055/62
1066/256	1075/39	1055/107
1074/142		1055/157
1076/162		1058/86
1076/218		1060/263
		1066/49
		1074/143
		1075/150
		1075/274
		1076/221

FIGURE No. 1

CUMULATIVE HEALING RATES
By the Kaplan-Meier Method
(All patients with 1 and 2 Baseline Ulcers)



Note: Patients with only baseline endoscopies were assumed unhealed to the end of the trial.

70-848

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

DATE: May 11, 1990

FROM: Robert Prizont, M.D., Medical Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: ANDA 70-848. Sucralfate. Consult from Division of Generic Drugs

TO: Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Biocraft Lab. Inc. filed this ANDA on August 1989 to demonstrate bioequivalence of clinical endpoints between the sponsor's sucralfate oral tablets and Marion's carafate oral tablets. This is a single three arm trial which included a total of 273 patients. At the request of this reviewer and the statistician reviewer, the sponsor filed on March 5, 1990, Case Report Forms of 53 dropout patients and a listing of patients enrolled with 2 ulcers. The tabulation of patients according to ulcer status was included in a diskette. On April 16, 1990 Biocraft filed an amendment with changes in the ulcer status of 15 patients. Eleven of these patients had been changed to "healed" while remaining with apparent duodenal erosions of 0.2 cm or ulcers of 0.3 cm at the site of the original ulcer. The healing status of the other four patients have been changed from either yes (healed) to no (unhealed) or vice-versa. Also included were new Primary Effectiveness and Intent to Treat Analyses. In the new PES two patients in the placebo arm and one in the sucralfate arm were excluded from the analyses. The original and new ITT included only 248 patients out of a trial of 273, with 25 excluded patients. The sponsor included in the Protocol and in the analyses patients with 0.2 cm erosions as second ulcers. My review of the dropout CRF's reveal discrepancies between the status of ulcers claimed by the sponsor and the ones actually reported by investigators.

The following is requested from the sponsor:

1. There is an inconsistency in the number of patients listed as dropped in Page 27, Vol 1/7 of the August 16, 1989 submission and in Page 28 of the same volume. Page 27 states that "a total of

52 patients, 20 in the placebo....., 14 in the carafate..... and 19 in the Biocraft sucralfate....." were dropped from the studies. The list of reasons for the dropouts in Page 28 shows a total of 55 patients, 20 in the placebo, 14 in the carafate and 21 in the sucralfate arm. The table lists that the 21 discontinuations in the sucralfate arm were due to: 2 adverse reactions, 2 intercurrent illness, 1 patient refused treatment, 6 lost to follow up and 10 for administrative reasons. The number of CFRs filed in the Agency in February 15, 1990 was 53. Please submit the remaining 2 Case Report Forms and/or clarify the discrepancy.

2. A total of 25 patients were excluded from the Intent to Treat analysis. Please provide the CRFs of these excluded patients. If some of these excluded patients were dropped and CRFs have been already forwarded, please provide the patient and investigator numbers.

3. Please provide an ITT analysis excluding those patients who had endoscopies on or prior the 25th day for the week 4 or on or prior the 55th day for the week 8, and excluding those patients who had endoscopies on or after the 35th day for week 4 or on or after the 65th day for week 8. Please include in this analysis all dropout patients, including those excluded in the sponsor's previous analyses.

4. My review of the 53 CRFs reveals that ulcers considered as healed by the investigator were corrected and included as unhealed by the sponsor. The sponsor should remember that surrounding duodenal inflammation does not affect the diagnosis of healing at the site of an ulcer. Please provide the correct account and analyses of healed and unhealed patients.

5. The following patients have discrepancies in the healing status and/or number of ulcers. Please provide their CRFs. The patient numbers are as follows:

#009	#118	#181	#199
#035	#130	#182	#204
#038	#131	#183	#234
#040	#148	#184	#243
#066	#152	#192	#261
#071	#176	#197	#291
#073	#180	#198	#298

6. As regards to the blinding, please provide a complete listing of persons who were acquainted with the code, e.g. statistitians, personnel on site, medical consultants, coordinators, at the time of enrollment, during the study and at the end of the Trial.

The clarifications, analyses and data requested are of utmost importance for the adequate continuation of my scientific-medical review.

Robert Prizont, M.D.

cc:
HFD-130
HFD-130/RPrizont
r/d 5/11/90, 5/14/90, 5/23/90
ft/5/23/90/jgw/w0883a

5/23/90
Forward this request
to Mr Robt Pollack
SP

STATISTICAL CONSULTATION

ANDA #: 70-848

APPLICANT: Biocraft

DRUG NAME: Biocraft's Sucralfate 1 gm tablet
(Generic Drug)

INDICATION: Duodenal Ulcer

DOCUMENTS REVIEWED:

Volumes I to III, dated August 15, 89
Volumes I to IV, dated February 15, 1990
Amendments: dated April 16, 1990
Some data on floppy diskettes submitted dated February 15 and April 16, 1990

More information is needed to review the current ANDA. Please see attached for details.

1. This reviewer found several inconsistencies in the healing status of the patients on going through the 53 patient case report forms versus the data submitted on floppy diskettes (February 15 and April 16, 1990) and the data in Volume III (August 15, 1989). The sponsor should check carefully the data base with regard to ulcer healing against the actual patient case report forms and provide the corrected data base for review on a floppy diskette and in a tabular listing form with format as in Volume III (August 15, 1989). If the investigator writes 'normal endoscopy' or 'ulcer is healed' in the patient case report form then the patient should be classified as healed. The definition of healing should be consistent with that defined in the protocol and not be modified after looking at the data.

2. Please provide a correct tabulation showing for each center and the treatment group:

(1) The total number of patients randomized.
(2) The total number of patients with week 4 endoscopy (include patients with endoscopies done in between week 0 and week 4).
(3) The total number of patients healed at week 4 (include patients who healed in between week 0 and week 4).
(4) The total number of patients healed at week 8 (include patients who healed in between week 4 and week 8).

3. Please provide a correct list of patients who had a second ulcer (or lesion) at baseline along with the size of the ulcer. An earlier list provided by the sponsor may contain errors. This list included patients #61, 71, 190, 204, 234, 72, 73, 191, 38, 40, 62, 183, 184 and 192 who do not seem to have second ulcer (or lesion) in the data submitted with the floppy diskette; the ulcer size information is missing. Surprisingly, a few placebo patients showed fairly large size second ulcers at post-baseline visits but not at the baseline visit (e.g., patient #s 228, #271 at week 4). Is this data correct?

4. Please provide for review the center by treatment frequency table which went into the calculation of each Mantel-Haenszel statistic and its p-value. Some of the centers are of small sizes and have small expected cell frequencies. Therefore, the p-values should be calculated either by the exact procedure or on merging centers having expected cell frequencies of less than 5 patients. (The sponsor may apply an exact method from the StatXact procedure for the calculation of the p-value for the Mantel Haenszel statistic which would not require merging of the small centers.)

5. Please provide for review a list of patients who were excluded from the intent-to-treat (ITT) analysis along with the reason(s) for exclusions. The sponsor should also provide the results at week 4 and at week 8 according to the following standard ITT principles:

a) Include all randomized patients and define the healing rate for each treatment group as the total number healed over the total number randomized in that treatment group.

b) Include all patients who were "treated" in the trial. That is exclude only those patients who dropped right after baseline and did not take any study medication.

6. The sponsor should also provide the following information:

a) Explain for review the procedure used for protecting the treatment blind during the conduct of this trial. Who had access to the treatment codes? Were there any interim or administrative looks of data during the conduct of the trial?

b) Were the decisions to include or exclude patients into the analyses were made before or after unmasking the treatment codes?

7. Please provide for review the patient case report forms from the centers #s 1052, 1055, 1059, 1075 and 1076. Please include patients only from the placebo and the generic sucralfate groups.

M. F. Huque

M. F. Huque, Ph. D.
(Mathematical Statistician)

Concur.

Dr. Chi

cc: Orig. ANDA No. 70-848
HFD-180/ Dr. Fredd
HFD-180/ Dr. Prizont
HFD-180/ Mr. Hassal
HFD-713/ Dr Dubey [File DMU 1-3-2 NDA]
HFD-713/ Dr. Chi
HFD-713/ Dr. Huque
Chron.
MHuque/x3[illegible]/huque/5/3/96

7.1

MEMORANDUM OF CONSULTATIONS

Date: October 22, 1991

From: M. F. Huque, Ph. D
Group Leader, SERB, Biometrics
HFD-713

To: Stephen Fredd, M.D.
Director, Division of GI & Blood Coagulation Drug Products - HFD-180

Subject: Confidence Intervals for the Carafate group in the ANDA 70-848; Sponsor: Biocraft; Drug: generic sucralfate; Indication: treatment of active duodenal ulcer

Please, find attached the requested 90 and 95 percent confidence intervals for the week 4 healing rate of the carafate group of the ANDA #70-848. These confidence intervals are shown at the bottom of the attached Tables 1 and 2 which give the week 4 healing rate results of this ANDA. [Also, see the Statistical Review & Evaluation of the ANDA #70-848, date: July 12, 1991, pages 10 and 11.]

As indicated to you earlier, Dr. Prizont has raised the issue that, although caratte treatment was effective in the sucralfate-carafate placebo controlled trial of this ANDA, the carafate week 4 healing rate was low in comparison to the historical sucralfate healing rates for duodenal ulcer.

I have calculated the above mentioned confidence intervals for the trial in question. These confidence intervals may not be useful in addressing this issue, because they need to be interpreted considering the facts that 1) trials vary in population mix and antacid usage, 2) patients may be more resistant to treatment now than before. It is possible for such an across-study comparison to be meaningful, if it were to be done for "naive" patients, i.e., for patients treated first time for the disease indication. However, such a comparison approach would require an extensive statistical meta-analyses on pulling the right data from the historical studies. This would be a difficult task because of the non-availability of the old historical data bases in the electronic form having each patient's demographic, efficacy, and antacid usage information.

M. F. Huque, Ph. D.

CC: Orig. ANDA: 70-848
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Mr. Hassall
HFD-713/Dr. Dubey
HFD-713/Dr. Huque
Chron.
Dr. Huque/x4594/mfh/10-22-91

[File: DRU 1.3.2], Generics

Table 1 - Week 4 results
(all randomized patients)

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	93	15	16%	S - P: 18%	.017
Carafate	89	35	39%	C - P: 23%	.0003
Sucralfate	91	31	34%	S - C: -5%	.701
Total	273	81		90% Confidence Interval (S - C)**: (-18%, 8%)	

* P = placebo, C = Carafate, S = Sucralfate
2-sided p by the Mantel-Haenszel test provided by the sponsor.
** Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

Confidence Intervals for the Carafate group
(all randomized patients included)

90% CI: 30.8%, 47.9%
95% CI: 29.2%, 49.5%

Table 2 - Week 4 results
(all randomized patients with only 1 baseline ulcer)

Treatment Group	No. of pts.	No. of pts. Healed	Week 4 Healing Rate	Difference in Healing Rates	2-Sided p*
Placebo	69	13	19%	S - P: 18%	.018
Carafate	75	29	39%	C - P: 20%	.010
Sucralfate	76	28	37%	S - C: -2%	.868
Total	220	70		90% Confidence Interval (S - C)**: (-16%, 13%)	

* P = placebo, C = Carafate, S = Sucralfate

** 2-sided p by the Mantel-Haenszel test provided by the sponsor. Confidence interval calculated by the reviewer on applying the formula given on page 29 of the book: Statistical Methods for Rates and Proportions, Second Edition, by Joseph Fleiss.

Confidence Intervals for the Carafate group
(all randomized patients with only 1 baseline ulcer)

90% CI: 29.4%, 47.9%
95% CI: 27.6%, 49.7%

FEB 15 1994

STATISTICAL REVIEW & EVALUATION

ANDA #: 70-848 Date: February 10, 1994

Applicant: Biocraft

Drug Name: Biocraft Sucralfate's 1 gm tablet
(Generic Drug)

Indication: Duodenal Ulcer

Statistical Review Request Date: December 10, 1993

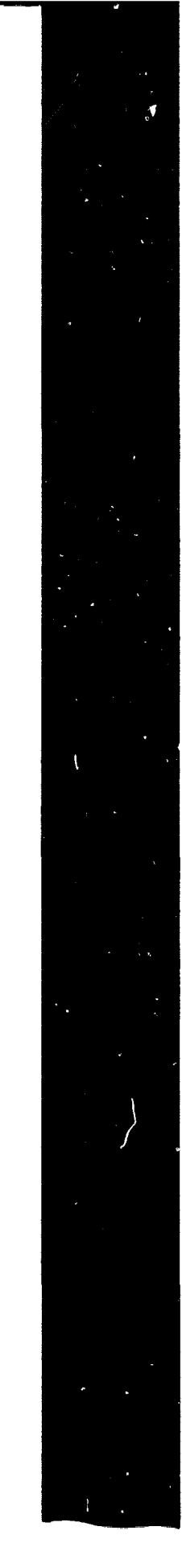
This review addresses issues raised by the medical officer Robert Prizont, M.D. These issues are concerning randomization and treatment allocation of the clinical trial which was designed and conducted as a 3-arm trial with treatments sucralfate, carafate and placebo. The trial purpose was to show that the generic sucralfate is bioequivalent to carafate having shown that carafate and sucralfate are effective in the trial. The Week 4 healing rate of acute duodenal ulcer was the main clinical endpoint. The trial was to be conducted as a double-blind randomized multi-center trial.

Randomization for the Trial

In this trial, patients were claimed to be randomized in blocks of 3 patients, and within each block, patients were to be assigned to treatments A=placebo, B=carafate, and C=sucralfate on using an appropriate sequence of random numbers. Exhibit #10 (attached) shows sponsor's documentation of the prospective (i.e., pre-established) randomization plan (chart) for the trial.

1. Concerns Regarding Prospective Randomization

If the treatment assignments used proper random number sequence, then within-block first-patient treatment assignments should follow a statistical random order. However, the medical officer noted that this may not be the case



Reviewer Table 1

Centers with Repetitive Treatment Assignments

Center 1052		Center 1055		Center 1059	
Patient #s	Assignments	Patient #s	Assignments	Patient #s	Assignments
(1, 2, 3)	A C B	(67, 68, 69)	C A B	(31, 32, 33)	A B C
(4, 5, 6)	A B C	(70, 71, 72)	C A B	(34, 35, 36)	A C B
(115, 116, 117)	A C B	(277, 278, 279)	C A B	(241, 242, 243)	C B A
(118, 119, 120)	C A B	(61, 62, 63)	A C B	(244, 245, 246)	C B A
(127, 128, 129)	A C B	(64, 65, 66)	B C A	(265, 266, 267)	B A C
(130, 131, 132)	C B A	(280, 281, 282)	C A B	(268, 269, 270)	B A C
(164, 163, 165) switching of patient order	A B C	(106, 107, 108)	B A C	(298, 299, 300)	B C A
(166, 167, 168)	B A C	(134, 135) did not ship the B of BCA	C A	(286, 287, 288)	B C A
(175, 176, 177)	A B C	(136, 137, 138)	C A B	(211, 212)	B A
(178, 179, 180)	A B C	(157) 1st assignment of Block # 53 (CAB)	C	(103, 213)	B C
(181, 182, 183)	A B C				
(184, 185, 186)	C A B				
(199, 200, 201)	A C B				
(202, 203, 204)	C B A				
(205, 206, 207)	C B A				

As seen in the above table, within-block first-patient assignments were dominated by A in Center 1052, by C in Center 1055, and by B in Center 1059. Also, in Center 1055, the pattern 'CAB' (i.e., the first patient receiving C, the second A and the third B), occurred in 6 out of the total 10 blocks used for this center. The medical officer therefore has raised the point: Could these unusual patterns have occurred by the chance factor alone?

REVIEWER'S COMMENTS

I. Sponsor's Prospective Randomization

This reviewer applied the statistical run test methodology to test for the randomness of occurrences of assignments A and B in Sequence 1 and of B and C in Sequence 2. Both these sequences are listed above. The run test methodology is described in the book by E. L. Lehman ("Nonparametrics", pages 313-315, published by Holden-Day, Inc., 1975). These pages are attached. The methodology is also discussed in a paper by A. M. Mood (Ann. Math. Statist., 11: 367-392; 1940).

This run test is based on the concept that, if either the treatment assignments alternate too frequently (e.g., in a systematic assignment ABABAB ...) or alternates too slowly resulting in long sequences of treatments (e.g., in the above Sequence 1 with respect to treatments A and B), then non-randomness of treatment assignments are suspected.

The results of the analyses performed by this reviewer were as follows:

Reviewer Table 2
Run Test Results for Treatment Assignments

Allocation Blocks	Treatment Assignments Tested[1]	2-sided P-Value
1 - 38	A and B	.016
77 - 113	B and C	.083

[1] These within-block first-patient treatment assignments of the prospective randomization plan were tested because they exhibited unusually long runs than expected under random assignment.

These results, suggest the possibility of a defective randomization in the prospective randomization plan, at least for the early the portion of the plan.

The sponsor's randomization document (see Exhibit 10) also gave a randomization seed number, which was read with difficulty by this reviewer as

#58566422, indicating that a seed number was used to generate the random number sequence for treatment assignments. One of the purposes for documenting and reporting such a seed number for a given trial is that one would be able to generate the original random number sequence and verify the random allocation used for the trial.

Verification of the sponsor's planned random allocation in Exhibit 10 has not been possible, because the sponsor's document did not contain the actual random number sequence used and did not describe the method applied to it in arriving at the planned treatment allocation claimed in the table given in Exhibit 10.

This reviewer did several experiments: 1) generated the random number sequence with the above seed number using the random number generator software "RANUNI" of SAS (Statistical Analysis System), 2) and used various commonly used approaches for arriving at the treatment allocations from this random number sequence. However, this reviewer was not able to replicate the sponsor planned treatment allocations as given in Exhibit 10.

As some statistical software generate "pseudo-random" numbers. The sponsor may have used a correct approach of randomization, but inadvertently generated an inappropriate pseudo-random number sequence and went ahead with treatment allocation.

II. Unusual Patterns at Centers 1052, 1055, and 1059

Center 1052

As seen in the Reviewer Table 1, within-block first-patient assignments occurred in the following sequence:

AAA C A C A B AAA C A CC.

Thus, with regard to within-block first-patient assignments, A occurred 9 times as compared to B which occurred only once and C which occurred 5 times. For a single randomization block of size 3, there are 6 equally likely assignments: ABC, ACB, BAC, BCA, CAB, CBA. This means that the

probability of occurring assignment A in the first position of a single block is 2/6 or 1/3. Therefore, the probability that assignment A would occur by chance in at least 9 times in the first position in 15 independent randomization blocks can then be calculated by the exact binomial probability calculations. This probability on using the function PROBBNML of the statistical software SAS comes out to be

$$\text{Probability}\{\ A \text{ occurs} \geq 9 \ / \text{ given } n=15,\ p_A = 1/3\} = .0085.$$

Center 1055

As seen in the Reviewer Table 1, there were at least 5 allocation blocks where 'ABC' replicated. Again, for a single randomization block of 3, there are 6 equally likely assignments: ABC, ACB, BAC, BCA, CAB, CBA. This means that the probability of occurring assignment 'CAB' in a single block is 1/6. Therefore, the probability that this particular allocation would replicate by chance at least 5 times in 10 independent allocation blocks shipped to this center is

$$\text{Probability}\{\ \text{'CAB' occurs} \geq 5 \ / \text{ given } n=10,\ p_{(CAB)} = 1/6\} = .0024.$$

Center 1059

As seen in the Reviewer Table 1, the first-patient within block assignments for this center had the following sequence:

AA CC BBBBBB

Thus, with regard to first-patient within-block assignments, B occurred 6 times as compared to A and C which occurred each twice. The probability of occurring B by chance at least 6 times is

$$\text{Probability}\{\ B \text{ occurs} \geq 6 \ / \text{ given } n=10,\ p_B = 1/3\} = .0197.$$

Reviewer Table 3 given below summarizes exact binomial probability calculations for unusual repetitive assignments for centers #1052, #1055, and #1059

Reviewer Table 3
Exact Binomial Probability Calculations for
Unusual Repetitive Assignments at Some Centers

Center	Total Blocks Allocated	---Repetitive Assignments---- 1st Patient Allocation	Block Allocation	Binomial Event	Probability of the Event by Chance
#1052	15	'A' occurred 9 times	-	# of 'A' $\geq$ 9	.0085
#1055	10	'C' occurred 7 times	'CAB' occurred 5 times	# of 'C' $\geq$ 7 # of 'CAB' $\geq$ 5	.0034 .0024
#1059	10	'B' occurred 6 times	-	# of 'B' $\geq$ 6	.0197

Low probabilities of repetitive assignments as shown in the last column of the above table do not support the hypothesis that these repetitive assignments to incoming patients at centers #1052, #1055, and #1059 occurred by the chance factor alone. These complications for this trial could have been avoided if the pr-established randomization was blocked by center.

III. Influence of Centers #1052, #1055, and #1059

Given that there were unusual patterns in randomization blocks used at centers #1052, 1055 and at 1059, the medical officer has raised the questions: Are results in these 3 centers influencing or biasing in a direction that if the results for these centers were similar to those observed for the remaining centers then

the claimed results of bio-equivalence of sucralfate versus carafate and/or of effectiveness of sucralfate and carafate would not occur? To answer this question, the sponsor needs to provide appropriate statistical analyses including some sensitivity analyses at least for the Week 4 healing rate.

FINAL COMMENTS

This reviewer's run test results detected the possibility of a defective randomization in the prospective randomization plan, at least for early the portion of the plan.

Therefore, the sponsor should provide the following details to further assess the validity of the claimed randomization plan:

1. Please regenerate the original random number sequence using the randomization seed number provided in Exhibit 10.

2. Describe the method used to arrive at treatment allocations in blocks of 3 as claimed in Exhibit 10.

3. Please provide computer outputs and details of each step for review and verification purpose.

Treatment allocation blocks for patient enrollment exhibited unusual patterns at some centers. In Center 1052, first-patient allocations were 'A' in 9 out of the total 15 treatment allocation blocks. In Center 1055, pattern 'CAB' (i.e., the first patient receiving C, the second A and the third B), occurred in 6 out of the total 10 blocks used for this center. In Center 1059 also first-patient allocations were B in 6 out of the total 10 treatment allocation blocks. Statistical evaluation did not support the hypothesis that these unusual patters were due to chance factor alone.

4. To evaluate the impact of problem centers #1052, 1055 and 1059, please provide appropriate statistical analyses including some

sensitivity analyses at least for the Week 4 healing rate to answer the question. Are results in these 3 centers influencing or biasing in a direction that if the results for these centers were similar to those observed for the remaining centers then the claimed results of bio-equivalence of sucralfate versus carafate and/or of effectiveness of sucralfate and carafate would not occur?

M. F. Huque

M. F. Huque, Ph. D.
Mathematical Statistician

Concur: Dr. Dubey 2-15-94.

[This review contains 9 pages of texts and 6 pages of attachments.]

cc: Orig. ANDA 70-848
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Ms. Walsh
HFD-713/Dr. Dubey [File: DRU 1.3.2] generics
HFD-713/Dr. Huque
Chron.
Dr. Huque/X34594/1-25-95

Reviewer Table 4*

Prospective (Pre-Established) Randomization Plan
Derived from Exhibit 10 by Biocraft-Almedica

BLK #s	Treat Codes	Patients #s	BLK #s	Treat. Codes	Patients #s	BLK #s	Treat. Codes	Patients #s
1.	ACB	1, 2, 3	39.	ACB	115, 116, 117	77.	ACB	229, 230, 231
2.	ABC	4, 5, 6	40.	CAB	118, 119, 120	78.	BCA	232, 233, 234
3.	CAB	7, 8, 9	41.	ABC	121, 122, 123	79.	CAB	235, 236, 237
4.	CBA	10, 11, 12	42.	CAB	124, 125, 126	80.	CBA	238, 239, 240
5.	ABC	13, 14, 15	43.	ACB	127, 128, 129	81.	CBA	241, 242, 243
6.	BCA	15, 17, 18	44.	CBA	130, 131, 132	82.	CBA	244, 245, 246
7.	BCA	19, 20, 21	45.	BCA	133, 134, 135	83.	CAB	247, 248, 249
8.	CBA	22, 23, 24	46.	CAB	136, 137, 138	84.	CBA	250, 251, 252
9.	ABC	25, 25, 27	47.	ACB	139, 140, 141	85.	CBA	253, 254, 255
10.	ACB	28, 29, 30	48.	ACB	142, 143, 144	86.	ABC	256, 257, 258
11.	ABC	31, 32, 33	49.	CAB	145, 146, 147	87.	BAC	259, 260, 261
12.	ACB	34, 35, 36	50.	BAC	148, 149, 150	88.	BCA	262, 263, 264
13.	ACB	37, 38, 39	51.	CBA	151, 152, 153	89.	BAC	265, 266, 267
14.	CBA	40, 41, 42	52.	BAC	154, 155, 156	90.	BAC	268, 269, 270
15.	CAB	43, 44, 45	53.	CAB	157, 158, 159	91.	ACB	271, 272, 273
16.	ABC	46, 47, 48	54.	CBA	160, 161, 162	92.	CAB	274, 275, 276
17.	CBA	49, 50, 51	55.	BAC	163, 164, 165	93.	CAB	277, 278, 279
18.	BCA	52, 53, 54	56.	BAC	166, 167, 168	94.	CAB	280, 281, 282
19.	BAC	55, 56, 57	57.	BCA	169, 170, 171	95.	CBA	283, 284, 285
20.	BCA	58, 59, 60	58.	CAB	172, 173, 174	96.	BCA	286, 287, 288
21.	ACB	61, 62, 63	59.	ABC	175, 176, 177	97.	ACB	289, 290, 291
22.	BCA	64, 65, 66	60.	ABC	178, 179, 180	98.	ACB	292, 293, 294
23.	CAB	67, 68, 69	61.	ABC	181, 182, 183	99.	CAB	295, 296, 297
24.	CAB	70, 71, 72	62.	CAB	184, 185, 186	100.	BCA	298, 299, 300
25.	BCA	73, 74, 75	63.	BAC	187, 188, 189	101.	ABC	301, 302, 303
26.	ABC	76, 77, 78	64.	ABC	190, 191, 192	102.	CBA	304, 305, 306
27.	ACB	79, 80, 81	65.	BCA	193, 194, 195	103.	ACB	307, 308, 309
28.	ABC	82, 83, 84	66.	CAB	196, 197, 198	104.	BAC	310, 311, 312
29.	ACB	85, 86, 87	67.	ACB	199, 200, 201	105.	ACB	313, 314, 315
30.	ACB	88, 89, 90	68.	CBA	202, 203, 204	106.	ACB	316, 317, 318
31.	BAC	91, 92, 93	69.	CBA	205, 206, 207	107.	CBA	319, 320, 321
32.	BAC	94, 95, 96	70.	ACB	208, 209, 210	108.	CAB	322, 323, 324
33.	BAC	97, 98, 99	71.	BAC	211, 212, 213	109.	ABC	325, 326, 327
34.	BCA	100, 101, 102	72.	ACB	214, 215, 216	110.	ACB	328, 329, 330
35.	BCA	103, 104, 105	73.	BAC	217, 218, 219	111.	ABC	331, 332, 333
36.	BAC	106, 107, 108	74.	ACB	220, 221, 222	112.	BAC	334, 335, 336
37.	BCA	109, 110, 111	75.	BCA	223, 224, 225	113.	CBA	337, 338, 339
38.	CAB	112, 113, 114	76.	BAC	226, 227, 228			

A=placebo, B=carafate, C=sucralfate

(*Table modified from the medical officer's review Table 2, page 9, 1994)

PAGE NO. 1

[illegible] BIDCRAFT

[illegible] 1K[illegible]

FILE
DATE 2/[illegible]/[illegible]
TIME 10:54:51

CENTER: 1

TREATMENT GROUP(S)
A B C ......1..............................

BLOCK SIZE
3

T.G. DESCRIPTION

A PLACEBO
B CARAFATE(MARION)
C SUCRALFATE(BIDCRAFT)

TREATMENT GROUPS SEED #: 5854[illegible]22

A	B	C
1	3	2 ←
4	5	6
8	9	7 ←
12	11	10
13	14	15
18	16	17
21	19	20
24	23	22
25	26	27
28	30	29
31	32	33
34	36	35
37	39	38
42	41	40 ←
[illegible]	[illegible]	[illegible]
102	100	101
[illegible]	[illegible]	[illegible]

Exhibit 10 Page 19

3/11/93-4/6/93
DAD

ACCEPTANCE APP.

BY:.........................

DATE:.........................

NAME OF STUDY

[redacted] KIRKCRAFT

[redacted] 143987

PATIENT TREATMENT GROUP ASSIGNMENT REPORT

FILE
DATE 2/08/88
TIME 10:55:26

PAGE NO. 2

CENTER: 1

TREATMENT GROUP(S)
A B C ..... BLOCK SIZE 3

TREATMENT GROUPS SEED #: [redacted]

A	B	C
173	174	177
178	179	180
181	182	183
183	184	185
186	187	188
189	190	192
193	195	196
197	198	199
199	201	200
204	203	202
207	206	208
209	210	205
212	211	213
214	216	215
218	217	219
220	222	221
223	224	225
227	226	228
229	231	230
234	232	233
236	237	235
240	239	238
243	242	241
244	245	246
248	249	247
252	251	250
253	254	255
256	257	258
260	259	261
264	263	262
265	266	268
271	270	269
273	274	272
276	275	277
280	279	278
283	281	282
286	284	285
287	288	289
292	291	290
294	295	293
298	297	296
301	302	300
304	303	305
307	306	308
311	309	310
313	312	314
316	315	317
318	319	320
321	322	323
325	324	326
328	327	329
331	330	332
334	333	335
337	336	338
340	339	341
343	342	344
346	345	347
349	348	350

91 48

Exhibit 10, Page 20

3/11/93-4/6/93
DAD

E.L. Lehman. Nonparametrics, pages 313-315; Holden-Day, Inc., 1975

were proposed by Theil (1950), who also suggested the median of the slopes $(Z_j - Z_i)/(j-i)$ as a point estimate of β. Some extensions of Theil's result and references to other estimation methods for β are given by Sen (1968). It is interesting to note, as is done by Bhattacharyya (1968), that the same point estimate of β is obtained by applying the method of Chap. 2, Sec. 6, to the test statistic D' instead of to B. The estimate is also derived from a completely different point of view by Beran (1971).

When one suspects a linear trend and hence a model of the form (7.32), it may be of interest to test the appropriateness of this model. Two simple tests for this purpose are proposed by Olshen (1967).

Important problems also arise in the comparison of several regression coefficients when one is dealing with more than one series of observations for each of which one assumes a model of the form (7.32) with common distribution function F. This situation is considered, for example, by Sen (1969), Hollander (1970), Adichie (1974), and Potthoff (1974).

For further work on inference concerning regression parameters, including multiple regression and other approaches to robust estimation, see Adichie (1967), Bickel (1971), Jurečkova (1971), and Koul (1969).

5C. Tests of Randomness Based on Runs

The alternatives of an upward or downward trend considered in Sec. 2 are not the only alternatives to randomness that may be of interest. Instead, a trend might be cyclical (for example, seasonal), or following some other pattern, or successive observations may be dependent, as is the case in model (7.32). The problem of testing for randomness against these or other less clearly specified alternatives arises, for example, in quality control if one wishes to know whether the quality of successively produced items behaves like a sequence of identically, independently distributed random variables; in the study of economic time series; or when considering a sequence of physiological or psychological measurements taken on the same individual over a period of time.

Although the alternatives to randomness are often not clearly defined, a common feature of a large class of alternatives is a tendency toward clustering so that high (or low) values tend to occur together. This can be exploited by considering various kinds of runs of like elements exhibited by the series of observations and rejecting the hypothesis of randomness when the number of runs is too small or when too many long runs occur.

Consider first the important special case in which the response is dichotomous, so that each observation represents either a success or a failure. If these two outcomes are denoted by 1 and 0, respectively, the N observations form a sequence of ones

and zeros. The hypothesis of randomness states that this sequence constitutes a sequence of N binomial trials with unknown success probability, say, p. A natural test statistic to test this hypothesis against the alternatives of clustering is the total number R of runs of ones and zeros. For example, in the series

$$1 \quad 0 \quad 0 \quad 0 \quad 1 \quad 1 \quad 0 \quad 0 \quad 1 \quad 1$$

there are three runs of ones (of lengths 1, 2, and 2) and two runs of zeros (of lengths 3 and 2), so that $R = 5$.

The null distribution of R depends on p; however, the conditional null distribution, given that the number of zeros is m and the number of ones is n, does not since the conditional probability of any particular arrangement of the m zeros and n ones is $1 \Big/ \binom{N}{n}$. The conditional distribution of R has in fact the simple expression

$$P(R = 2k) = \frac{2\binom{m-1}{k-1}\binom{n-1}{k-1}}{\binom{N}{n}} \tag{7.43}$$

and

$$P(R = 2k+1) = \frac{\binom{m-1}{k-1}\binom{n}{k} + \binom{m-1}{k}\binom{n-1}{k-1}}{\binom{N}{n}} \tag{7.44}$$

As N (and n) tend to infinity with m/n tending to a limit, it is shown by Wald and Wolfowitz (1940) that the distribution of

$$\frac{R - 2m(1-c)}{\sqrt{2m(1-c)}}$$

tends to the standard Normal distribution. (Wald and Wolfowitz discuss R in the context of the two-sample problem. For this problem, the R test is now known to be very inefficient.) Tables of the null distribution of R are given by Swed and Eisenhart (1943). As pointed out by David (1947) and Lehmann (1959, pp. 155–156), the R-test has certain optimum properties against the alternatives that the observations come from a stationary Markov chain. For further work on the application of run tests to Markov chains, see Goodman (1958) and a survey paper by Billingsley (1961).

Other run statistics that have been considered for testing randomness in a sequence of zeros and ones are the number of runs of length greater than l and the length of the longest run. For a discussion of some interesting early applications of runs, see von Mises (1931, Sec. 4.2). A systematic account of the theory of runs of

two kinds of elements and i
Mood (1940). Additional m
(1962).

Let us now return to th
hypothesis of randomness (in
identically and independently
clustering of like values. V
by a zero if it falls below and
by taking as test statistic the
zeros. The statistic R clearly
when $N = 2n + 1$ and when N
$m = n$ and N replaced by $2n$

A class of run statistics
the median is obtained by con
$Z_1 = Z_2, \ldots, Z_N = Z_{N+1}$. This
(a plus sign if $Z_i - Z_{i-1} > 0$,
up (i.e., runs of plus signs) and
null distribution. A simple t
which is essentially the numbe
considered by Wallis and Moo
Edgington (1961). The distrib
joint distribution of numbers
among others, Kermack and
Wolfowitz (1944), and Olmste
problem of choosing a test that
is discussed by Levene (1952).

5D. Other Tests of Independe

The statistic $B = \sum_{i<j} U_{ij}$ discuss
an upward or downward tren
independence against positive
pairs of observations $(X_1, Y_1), \ldots$
B counts the number of pairs
first ordered, it follows that B
$Y_i < Y_j$. Thus, in general, B is
$X_j - X_i$ and $Y_j - Y_i$ have the same
(7.45)

Such pairs are said to be *concor*

two kinds of elements and its extension to the case of more than two is given by Mood (1940). Additional material can be found in the book by David and Barton (1962).

Let us now return to the general problem of a series $Z_1, \ldots, Z_N$ for which the hypothesis of randomness (in the population model, the hypothesis that the Z's are identically and independently distributed) is to be tested against the alternative of clustering of like values. A possible test is obtained by replacing each observation by a zero if it falls below and by a one if it falls above the median of the Z's and by taking as test statistic the number R of runs in the resulting series of ones and zeros. The statistic R clearly depends only on the ranks of the observations. Both when $N = 2n + 1$ and when $N = 2n$, the null distribution of R is given by (7.43) with $m = n$ and N replaced by $2n$.

A class of run statistics different from those based on runs above and below the median is obtained by considering the signs of the successive differences $Z_2 - Z_1$, $Z_3 - Z_2, \ldots, Z_N - Z_{N-1}$. This again constitutes a sequence of two kinds of elements (a plus sign if $Z_i - Z_{i-1} > 0$, a minus sign if $Z_i - Z_{i-1} < 0$) but the associated runs up (i.e., runs of plus signs) and runs down (i.e., of minus signs) have a quite different null distribution. A simple test statistic is the total number of runs up and down, which is essentially the number of turning points or of peaks and troughs in the series, considered by Wallis and Moore (1941). A table of the null distribution is given by Edgington (1961). The distribution of the number of runs of given length and the joint distribution of numbers of runs of several different lengths has been studied by, among others, Kermack and McKendrick (1937a,b), Levene and Wolfowitz (1944), Wolfowitz (1944), and Olmstead (1946). The power of the associated tests and the problem of choosing a test that is appropriate against a specified class of alternatives is discussed by Levene (1952).

5D. Other Tests of Independence

The statistic $B = \sum_{i<j} U_{ij}$ discussed in Sec. 5B above for testing randomness against an upward or downward trend can also be adapted to the problem of testing independence against positive or negative association of two variables. If the N pairs of observations $(X_1, Y_1), \ldots, (X_N, Y_N)$ are arranged in increasing order of the X's, B counts the number of pairs (i,j) with $i < j$ for which $Y_i < Y_j$. If the X's are not first ordered, it follows that B is the number of pairs (i,j) with $X_i < X_j$ for which $Y_i < Y_j$. Thus, in general, B is the number of pairs (i,j) for which the differences $X_j - X_i$ and $Y_j - Y_i$ have the same sign, or equivalently, the number of pairs for which

$$(X_j - X_i)(Y_j - Y_i) > 0 \tag{7.45}$$

Such pairs are said to be *concordant*. The probability p of the event (7.45), which is

STATISTICAL REVIEW & EVALUATION

Date: **March 15, 1994**

ANDA #: **70-848**

Applicant: **Biocraft**

Drug Name: **Biocraft Sucralfate's 1 gm tablet (Generic Drug)**

Indication: **Duodenal Ulcer**

This review is an **addendum** to the statistical review of the ANDA dated February 10, 1994. This review addresses some new analyses results.

The medical officer's recent review indicated randomization and randomization related concerns for study centers #1052, 1055, 1059, 1066, and 1075. The statistical review of February 10, 1994 indicated similar concerns for centers #1052, 1055, and 1059. This review, therefore, examined some results for the following subgroups of centers:

(1) Centers #1052, 1055, 1059, 1066, 1075 vs. the remaining Centers 15 centers; 13 of these 15 remaining centers had sample sizes of less than 6 patients per treatment arm.

(2) Centers #1052, 1055, 1059 vs. the remaining 17 centers. These 3 centers had randomization related concerns and are addressed in the stat review of February 10, 1994.

The analyses (1) and (2) above were requested in January 1994 by the Medical Officer, Robert Prizont, M.D. In addition to these, this reviewer did the large vs. small centers analyses. The subgroup of centers with less than 6 patients per treatment arms was called 'small centers.'

Reviewer's Analyses Methods

For these subgroupings, this reviewer calculated the following for the primary endpoint (week 4 healing rate):

1. Sucralfate vs placebo comparison 2-sided p-values using Fisher's exact test.

2. 90% confidence intervals for the sucralfate minus carafate healing rates using the formula given at the bottom of Table B1. Such confidence intervals, if they fell within ± 20 percent clinical bio-equivalence limits, satisfies the given ± 20 percent clinical bio-equivalence criteria for such trials.

3. The Breslow Day test for the center by treatment interaction. In this test, because of low power, only extreme cases would be detected for the sample sizes observed in the two groups of centers examined.

Tables (A1, B1) through (A3, B3) provide results of the above analyses for the respective subgroups of the centers. Tables C and D (attached), provided by the medical officer, give the week 4 healing rates by treatment group and center. Note that in the latter tables total healing rate for the sucralfate group is 33/91 as compared to 31/91 considered in the original stat review of July 12, 1992.

Table A1

Results: Centers 1052, 1055,1059, 1066,1075 Vs. Remaining
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2 sided p by Exact Test
5 Centers #	5/55 9.1%	20/53 37.7%	6.1	28.6%	< 0.001
Remaining-Centers ##	10/38 26.3%	13/38 34.2%	1.5	7.9%	0.618
All Centers	15/93 16.1%	33/91 36.3%	3.0	20.2%	0.002

Interaction Test: Breslow Day Chi-Square = 3.771, 1 df
2-sided p = .052

Note: In this interaction test the sucralfate versus placebo effect of the 5 centers is compared with that of the remaining centers.

Table B1

Results: Centers 1052, 1055,1059, 1066,1075 Vs. Remaining
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	@90 Percent Confidence Interval*
The 5 Centers#	18/52 34.6%	20/53 37.7%	+3.0%	(-12.3%, 18.4%)
The Remaining Centers##	17/37 46.0%	13/38 34.2%	-11.8%	(-30.3%, 6.7%)**
All Centers	35/89 39.3%	33/91 36.3%	-3.0%	(-13.9%, 8.9%)

Interaction Test: Breslow Day Chi-Square = 1.01, 1 df
2-sided p = 0.316

Note: In this interaction test the sucralfate versus placebo effect of the 5 centers is compared with that of the remaining centers.

#See Table C, ##See Table D

@This 90% confidence interval being within 20 percent limits on each side establishes clinical bio-equivalence between the test and the reference drugs with 5% risk of being not clinically bio-equivalent.

* Confidence intervals were calculated using the formula:

$$90\%\ CI = (p_2 - p_1) \pm 1.645\sqrt{p_1(1-p_1)/n_1 + p_2(1-p_2)/n_2}$$

where p_1 and p_2 are sucralfate and carafate rates and n_1 and n_2 are corresponding sample sizes.

**This wide confidence interval indicating non-equivalence for this subgroup of centers could be due to small sample sizes.

Table A2

Results: Centers 1052, 1055, 1059 Vs. Remaining Centers
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2-sided p by Exact Test
Centers 1052, 1055, 1059	2/33 6.1%	13/34 38.2%	9.6	-32.1%	0.001
Remaining Centers	13/60 21.7%	20/57 35.1%	2.0	-13.4%	0.728
Interaction Test: Breslow Day Chi-Square = 3.269, 1 df **2-sided p = .0706**					

Table B2

Results: Centers 1052, 1055, 1059 Vs. Remaining Centers
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	90 Percent Confidence Interval
Centers 1052, 1055, 1059	9/33 27.3%	13/34 38.2%	10.9%	(-7.7%, 29.9%)
Remaining Centers	26/56 46.4%	20/57 35.1%	-11.3%	(-26.5%, 3.8%)

Interaction Test: Breslow Day Chi-Square = 2.242, 1 df
2-sided p = .134

Table A3
Results: Large Vs. Small Centers
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2-sided p by Exact Test
Large Centers #	10/71 14.1%	27/69 39.1%	3.9	25.0%	0.001
Small Centers	5/22 22.7%	6/22 27.3%	1.3	4.6%	0.728
Interaction Test: Breslow Day Chi-Square = 1.938, 1 df **2-sided p = .164**					

Table B3
Results: Large Vs. Small Centers
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	90 Percent Confidence Interval
Large Centers#	27/66 40.9%	27/69 39.1%	-1.8%	(-15.7%, 12.1%)
Small Centers	8/23 34.8%	6/22 27.3%	-7.5%	(-30.1%, 15.1%)

#Centers which had 6 or more patients in each treatment arm.

Reviewer's Comments

The above analyses are post-hoc subgroup analyses and as such have limitations. However, these analyses are driven by the randomization and randomization related concerns and provide following insights to the week 4 healing data of this trial.

1. The interaction test result for the sucralfate versus placebo comparison indicates

inconsistency among the two groups of centers (i.e., centers 1052, 1055, 1059, 1066 and 1075 as a subgroup versus the remaining 15 centers as another subgroup). The Breslow Day p-value for this interaction test is .052 (see Table A1). The observed effect size in the 5-centers subgroup is 4 fold greater in terms of the odds ratio and 3.6 fold greater in terms of the absolute difference in comparison to those for the remaining 15- centers subgroup (see Table A1).

Also, the placebo rate of 9.1% for the 5-centers subgroup is low as compared to the placebo rate of 26.3% for the remaining 15-centers subgroup when given that the sucralfate healing rate for the two subgroups are about the same (37.7% vs. 34.2%, see Table A1). These inconsistencies are of concern because of randomization and randomization related questions for these centers.

2. The above inconsistency is also observed for the 3-centers subgroup (centers #1052, 1055, 1059) vs. the remaining 17 centers. The Breslow Day test for treatment by center interaction p-value of is .071. [This p-value is of concern when given that the power of the Breslow Day test is low.] Also, the placebo rate for the 3-centers subgroup of 6.1% is low in comparison to 21.7% for the remaining 17 centers when given that the sucralfate rates for these two subgroup of centers are about the same (38.2% vs. 35.1%, see Table A2).

In addition, the observed sucralfate minus carafate difference is in favor of sucralfate in the 3-center subgroup and in favor of carafate in the remaining 17-centers subgroup (see Table B2); however, this consistency is not statistically significant by the Breslow Day Test.

3. The large vs. small center results indicate overall results driven by large centers contributing the majority of the patients (see Tables A3, B3).

4. The p-values and confidence intervals calculated by this reviewer in the above tables assume proper randomization of the trial; otherwise these p-values are likely to be biased.

M. F. Huque

M. F. Huque, Ph. D.
Mathematical Statistician

Concur: Dr. Dubey 3-23-94

[This review contains 7 pages of texts and 2 pages of attachments]

cc: Orig. ANDA 70-848
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Ms. Walsh
HFD-713/Dr. Dubey [File DRU 1.3.2] generic
HFD-713/Dr. Huque
Chron.

Dr. Huque/x34594/3-14-94

Table C (Medical Officer's Table)

Four Week Healing Rate of Centers 1052, 1055, 1059, 1066 and 1075. All Patients

Center	Number Pts	Placebo	Carafate	Sucralfate
1052	45	1/15 (7%)	3/15 (20%)	4/15 (27%)
1055	37	0/8 (0%)	2/8 (25%)	5/11 (50%)
1059	28	1/9 (10%)	4/10 (40%)	4/8 (40%)
1066	25	1/8 (10%)	3/8 (38%)	2/8 (25%)
1075	35	2/13 (15%)	6/11 (55%)	5/11 (45%)
All Five Centers	160	5/53 (9%)	18 32(56%)	20/53 (38%) 10 8

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Table D (Medical Officers Table)

Four Week Healing in Centers 1053, 1060, 1064, 1076 and Centers with Low Enrollment. All Patients Included

Centers	Enrollment	Placebo	Carafate	Sucralfate
1053	20	1/7(14%)	3/8(50%)	1/7(14%)
1060	12	2/4(50%)	1/4(25%)	1/4(25%)
1064	10	1/4(25%)	2/3(67%)	2/3(67%)
1076	25	4/9(44%)	6/8(75%)	6/8(67%)
[illegible]	7	0/2(0%)	0/2(0%)	1/3(33%)
[illegible]	7	2/3(67%)	0/2(0%)	0/2(0%)
[illegible]	6	0/2(0%)	1/2(50%)	1/2(50%)
[illegible]	6	0/2(0%)	1/3(33%)	0/2(0%)
[illegible]	5	0/2(0%)	0/1(0%)	0/2(0%)
[illegible]	4	0/1(0%)	1/2(50%)	0/1(0%)
[illegible]	3	0/1(0%)	0/1(0%)	1/1(100%)
[illegible]	3	0/1(0%)	0/1(0%)	0/1(0%)
[illegible]	2		1/1(100%)	0/1(0%)
[illegible]	1		1/1(100%)	
[illegible]	1		0/1(0%)	
Total	115	10/38(26%)	17/37(46%)	13/38(34%)

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER CONSULT REVIEW

ANDA: 70-848

Sponsor: Biocraft Laboratories

Drug: Generic Sucralfate Oral Tablets

Indication: Acute Treatment of Duodenal Ulcer

Document to be Reviewed: Report from the Department of Scientific Investigations, FDA Office of Compliance

Documents Submitted: (a) Memorandum from Dr. Bette Barton, M.D., Ph.D., (b) Report from the Field Investigator Officers, Ms. Daryl DiWoskin, Ms. Barbara Schultz (c) Information on Implementation of Randomization and Drug Distribution Submitted by and (d) Information on Implementation of Randomization and Drug Distribution submitted by Biocraft.

Dates Submission Received by Medical Officer: May 15, June 16, 1993, September 3, 1993 DSI Exhibits (28, 33, 38, 39) September 8, 1993 (Biocraft Information and Exhibits), September 30, DSI Report on Biocraft Inspection and Correspondence from Compliance to CDER Requesting Disqualification of Biocraft's Study.

Date of Initial Rough Drafts: August 24, 1993 and March 2, 1994

Date Finalized: March 10, 1994

Medical Officer: Dr. Robert Prizont, M.D.

- The DSI investigation was conducted in relation to the involvement of participants in the randomization, patient assignment, distribution of tested drugs and blinding which occurred during the Clinical Trial sponsored by Biocraft and conducted by The clinical trial was performed on patients with active duodenal ulcer to determine equivalence between Biocraft's generic sucralfate 1 gram tablets and Marion's marketed 1 gram sucralfate tablets (Carafate®). Biocraft had prospectively designed this clinical trial under Protocol 8619. According to the materials included in Biocraft's original submission, Protocol 8619 was finalized on March 2, 1988 (page 100251, Vol.1 of 7). Biocraft submitted this trial as a randomized, double blind DU study.

- On August 16, 1993, the HFD-180 Division Director requested this medical officer to describe and review findings in the DSI report pertaining only with randomization, distribution of tested drugs and assignment sequences.

- On August 26, 1993, The Division Director requested this reviewer to concentrate the commentary on the interpretation of possible causes which might have led to the repetition of block assignments found in the five centers with high patient enrollment (the details of this finding were discussed in my review of September 18, 1991, pages 20-23).

- Subsequent reviews will assess DSI reports and sponsor information on blinding.

A. Background.

1. Summary of Prior Submissions and Overall Reviewers Conclusions.

Biocraft submitted to the Office of Generics ANDA 70-848 on August 16, 1989. The Division of Gastrointestinal and Coag. Products received a consult from the Office of Generics on August 25, 1989. The original application showed inconsistencies and was incomplete, i.e., the sponsor had not submitted listing of endoscopy results for sucralfate patients enrolled with two duodenal ulcers, and had not performed analyses at the prospectively established 4 and 8 week endpoints with inclusion of all-randomized patients . Four subsequent Amendments were submitted by Biocraft. This division received these four consecutive Amendments on February 16, 1990, March 5, 1990, April 16, 1990, July 9, 1990 and August 9, 1990, respectively. Additional information related to placebo composition, blinding, randomization and shipment of drugs were submitted to this medical officer (through Office of Generics) on June 17, 1991, July 30, 1991 and July 15, 1991, by Nicholas Maselli, Biocraft's Assistant Director of Regulatory Affairs and by Debbie Parker, Biocraft's Regulatory Submission Coordinator, on July 15, 1991.

- The review of this medical officer was finalized on September 18, 1991. It contained the 4 and 8 week efficacy results for sucralfate and Carafate submitted by Biocraft in its original application and Biocraft's post-hoc, unblinded analysis of efficacy for sucralfate and carafate submitted with the amendments. The medical officer review included the FDA statistician analyses of the 4 week equivalence (90% confidence interval of the difference between s-c) of clinical endpoints and the efficacy results over placebo for sucralfate and carafate. *The FDA statistician reviewer reported that at week 4, sucralfate showed equivalence to carafate: 90% confidence interval (C.I.) of s-c was -17% to 7%*

(corrected by Dr. Huque). At week four, carafate and sucralfate were significantly better than placebo ($p < 0.05$). At week 8 carafate was significantly better than placebo (two sided $p = 0.026$, page 51, MO review). At week 8, sucralfate was not significantly superior to placebo (two sided $p = 0.102$, page 51, MO review).

(a) Biocraft's Design of the Trial Included a Prospective Randomization Plan.

Biocraft contracted) for the preparation of a prospective randomization plan.

Almedica prepared a computer-generated prospective randomization plan on February 6, 1988.

Biocraft approved the prospective randomization plan created by on February 8, 1988. The prospective randomization plan created by was submitted by Biocraft to this Agency as Appendix III, Vol. 1, in the 1989 submission, and is part of Exhibit 10 in DiWoskin (FDA) report.

A copy of Exhibit 10, pages 19 and 20, from DiWoskin report with randomization plan is included as Appendix 1 of this review.

2. Summary of Medical Officer Findings About Centers with Repetitive Block Sequences.

In the review of Biocraft's initial submission, this medical officer matched **treatment assignments, center by center**, with the chronological patient entry submitted by Biocraft to Scientific Investigations on November 9, 1989 by David Zuchero, then Biocraft Director of Regulatory Affairs, and submitted to this medical officer on July, 1991 (see Attachment 1 in Appendix 1, MO review, September 18, 1991). **All centers were assessed for presence in sequence repetition.**

In order to better facilitate the understanding of my finding of centers with repetitive first assignment or sequences, the following paragraphs includes a brief review of the repetitive patterns shown in the five centers described in detail in this medical officer review of September 18, 1991.

i. *Centers with Repetitive Sequences.* Centers displaying repetitive block sequences and repetitive initial block assignments were in ascending numerical order centers 1052, 1055, 1059, 1065 and 1075. The "pattern" in each one of these centers was the following:

- *Center 1052.* The "patterns" of block sequences is evident in the Reviewer Scheme I shown below (taken from this reviewer's review of

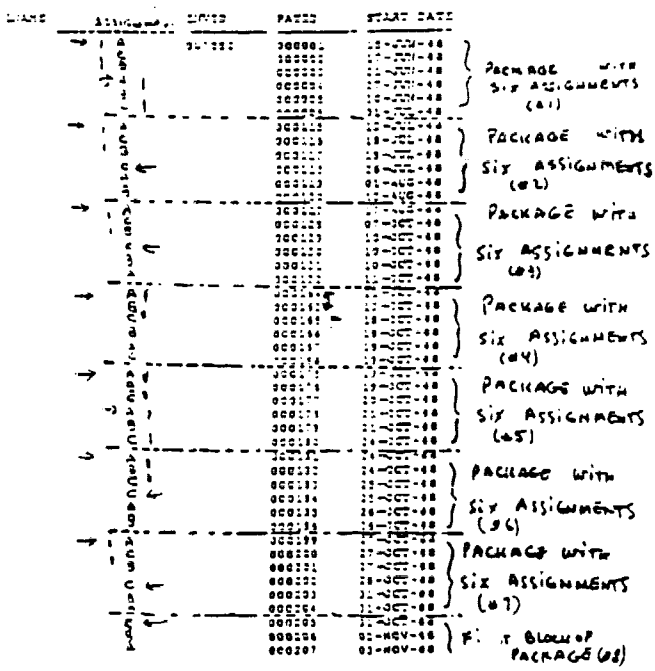
September 1991, page 20). As illustrated in the scheme, *9/15 (60%)* of the used blocks started with assignment *A = Placebo;* 5/15 (33%) used blocks started with assignment C = Sucralfate while *only 1/15 (7%) used blocks start with assignment B = Carafate.*

Five of the blocks starting with A, had the sequence ABC, 4 were ACB. The only block starting with B had the sequence BAC.

Reviewer Scheme I

Center 1052

Center 1052-Assignment Matching With Patient ID and Chronological Entry Included in Page 18x of Information Sent by Biocraft to Scientific Investigations



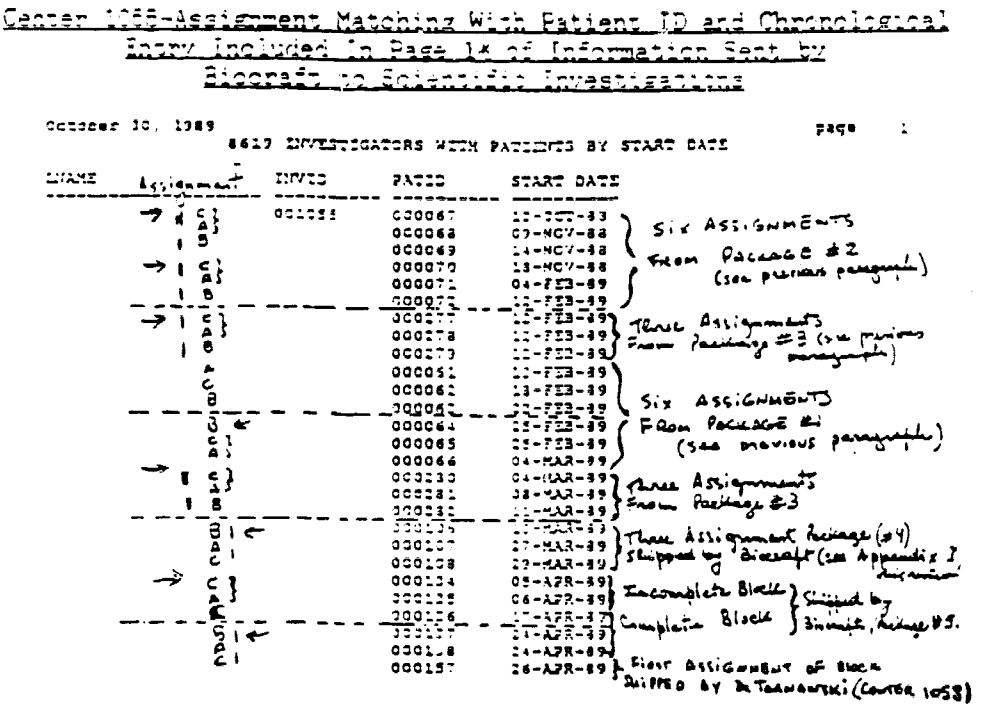
The ↕ symbol indicates reversion of consecutive patient assignment.
*Attachment 2

- *Center 1055.* This center used 9 blocks (Reviewer Scheme II shown below). Of the total 9 used blocks, *5/9 (56%) started with C = Sucralfate,* 3 started with B = Carafate, while *only 1(11%) started with assignment A = Placebo.*

Of the 5 blocks initiating with C, 4 had the sequence CAB, the remaining had a sequence CAC without B assignment representation. Thus, the successive first two assignment CA were present in 5/5 (100%) of the sequences.
Of a total 9 possible C assignments (9 blocks), this center enrolled 10 C assignments.

Reviewer Scheme II

Center 1055



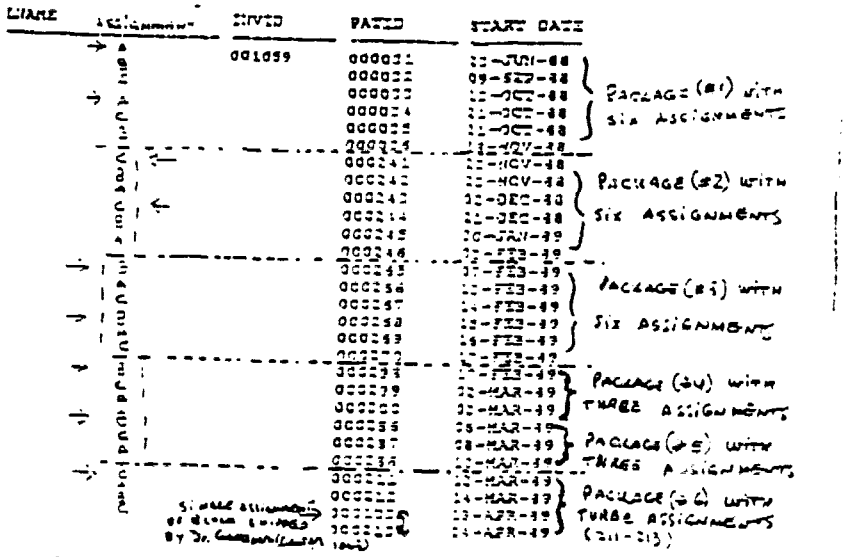
- *Center 1059.* This center used 9 blocks (sequences shown below in reviewer Scheme III). Of the 9 blocks used, *5/9 (56%) started with assignment B = Carafate.*
A 10th initial assignment was also supposed to have started with assignment B, but was reversed with the last assignment of the 9th block (see assignments 213 and 103 reversed in Scheme III).

Of relevance to note in this center, is that *4 of the 6 packages shipped by Biocraft had identical successive sequences, i.e., package # 3 had BAC and BAC* (see Scheme III below).

Reviewer Scheme III

Center 1059

Center 1059-Assignments Matching With Patient ID and Chronological Entry Included in Page 5* of Information Sent by Biocraft to Scientific Investigations



The ↕ symbol indicates reversal of consecutive patient assignment
*Attachment 2

- Centers 1052, 1055, 1059 exhibited enrollment of patients in patterns of repetitive block sequences. Centers 1066 and 1075 also exhibited repetitive sequences, though "patterns" were not so clearly evident.

Repetitive sequences in Centers 1066 and 1075 are included as Appendix 2 of this review.

ii. *Efficacy and Equivalence Results in Centers With Repetitive Sequences.* In my review of September,1991, I showed the 4 week endoscopy results in each of the five centers with repetitive sequences (Reviewer Table 19, page 45). In the following Reviewer Table 1, I am summarizing the 4 week DU healing equivalence between sucralfate and Carafate® in centers with repetitive sequences and compare the equivalence of s-c in these 5 centers to the equivalence between active treatments in all remaining other centers. The table also compares the healing efficacy of Biocraft's sucralfate to the efficacy shown by the placebo control.

Reviewer Table 1

Four Week Healing Rates in Five Centers with Repetitive Sequences

Centers	Placebo	Carafate	Sucralfate	90% C.I. s-c	p-Value,s-p*
1052,1055,1059, 1066,1075, N°160	5/55 (9%)	18/52 (35%)	20/53 (38%)*	-16%, 15%	p=0.002
All Other 15 Centers, N°113	10/38(26%)	17/37 (46%)	13/38 (34%)	*-30%, 7%*	*p=0.62* ◆

* Two Sided Fishers Exact Test. Statistical analyses in this table were calculated by Dr. Huque .
* This results amend results shown in Reviewer Table 19, medical officer review, September, 1991.
◆ *All italic font illustrates non-equivalence or non-significance*

- Reviewer Observations.

This reviewer examined treatment assignment sequences shipped and enrolled by all 20 enlisted centers participating in the trial. Centers 1052, 1055, 1059, 1066, 1075 exhibited patterns with repetition of first treatment assignments or repetition of sequences.
Of the remaining 15 centers, 4 had high patient enrollment (1053, 1060, 1064, 1076). Although some repetition occurred in these latter centers, this medical officer was unable to establish any patterns with repetitive treatment assignments.
This reviewer's assessment of centers with and without repetition of treatment assignments was done *prior* to any assessment of efficacy in any of these centers.

Appendix 3 of this review includes 19 and 20 from pages 45-46 of this MO review finalized in September 18, 1991. The population size and 4 week endoscopy results in the 5 centers with repetitive treatment assignments and in the remaining 15 centers, is seen in Reviewer's Tables 19 and 20 from my 1991 review.

An initial difference noticeable in the comparisons shown in the above table, are the placebo healing rates. While the 15 centers exhibited an acceptable 26% placebo 4 week healing rate customarily seen in DU trials, the 5 centers with repetitive sequences revealed a markedly low 9% healing rate. The markedly low healing rate of the control population is responsible for the highly significant superiority of sucralfate over placebo in these 5 centers and ostensibly drives down the trial's overall placebo results.

Of more relevance to this particular trial is the divergence in healing efficacy exhibited by Carafate® in the two centers' populations. As observed in the table, Carafate® patients in the five centers with repetitive sequences revealed 11% lower healing rate than Carafate® patients in the remaining 15 centers.

Carafate® efficacy in those 5 Centers was mainly determined by the very low healing rate exhibited by Carafate patients in centers *1052, 1055 and 1059*, the centers with more visible patterns of repetitive sequences.
In these three centers (total patient N° = 100, Carafate = 33), only 27% (9/33) of carafate patients were declared healed, as compared to 46% healed on Carafate in the remaining 17 centers.

Hence, overall equivalence results appears to have been driven by the low Carafate healing rates from patients enrolled in the three centers showing apparent patterns of repetitive sequences .

B. Reviewer Comments on Possible Causes for Repetitive Block Sequences.

The following are possible reasons which might have contributed to patterns of repetitive sequences:

1. Deficiencies in the prospective randomization plan.

2. Deficiencies in the implementation of the randomization plan

3. Disruption of randomized blocks.

1. *Reviewer's Assessment of Prospective Randomization Plan.*
As noticed in the prospective randomization plan, Almedica randomized the 3 possible assignments in blocks of three; A = Placebo, B = Carafate, C = Sucralfate. Almedica created 113 blocks containing 339 assignments.

Assignments were consecutively numbered in ascending order from 1 to 339 (see Appendix 1 of this review).

In order to facilitate understanding of the random scheme, this reviewer *derived the random numbers into assignments; i.e., the first block numbered consecutively 1-3-2 translated into ACB* (Reviewer Table 2, page 9). A copy of the decoded plan was provided to the statistician reviewer, Dr. Huque. Dr. Huque modified this reviewer's table by adding the consecutive numbers, i.e., Block 1. ACB is 123.

Reviewer Table 2. PROSPECTIVE RANDOMIZATION PLAN Biocraft

Block Size: 3 assignments; A = Placebo; B = Carafate; C = Sucralfate
Block Sequences from 1 to 339 (Total Random Assignments Used: 273)
Total Shipped : 99 Blocks (Blocks 75 and 76 were skipped)

1. ACB	39. ACB	77. ACB
2. ABC	40. CAB	78. BCA
3. CAB	41. ABC	79. CAB
4. CBA	42. CA***B***	80. CBA
5. ABC	43. ACB	81. CBA
6. B***CA***	44. CBA	82. CBA
7. BCA	45. BCA	83. CAB
8. ***CBA***	46. CAB	84. CBA
9. ABC	47. ACB	85. CBA
10. ACB	48. ACB	86. ABC
11. ABC	49. CAB	87. BAC
12. ACB	50. BAC	88. BCA
13. ACB	51. CBA	89. BAC
14. CBA	52. BAC	90. BAC
15. CAB	53. C***AB***	91. ACB
16. ABC	54. CBA	92. CAB
17. CBA	55. BAC	93. CAB
18. BCA	56. BAC	94. CAB
19. BAC	57. BCA	95. C***BA***
20. BCA	58. CAB	96. BCA
21. ACB	59. ABC	97. ACB
22. BCA	60. ABC	98. ACB
23. CAB	61. ABC	99. CAB
24. CAB	62. CAB	100. BCA
25. BCA	63. BAC	101. ABC
26. A***BC***	64. ABC	---
27. ACB	65. BCA	102. CBA
28. ***ABC***	66. CAB	103. ACB
29. ACB	67. ACB	104. BAC
30. ACB	68. CBA	105. ACB
31. BAC	69. CBA	106. ACB
32. ***BAC***	70. ACB	107. CBA
33. BA***C***	71. BAC	108. CAB
34. ***B***CA	72. A***CB***	109. ABC
35. B***C***A	73. BAC	110. ACB
36. BAC	74. ACB	111. ABC
37. BCA	---	112. BAC
38. CAB	75. BCA	113. CBA
	76. BAC	

Assignments in Bold Italic Were Not Randomized. Assignments in Smaller Font Below Dotted Lines Were Not Shipped .

i. Observations.

• As seen in Reviewer Table 2 , the prospective randomization plan is composed of random blocks with 2 active treatment assignments (A,C) and control assignment B. The used of prospective random blocks was confirmed by then Pharmakinetics Director for Regulatory Affairs, in correspondence to Dr. Bette Barton, FDA, DSI, on November 3, 1989. This correspondence was included as Appendix 1 in the medical officer review, September 18, 1991.

• According to Biocraft and generated the prospective randomization plan by a computerized program. The program number was displayed above the generated randomization plan as observed in Appendix 1 of this review. Though not easily legible, the computer number reads "58566422".

This reviewer requested to the FDA statistician reviewer, Dr. Mohammad Huque, the verification of the submitted prospective randomization plan using the displayed seed number.

In spite of several experimental attempts, the statistician reviewer was not able to replicate (and thus verify) the sponsor's random allocation plan. According to the statistician reviewer, replication of the sponsor's allocation plan might not be possible unless Biocraft submits the precise methodology used by for the creation of the allocation system (see Dr. Huque's review, February 10, 1994).

• Careful inspection of the allocation system shown in Reviewer Table 2, revealed to this medical officer the presence of repetition of specific treatment assignments along different regions of plan. For instance, *of the seemingly equal probability of initial treatment assignments A,B,C,* (2/6 or ⅓ for each treatment assignment) *the first 38 blocks of the plan contains 15 initial assignments A,* 14 B *and only 9 initial assignments C.* To note is the repetition of initial assignments, *i.e., blocks 1-16 started A,A, C,C, A,B,B,C, A,A,A,A,A,C,C,A; blocks 26-38 started A,A,A,A,A B,B,B,B,B,B,B,C.*

Similar to the high frequency and aggregation found in the first region of the scheme, *the last 37 blocks of the used system contains 16 initial treatment assignments C,* 12 A *and only 9 initial assignments B. Blocks 77-95 started C,C,C,C,C,C,C,C, A,B,B,B,B,A, C,C,C,C.*

It can be noted that in decoding sequential random numbers into treatment assignments *ABC*, this medical officer divided the submitted randomization plan into sections with similar number of blocks, i.e., Section 1 = 38 blocks, Section 2 = 38 blocks, Section 3 = 37 blocks. Since blocks were constructed with 3 treatment assignments, the 3 similar parts would allow easy assessment of

increased repetition in any of the 3 treatment assignments. For instance, a blocking organization plan with blocks 1-38 *all* starting in A, blocks 39-76 *all* starting in B and blocks 77-113 *all* starting in C, would probably not satisfy the requirements of an acceptable random block design.

The statistician reviewer applied "the run test", which assesses frequency of treatment assignments, to analyze the randomness of treatment assignments observed in the first and last sections of the prospective allocation system.

Based on the run test, the higher than expected repetition of initial allocation A in the first 38 blocks is statistically significant, and implies an abnormality in the prospective randomization scheme. The statistician reviewer table is shown below.

The results of the analyses performed by this reviewer were as follows:

Reviewer Table 2
Run Test Results for Treatment Assignments

Allocation Blocks	Treatment Assignments Tested[1]	2-sided P-Value
1 - 38	A and B	.016
77 - 113	B and C	.083

[1] These within-block first-patient treatment assignments of the prospective randomization plan were tested because they exhibited unusually long runs than expected under random assignment.

2. Reviewer Assessment of Block Shipments. Summary of Shipment Sequence as Reported by Biocraft and the FDA Field Investigator.

- FDA Scientific Investigations performed two on-site field investigations related to this study. The two FDA field investigators, Ms. DiWoskin and Ms. Schultz, carried out investigations on records and personnel involved in the implementation of the prospective randomization plan and distribution of test articles (drugs) of and Biocraft, respectively.

In their reports, the two field investigators agreed in their findings about deficiencies in shipping of test articles and both stated irregularities in the

implementation of the prospective randomization plan and drug distribution. According to the FDA field investigators, the sponsor did not adhere to the prospective randomization plan, it recirculated test drugs between investigators and did not fully comply with shipping the prospectively established blocks containing the *A,B,C*, treatment assignments.

- A contractual agreement between Biocraft - and Biocraft - established the arrangement for drug distribution to enlisted centers. The agreement between these parties established that drug distribution was supposed to be as follows:

    1. Biocraft would provide raw material for manufacturing to would manufacture test articles (i.e., sucralfate or placebo, 1 gram tablets). would be in-charge of placing test articles in blister cards. Blister cards containing A,B,C experimental drugs would be numbered in succession following the randomization plan created by and approved by Biocraft. Numbered blister cards containing test articles A,B or C would be sent back to Biocraft.

    2. When enlisted centers required supplies, through center monitors, would request supply of randomized blocks to Biocraft (requisition orders to Ms. Debbie Parker).

    3. Biocraft would be responsible of verifying requisitions and of shipping blister cards containing two successive randomized blocks (six treatment assignments) to requesting centers.

Of relevance to note is that Biocraft had copies of randomization scheme (though had access to the randomization plan, apparently did not open it during the trial) .

- provided to Biocraft blister cards containing treatment assignments numbered from 1-311 (see Exhibit 10, page 21, from DiWoskin report).

The chronology of drug shipment followed in the trial is listed in a table created by and submitted to DSI on June 3, 1993. table lists requisition numbers and day of packing (supposedly day of shipment).

table of drug shipment is included as Appendix 4 of this review.

- This DU trial was initiated on 5/13/88 and completed on 6/26/89.

According to Ms. DiWoskin, "Clinical Supply Requisition Log" shows that, with the exception of Requisition 16, patient packs were sent out sequentially in ascending numerical order and in blocks of 6 until 1/89. This FDA field investigator further noted that "after 1/89 until the end of the study, patient pack numbers were not sent out in numerical order or in blocks of 6" (page 8, DiWoskin report).

DiWoskin stated that the approximate date of commencing the out of sequence distribution was 1/27/89.

Ms. DiWoskin reports that some pack assignments corresponded to different sequence numbers. For instance, patient pack assignments 098-100 were not found in the prospective randomization code, but were put together by placing the last two numbers of the random sequence 097-099 with the out of sequence number 100 (carafate).

- Ms. Schultz, the DSI officer in-charge of Biocraft's investigation, noted that according to Biocraft tablet accountability records, there was a balance of "0" patient pack by requisition 55 (2/17/89). Biocraft records showed a total of 65 requisitions (see page 7, Schults report).

Ms. Schultz also noted that Biocraft allowed shipment between investigators of out of sequence patient packs, i.e., patient packs 17-18, 101-102, 103-104, 134-138, 284-285 (pages 7-9, Schultz report).

- Biocraft (Debbie Parker) claimed that center to center shipments were supervised by monitors (page 6, Schultz report). Debbie Parker explained that "due to this change of procedure (that) the accountability of clinical supplies was difficult".

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2i. Reviewer Observations.

- Biocraft was supposed to chronologically distribute to enlisted centers shipments containing six sequential assignments (two packs or blocks). The blocks would follow an uninterrupted ascending order with sequential assignments numbered from 1-339 as established in the prospective randomization plan (Biocraft enrolled a total of 273 patients).

In view of the limited possibilities in the order of sequences for blocks of three assignments, this rigorous adherence to the continuity of the sequential numbering appears essential (this concept acquires more relevance if one of the treatment assignments = B, may be potentially unmasked. Preferably, a block size with a multiple of treatments, i.e., 6, would have been better suited for this trial's randomization scheme. C.L. Meinert. Clinical Trials, Page 68, 1986).

- As shown in the distribution list provided by (see Appendix 4 of this review), Biocraft followed the sequential order with six assignments per center up to assignment number 300, January 27, 1989, with the *exception of 5 shipments* (rather than one, as stated by the FDA field investigator).

These 5 shipments were the following:

I. *Requisition 12* (5/17/88, /1055A. This investigator was initiated with *12 assignment numbers*, 061-072 (reasons are unclear). (Center 1055A was one of the five centers mentioned in the medical officer review as having received repetitive sequences, page 21, September 18, 1991, MO review).

II. *Requisition 16* (5/25/88) /1057A. Assignment numbers had been initially shipped to on May 3, 1988 (Requisition 4). On May 12, 1988, site was terminated and drugs shipped directly from site to

III. *No Requisition Number* (10/27/88) /1052A. *12 assignments, numbers 205-216, were sent in this shipment.* only enrolled the first three assignments. (Center 1052 was one of the five centers with repetitive sequences).

IV. *Requisition 38* (11/4/88) /1075. This initial shipment was canceled by Debi Parker. In Exhibit 10 from DiWoskin report, Debi Parker (in correspondence to states that assignment 226 (carafate) was missing from the package. The two blocks, *223-225 and 226-228 were*

never shipped (see Reviewer Table 2, this review). (Center 1075 was one of the five centers with repetitive sequences).

V. *Requisition 40* (1/27/8, '1049. Ms. Parker canceled the shipment of assignment packs 295-300 to (Exhibit 49, package). No reasons were given for this center cancellation.

- During the period between January 30, 1989 until the end of drug distribution, April 20, 1989, there were a total of *20 shipments* of tested drugs (out-of-sequence). *The majority of these shipments contained blocks with three assignments, recirculated from one site to another by site monitors (6) or through Biocraft (15). There were a number of shipments that had out-of-sequence 2-4-6 treatment assignments.*

- The documentation provided by the FDA field investigator indicates that Biocraft recirculated out of sequence drug numbers from one site to another while having a stock of approximately 27 unused prospective drug assignments, packed sequentially by A Memorandum dated March 7, 1989, from Debi Parker to files, indicates consecutive drug numbers 305-332 were in stock but were never shipped.
Debbie Parker's memo is included as Appendix 5 of this review.

The above unused stock of patient assignments are in addition to the stocked six patient packs mentioned in point IV (page 14, this review). Altogether, Biocraft stocked 11 blocks containing 33 packed test articles.

It appears possible that shipment of the stocked 33 tested drugs would have considerably decreased the requirement for recirculating blocks from center-to-center and would have probably avoided proceeding with shipments containing out-of-sequence 2-4-5 treatment assignments.

- *The examination of possible causes for drug recirculation between centers is of relevance to this review, for Center 1055 and also Center 1059 two centers with overt patterns of repetitive sequences, received a considerable number of test articles via recirculation from other centers.*

Biocraft's justification for recirculating test drugs from one center to another was included in both FDA field officers' report. Biocraft stated that as the trial progressed, it feared not to have enough test articles left to complete the prospective randomization plan (see Ms. Parker's explanation in the third paragraph, page 6, Ms. Schultz report).

As stated in the "accountability of tablets blistered" included in the Biocraft DSI report, indicates that up to April 21-2[illegible] had blistered enough test articles to supply the *113 treatment assignments per each* experimental drug (A,B, or C) numbered in the prospective randomization plan (i.e., *sucralfate supply required 4 tablets x 56 days = 224 tablets per patient ∴ 224 x 113 = 25,312 tablets for the 113 treatment assignmen[illegible] blistered 29,860 sucralfate tablets*).

Biocraft's drug accountability is included as Appendix 6 of this review.

As observed, my estimate was based on the anticipated requirement of 4 tablets of test article per patient x 56 days of study.
Instead of packing adequate number of test article/patient to last the 56 days of the study, Biocraft[illegible] packed enough test article/patient to last 72 days of study. Apparently, Biocraft anticipated an extra test article requirement of 8 tablets per week/patient (2 days dose x 8 weeks = 16 days extra dose. See report of FDA field officer DiWoskin, page 6).

The 5000-5500 tablets per test article (64 extra tablets/patient) given in excess to the approximately 90 patients enrolled per treatment generated a shortage in test articles. This shortage in test articles disallowed the completion of the prospective randomization plan and led to recirculation of shipped blocks from center-to-center.

Unclear are to this reviewer the reasons for the sponsor's deficiency in the planning of drug availability and distributions. Biocraft's rationale behind the provision to patients of a 16 day supply *of extra* test article for each of the two 28 day study periods *seems unwarranted, if we consider a maximum + 3 day endoscopy window beyond the prospectively established 28th day end point.*

3. Reviewer Assessment of Drug Distribution in Centers with Patterns of Repetitive Sequences.

- In addition to the described deficiencies in the prospective randomization plan (consecutive repetition of treatment assignments), the order, selection and timing of shipments appear to have considerably influenced the formation of patterns with repetitive sequences in the five centers listed in pages 20-23 of my review of September 18, 1991.

The following paragraphs will be focused on the relationship between Biocraft's drug distribution system and the formation of repetitive sequences shown in Centers 1052 , 1055 1059 Although 5 centers showed repetitive sequences, Centers 1052, 1055 and 1059 exhibited overt patterns of repetitive sequence assignments (whether 2 or 3 consecutive

assignments). Mention should be made of the patterns with repetitive assignments observed in Center 1075 , similarly influenced by the drug distribution system.

(a) Lack of Prospective "Blocking-by-Center" System and Selection of Blocks.

The reasons for the order in the initial shipments of drugs to various centers continues unexplained to this reviewer. The sponsor's claim that shipments were sent to investigators with DU patients "ready" to be enrolled appears not to hold after careful examination of the order of shipments and the chronology of first patient enrollment. The following short list of shipments illustrates this point:

Reviewer Table 3

Order of Shipments According to Biocraft (Appendix 6, This Review)

Shipment # 1.	4/28/88	001-006
Shipment # 2.	5/3/88	007-012
Shipment # 3.	5/3/88	013-018
.....		
Shipment # 6.	5/3/88	031-036
.....		
Shipment # 9.	5/18/88	049-054
.....		
Shipment # 11.	5/18/88	055-060
Shipment # 12.	5/19/88	*061-072*
.....	.....	
Shipment # 15.	5/25/88	085-090

Let us now compare the order of shipments listed in Reviewer Table 3 with the order of initial patient enrollment shown in the following Reviewer Table 4.

Reviewer Table 4

Chronology of First Patient Enrollment in Centers Listed in Reviewer Table 3

Investigator / Center	*Date 1st Patient Enrollment **
	5/13/88
	5/22/88
	6/8/88
	6/15/88
	6/23/88
	7/11/88
	8/17/88
	10/12/88

* Taken from Appendix 2, Attachment 2, MO Review, September 18,1991

The sponsor's order in the shipments of block sequences (see Reviewer Table 3) started the string of repetitive assignments observed in Centers 1052, 1055 and 1059. The following were the actual initial sequence of assignments shipped to these centers (highlighted are the repetitive assignments).

For Center 1052

Blocks 1-2-3 represented **ACB**
4-5-6 **ABC**

Should have received the fourth shipment (see Reviewer Table 4), the sequence would have been:

Block 019-024 or **BCA and CBA**

For Center 1055

This center received 12 assignments; 061-072.
The monitor instructed the center to supply 061-066 to the affiliated V.A. Medical Center, and 067-072 for the use of patients at Tulane University Medical Center (see Exhibit 11, package). The reason for this particular order in the partition is unclear. The sequences were the following:

Block 061-066 (VAMC) represented		ACB BCA
Block 067-072		CAB CAB

For Center 1059

Block 031-036	represented	ABC ACB

Of interest to note is that in the hypothetical case would have received shipment 5 (instead of shipment 6), the cluster of identical first treatment assignments observed in consecutive numbers 25-39 (15 assignments), would have led to similar initial block sequences. For instance:

Block 025-030 (b)	represented	ABC and ACB

(b) Frequent Shipments in Brief Time Periods. The Case of Center 1052

The presence in the randomization plan of sections with repeated first treatment assignment or repeated sequences would, conceivable, result in the distribution of these repeated sequences or first assignments to various centers. In a multicenter trial listing 20 actively enrolling centers, the possibilities for a single center receiving sections with repeated sequences appear more unlikely, unless there are multiple shipments in rapid succession within a rather short period of time. This situation appears to have occurred with shipments distributed to *Center 1052 during October, 1988.*

As mentioned, Biocraft initiated the implementation of the randomization plan with shipments of the first two blocks to This first shipment was sent on 4/28/88 started enrolling patients in mid June, 1988 and by July 1, 1988 had enrolled all the submitted six treatment assignments. Biocraft shipped two more blocks of assignments to on July 7, 1988 (no requisition order was placed prior to this second shipment. Apparently, there was a telephone contact from the monitor to Biocraft requesting more blocks, made on 7/5/88).

The initial two shipments to had the following sequences:

Blocks # 1-2 (4/28/88) ACB (see Reviewer Table 2, page 9, this review)
ABC

Blocks # 39-40 (7/7/88) ACB
CAB

Two weeks later, Biocraft shipped two more blocks. As in the previous shipment, there was no requisition order placed. At the time this third shipment took place, the investigator had still 3 unused patient packs. The sequence of this third shipment was the following:

Blocks # 43-44 (7/20/88) ACB
CBA

From wednesday October 12 to thursday October 27, 1988, Biocraft made a total of 8 shipments to this center. During this span of 15 days, Biocraft shipped 36 assignments tc . During the week of thursday October 20 to thursday October 27, Center 1052 received an additional 24 assignments.

It is likely that TV advertising campaign for DU patients (see monitoring report Exhibit 30, package) elicited higher patient enrollment and consequently prompted these multiple shipments from Biocraft.

The sequences shipped in this brief period, were the following:

Shipment 4. (10/12/88), Blocks # 55-56 BAC (*) - BAC (*) *See Section (d) below.*

Shipment 5, (10/18/88), Blocks # 59-60 ABC
ABC

Shipment 6, (10/20/88), Blocks # 61-62 ABC
CAB

Shipment 7, (10/25/88), Blocks # 67-68 ACB
CBA

Shipment 8, (10/27/88), Blocks # 69-72 CBA
ACB *
BAC *
ACB *

* Blocks not enrolled. Some of these blocks were shipped to other centers later in the trial.

Whatever the reasons, the association of multiple shipments and blocks with repetitive sequences or first treatment assignment, led to the formation of an apparent pattern.
The above series of sequences illustrates the repetition of assignments.
Of the 10 blocks shipped in the period between 10/18 to 10/27, six (60%) start with treatment A (overall, received from Biocraft a total of 18 blocks, 10 started in treatment A, 5 started in treatment C and 3 started in treatment B).

(d) Combination of Multiple Shipments with Shipments from Center-to-Center and Out-of-Sequence. Case of Centers 1055 and 1059

For better understanding of this section, I will include as Appendix 7, pages 10-12 from Biocraft submission, Vol. on "Audit Response from ", July 23, 1993.

- *Center 1055.* As observed in Reviewer Table 3 (page 17), this center had a first shipment of 12 assignments in May, 1988. The following were the sequences shipped:

5/19/88

061-067
ACB (V.A.M.C.)
BCA

067-072
CAB (Tulane Medical Center)
CAB

From February 2, 1989 to March 11, Biocraft made a total of 4 shipments containing 18 treatment assignments. All of these shipments were out-of-sequence and were either directly mailed from another center or indirectly via a center-Biocraft table of drug shipment, Appendix 4, this review). The sequences shipped were the following:

2/3/89
277-282 (Shipped from see Appendix 3, page 5).
There was requisition number for this shipment (see Appendix 3, page 5)
CAB
CAB

2/22/89
106-108 (Shipped by Biocraft, unused block assigned originally to)
BAC

3/9/89
157-159 (Shipped from see Appendix 3, page 6).
There was no requisition number for this shipment (see Appendix 3, page 6)
CAB •

3/11/89
134-138 (Apparently, Biocraft shipped these 5 assignments, returned from to Biocraft on 2/[illegible]/89. As can be seen below, the first block is incomplete. For more information, see Requisition # 56, package)
CA
CAB

• Assignments AB were not enrolled.

On page 5 of the table of drug shipments (Appendix 3), it is readily noticeable a discrepancy in the order of shipments made to and . It is also noticeable that shipments to did not follow appropriately numbered requisitions.

As seen in page 5 (see Appendix 3, this review), Biocraft elected to send the *higher* assignment numbers 259-264 to and 277-282 to on *2/3/89*. The *lower* assignment numbers 079-084 were then shipped to on *2/6/89*.
If Biocraft would have followed the natural progression in these three shipments, would have received assignments BAC-BCA, (259-264) instead of the repetitive CAB-CAB.

On page 10 of Biocraft's "Audit Response from " (see Appendix 6), reports that assignments 079-084 had been returned to Biocraft on December 12, 1988 (typo error states 1989). Therefore, at the time shipments were made to Biocraft had available the option of following the natural ascending progression in assignment numbers.

• *Center 1059*. The succession of two blocks shipped to this center had either identical first assignment or identical sequence. The first two blocks were shipped on May 3, 1988. Two more shipments were made between end November to end December. The sequences shipped were the following:

5/3/88
031-036
ABC
ACB

11/21/88
241-246
CBA
CBA

12/30/88
265-270 There was no actual requisition made from the center for another shipment. This shipment was made on the sponsor's apparent perception that this investigator would have completed the previous sequence 244-246 by the end of December, 1988. In actuality, enrolled assignments 245-246 on 1/30/89 and 2/3/89, respectively (see Appendix 1, MO review, Sept. 1991).
BAC
BAC

2/17/89
298-300
BCA

From February 3 to February 23, 1989, Biocraft made 4 more shipments to These shipments had 2-3 assignments and were unused or incomplete blocks shipped directly from other centers or via Biocraft (see pages 6-7, Appendix 3, this review). The sequences shipped were the following:

3/3/89
286-288
BCA

3/9/89
211-213
BAC

3/14/89
103-104 Incomplete block # 35. Shipped directly from .
(see Appendix 4, page 6).
BC •

3/23/89
284-285 Incomplete block shipped directly from *(see Appendix 4, page 7).*
BA [b]

[a] Last assignment not enrolled
[b] Block not enrolled.

To note is that assignments 298-300 shipped on 2/15/89 to were intended to be shipped to _ on 1/30/89. Shipment of assignments 298-300 on 1/30/89 would allowed completion of the natural ascending order after the previous shipment of assignments 289-294 to on 1/26/89 (see page 4, Appendix 4, this review).

Biocraft canceled the 1/30/89 shipment to requested in *Requisition 050*. The reasons for the cancellation were not specified (Exhibit 49 does not provide any explanation for cancellation of this shipment. At the time of cancellation was actively enrolling patients; last patient enrolled by this investigator was on 2/27/89).

If Biocraft would have further followed the natural order of shipments after cancellation, (*next in line with Requisition 051*) should have received assignments 298-300 on 1/30/89 (see page 4, Appendix 4).

After cancellation of shipment on 1/30/89, Biocraft opted not to use assignments 298-300 until six shipments later, when it was sent to

In the hypothetical case Biocraft would have pursued this natural order, the 1/30/89 shipment to would have included assignments 298-300 and all subsequent shipments listed in the table (page 5, Appendix 4) would have received the next in line sequence, i.e., 037-042 to on 2/6/89. According to the progression indicated on page 5 of the table (see Appendix 4) would have received on 2/17/89 assignments 295-297(instead of 298-300). Sequence 295-297 had as first assignment CAB, instead of the repetitive BCA.

- Careful examination of pages 5-7 of the table (see Appendix 3) and page 11 of Biocraft recent submission (see Appendix 7, this review) suggest that the sponsor had better options of progressing with an ascending order of assignments than those actually implemented.

On page 11 (see Appendix 7) it can be noted that another center had previously returned to Biocraft the sequence of assignments 208-216, on *1/19/89.*

Appropriate use in natural progression of ascending order indicated that sequences 208-210, 211-213 and 214-216 should have come after the shipment of sequence 079-084 to on 2/2/89 (instead of the elected higher sequence 259-264, see page 5, Appendix 4).

On page 6 and 7 (see Appendix 4) it is seen that sequences 208-210, 211-213 and 214-216 were shipped to on *3/3/89, 3/8/89 and 4/19/89*, respectively.

The use of these sequences in the appropriate order would have changed the subsequent choice of assignments shipped to from mid February '89 to mid March '89, and may have partially avoided shipment of repetitive sequences to these investigators.

(d) Contribution of Investigators to Repetitive Assignments.

In a few occasions, the investigator or the center contributed to the formation of repetitive sequences by altering the order of consecutive treatment assignments.

- On page 20, (*) shows Biocraft shipped to sequences 163-168 on 10/12/88. Unlike the other shipments, the first assignment on sequence 163-165 starts in B, instead of the repetitive assignment A.

In the chronology of assignments enrolled by (see Appendix 1, medical officer review, September 18, 1991 review), it is noticed that this investigator enrolled assignment *164 before assignment 163*, compounding the pattern by initiating the sequence with the repetitive assignment A (Incidentally, this reversion of the natural sequence assignment on the part of the investigator led, in the enrollment of two successive A-A, of the successive enrollment of identical male twins . Both were 30 years old and both had DUs' diagnosed in their early 20's. One of the twins was started on placebo 4 days after enrollment; see Exhibit 30, package. Both were discontinued after 2 weeks in the trial, for treatment failure. DU's in identical twins have been reported to be associated with other hereditary malformations and may have a more severe course. Jensen G.K. Genetics of peptic ulcer-a brief survey. Scand. J. Gastro. 15(Suppl 63):11, 1980. Eberhard G. Peptic ulcer in twins. Acta Psych. Scand. 44(Suppl 205:1-118, 1968). *Endoscopy 4 week healing rates for Center 1052 can be seen in Appendix 3, this review.*

It is of relevance to note that the chronology of enrollment observed in Attachment 1 (Appendix 1, MO review, September 1991) indicates *had enrolled assignment # 164, on 10/11/88*. According to shipments listed in page 3, table of drug distribution (see Appendix 4, this review), *Biocraft packed and shipped sequence 163-168 on 10/12/88*.

- Center 1055 chronology of enrollment did not follow the ascending order of blocks or the chronology of shipments.

First sequences used for enrollment were 067-072 (CAB-CAB) *instead of sequences 061-067 (ACB-BCA)*. The next sequence enrolled 277-279, CAB, was the first block from the second shipment on February 1989 (see page 21, this review). The next sequences enrolled 061-066, ACB-BCA, were left from the first shipment (I supposed these patients were enrolled at the V.A.M.C.). Then came 280-282, the second sequence left from the second shipment (CAB). Afterwards was sequence 106-108 (BAC) . Enrollment followed with incomplete sequence 134-135 (CA), then 136-138 (CAB; and assignment 157 (C) *these last two assignments are amendments of Reviewer Scheme II, page 5, this review*). *Endoscopy 4 week healing rates for Center 1055 can be also seen in Appendix 3, this review*.

- Center 1059 ' reversed the last assignment # 213 (from block 211-213) for assignment # 103. The resulting sequence was BAB-C (*last sequence amends Reviewer Scheme III, page 6, this review*).

(e) Probabilities in Formation of Repetitive Assignments.

This medical officer requested to the statistician reviewer, the calculation of the probabilities for the repetition in assignments observed in Centers 1052,1055, Centers 1059.

In his review, page 6, Dr. Huque stated that, "the low probabilities of repetitive assignments" observed in centers 1052, 1055, 1059, "do not support the hypothesis that the repetitive assignments to incoming patients" at these 3 centers "occurred by the chance factor alone".

The Statistician Reviewer Table 3 is shown below.

Reviewer Table 3
Exact Binomial Probability Calculations for
Unusual Repetitive Assignments at Some Centers

Center	Total Blocks Allocated	—Repetitive Assignments— 1st Patient Allocation	Block Allocation	Binomial Event	Probability of the Event by Chance
#1052	15	'A' occurred 9 times	-	# of 'A' ≥ 9	.0085
#1055	10	'C' occurred 7 times	'CAB' occurred 5 times	# of 'C' ≥ 7 # of 'CAB' ≥ 5	.0034 .0024
#1059	10	'B' occurred 6 times	-	# of 'B' ≥ 6	.0197

C. Conclusions and Recommendations for Regulatory Actions.

• This reviewer was given the task of assessing possible factors which may have led to the development of patterns with repetitive assignments in Centers 1052, 1055, 1059 (as well as Centers 1066 and 1075, not discussed in detail in this review). From the examination of the information available for this review, this medical officer considers that a number of factors appear to have combined in the formation of repetitive assignments and/or sequences observed in Centers 1052, 1055, 1059. The following is the enumeration of the possible factors or causes:

1. *Deficiencies in the computer generated randomization scheme prepared by for Biocraft.* Segments of the randomization scheme contain a higher then expected repetitions for A or C as initial block assignments, i.e., the first 38 blocks have significantly more repetitions for A's.

2. *Absence of a prospective block-by-center system for determining block assignments.* There was no prospective blocking-by-center system, and the claim blocks were sent to centers with lining and available DU patients is not sustainable by the chronology of centers' first patient enrollment (see Reviewer Tables 3 and 4, page 17). Apparently, this arbitrary order of shipments favored the initiation of repetitive assignments in *Center 1052* = ACB, *Center 1055* = CAB and CAB.

3. *Center Receiving Multiple Successive Shipments (Center 1052).* Combination of a randomization plan containing regions with successively repetitive first assignments or sequences plus multiple successive shipments to one center, may have favored the formation of repetitive sequences in that

particular center. This was the case with Center 1052 for shipments made between July 7-20, 1988 (ACB-CAB; ACB-CBA) and between October 12-27, 1988 (6/12 blocks starting in repetitive first assignment A). The reasons for these multiple shipments of determined regions in the randomization plan, may have just been coincidental to or motivated by a potentially high patient enrollment in this center, at the time of a TV campaign recruiting DU patients.

4. *Recirculation of Shipped Blocks or Assignments.* Shipments made initially to a participating investigator and subsequently *recirculated during the course of the trial* (through Biocraft or directly from the center) *to Center 1055 and Center 1059* apparently increased the probabilities of shipping repetitive sequences; i.e., received on 2/3/89 (from CAB-CAB), on 3/9/89 (from = CAB), and on 3/11/89 (from Biocraft = CA and CAB), received on 3/14/89 (from = BC) and on 3/23/89 (from = BA)

5. *Lack in Natural Progression of Ascending Block-Number Order.* In several instances, Biocraft discontinued the natural progression of ascending numbers and later recirculated the halted block to a center with repetitive assignments. This was the case with sequence 298-300. The shipment of this block to was canceled *(Requisition 50).* This block was *not shipped in next Requisition 51, but later in Requisition 54,* to (298 = B).

6. *Reversal of Assignments by Centers.* One of the example provided occurred with sequence 163-165. Center 1052 reversed first block number 163 = B for next number 164 = A, a repetitive assignment in this center. The presence of two successive A-A was associated with enrollment of two identical twins with DU's on the placebo arm (both were discontinued unhealed after two weeks).

- This reviewer asked the statistician to validate the prospective randomization plan; the statistician reviewer was unable to reproduce it. My review has shown further deficiencies in the implementation of randomization and potential center interactions. Therefore, I recommend petition the following from the sponsor.

a. As requested by the statistician reviewer, methodology used in the organization of prospective random sequences.

b. Equivalence of healing results between s-c, at 4 week endoscopy in:

Centers 1052-1055-1059 (all randomized patients)

Centers 1052-1055-1059-1066-1075 (all randomized patients)

c. Compare the calculated 4 week equivalence in these 3 and 5 centers with equivalence calculated in:

All other 15 or 17 centers (all randomized patients but exclude the above centers)

Equivalence should be calculated applying 90% confidence intervals of healing results between active treatments s-c.
Healing results should be calculated after adjustment of 4 week endoscopy violations (+ 3 days) and carry over of prematurely discontinued patients.

d. Calculate primary efficacy of sucralfate vs placebo (two-sided p-Values) in above 3-5 centers (b) vs. other 15-17 centers (c).

e. Provide rationale for supplying 16 days of extra test article to each enrolled patient.

f. Reasons for cancellation of center at the time investigator was actively enrolling patients.

g. Rationale for not continuing with ascending random sequences after cancellation of requisition **050**; i.e., sequence **295-300**, should have been shipped to next requisition in-line **051**

h. Biocraft had in stock consecutive nine assignments **208-216** since 1/19/89. Provide rationale for not shipping these sequences after requisition **052** (to on **2/2/89**) instead of starting higher numbered assignments **295-264** (to on **2/3/89**) and then **277-282** (on **2/3/89**).

i. Table of Drug Distribution (Audited by Biocraft) indicates Biocraft apparently shipped assignment #s' **163-168** to on 10/12/88. Page 18 in Exhibit 30 package) and information submitted to FDA DSI on November 3, 1989, show enrolled assignment # **164** on 10/11/88. Provide explanation for this discrepancy.

j. Provide rationale for mismatch between chronology of sequence in assignments enrolled and chronology in sequence of shipments observed in Center 1055

The assessment of the sponsor responses will allow completion of plausible causes in repetitive assignment formation in aforementioned centers as well as to determine the impact of centers with patterns of repetitive assignments in overall equivalence results.

Robert Prizont, M.D.

cc:
ANDA 70-848
HFD-180
HFD-180/SFredd
HFD-180/RPrizont
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 3/12/94 jgw
MED\C\70848403.ORP

3/14/94
To OGD:
The requests from the medical officer should be added to those of the statistician and transmitted to Bioapt. I would also like to see a display of results center by center, and an analysis of results for large (i.e. 6 or more patients) versus small (i.e. less than 6 patients) centers. We must establish whether the sponsor had a randomized plan to begin with, and if so whether the plan was adhered to.

SP

Appendix 1

Reviewer Table 4

Center 1066-Assignment Matching With Patient ID and Chronological Entry Included in Page 5* of Information Sent by Biocraft to Scientific Investigations

LNAME	ASSIGNMENT	ENVID	PATID	START DATE	
→	C	001066	000049	23-MAY-88	PACKAGE WITH SIX ASSIGNMENTS
	B		000050	15-JUN-88	
	A		000051	14-JUL-88	
	B		000052	02-AUG-88	
	C		000053	02-SEP-88	
	A		000054	07-SEP-88	
→	C		000151	09-SEP-88	PACKAGE WITH SIX ASSIGNMENTS
	B		000152	26-SEP-88	
	A		000153	12-OCT-88	
	B	←	000154	20-OCT-88	
	A		000155	20-OCT-88	
	C		000156	01-NOV-88	
	B	←	000187	03-NOV-88	PACKAGE WITH SIX ASSIGNMENTS
	A		000188	08-NOV-88	
	C		000189	15-NOV-88	
	A		000190	30-NOV-88	
	B		000191	21-DEC-88	
	C		000192	09-JAN-89	
→	C		000253	16-FEB-89	PACKAGE WITH SIX ASSIGNMENTS
	B		000254	22-FEB-89	
	A		000255	28-FEB-89	
	A		000256	09-MAR-89	
	C		000257	18-APR-89	
	A		000258	21-APR-89	
	A		000214	26-APR-89	

*Attachment 2

Reviewer Table 5

Center 1075-Assignment Matching With Patient ID and Chronological Entry Included in Page 2* of Information Sent by Biocraft to Scientific Investigations

8613 INVESTIGATORS WITH PATIENTS BY START DATE

LNAME	ASSIGNMENT	ENVID	PATID	START DATE	
	C ←	001075	000145	13-OCT-88	PACKAGE WITH SIX ASSIGNMENTS (#1)
	A		000146	14-OCT-88	
	B		000147	19-OCT-88	
	A		000148	22-OCT-88	
	C		000149	01-NOV-88	
	C		000150	01-NOV-88	
	C ←		000194	03-NOV-88	PACKAGE WITH SIX ASSIGNMENTS (#2)
	A		000195	03-NOV-88	
	B		000193	05-NOV-88	
	C ←		000196	05-NOV-88	
	A		000197	10-NOV-88	
	B		000198	12-NOV-88	
→	C		000209	17-NOV-88	PACKAGE WITH SIX ASSIGNMENTS (#3)
	C		000210	22-NOV-88	
	B		000211	29-NOV-88	
	A		000212	05-JAN-89	
	B		000213	10-JAN-89	
	A		000214	21-JAN-89	
→	A		000271	21-JAN-89	PACKAGE WITH SIX ASSIGNMENTS (#4)
	C		000272	21-JAN-89	
	B		000273	24-JAN-89	
	C ←		000274	27-JAN-89	
	A		000275	28-JAN-89	
	B		000276	04-FEB-89	
→	A		000037	07-FEB-89	PACKAGE WITH SIX ASSIGNMENTS (#5)
	A		000038	11-FEB-89	
	C		000039	11-FEB-89	
	C		000040	14-FEB-89	
	B		000041	18-FEB-89	
	A		000042	18-FEB-89	
	C ←		000295	22-FEB-89	PACKAGE WITH THREE ASSIGNMENTS (#6)
	B		000296	22-FEB-89	
	A		000297	25-FEB-89	
	A		000075	15-MAR-89	→ INCOMPLETE BLOCK; LAST ASSIGNMENT
	A		000076	13-APR-89	→ COMPLETE BLOCK; FIRST ASSIGNMENT

*Attachment 2

The]↓↑[indicate the adequate sequence of a disrupted block.

Appendix 2

[redacted] PAGE NO. 1

[redacted] FILE
DATE 2/08/93
TIME 10:54:51

CENTER: 1

TREATMENT GROUP(S) BLOCK SIZE
A B C 3

I.D. DESCRIPTION

A PLACEBO
B CARBAMAZEPINE (TEGRETOL)
C [redacted] (OXCARBAZEPINE)

TREATMENT GROUPS SEED 1: 9834922

A	B	C
1	2	3

Exhibit 10, Page 1.9

3/11/93-4/6/93
DAD

[redacted] NOT INPUT

BY:.....

DATE:.....

NAME OF STUDY [redacted]

/ BIOCRAFT [redacted]

NDA 143987 [redacted]

PATIENT TREATMENT GROUP ASSIGNMENT REPORT

FILE
DATE 2/08/88
TIME 10:58:24

PAGE NO. 2

CENTER: 1

TREATMENT GROUP(S) A B C .... BLOCK SIZE 3

TREATMENT GROUPS SEED #: [illegible]

A	B	C
175	176	177
178	179	180
181	182	183
185	184	186
188	187	189
190	191	192
195	193	194
197	198	196
199	201	200
204	203	202
207	206	208
208	210	[illegible]
212	211	213
214	216	215
218	217	219
220	222	221
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	228
229	231	230
234	232	233
236	237	[illegible]
240	239	[illegible]
243	242	[illegible]
244	[illegible]	[illegible]
248	[illegible]	[illegible]
252	251	250
255	254	253
256	257	258
260	259	261
264	262	263
266	265	267
269	268	270
271	273	272
275	274	276
278	279	277
[illegible]	282	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
300	[illegible]	[illegible]
301	302	303
[illegible]	[illegible]	[illegible]
307	[illegible]	[illegible]
311	[illegible]	[illegible]
313	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
321	320	[illegible]
323	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
331	[illegible]	[illegible]
333	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

91 48

Exhibit 10, Page 20

3/11/93-4/6/93
DAD

Appendix 3

Reviewer's Table 18

Four Week Healing of Patients Enrolled With Two DU as Filed by Biocraft on July 5, 1990

	Placebo	Sucralfate	Carafate
Total Patients	24	15	14
Discontinued	4	6	0
Healed/Total	2/24	3/15	6/14
Percent	8%	20%	43%

c. In the subsection "a" of the section on "concerns about implementation of randomization...", page 19 of this review I listed five centers which had patterns of repetitive sequences. Combined, these centers enrolled 160 patients. It is of interest to assess the possible impact that the disruption in the implementation of randomized code had on the healing rates in these centers. The following table summarizes the results.

Reviewer Table 19
Four Week Healing Rate of Centers 1052, 1055, 1059, 1066 and 1075. All Patients

Center	Number Pts	Placebo	Carafate	Sucralfate
1052	45	1/15 (7%)	3/15 (20%)	4/15 (27%)
1055	27	0/9 (0%)	2/8 (25%)	5/10 (50%)
1059	28	1/9 (10%)	4/10 (40%)	4/9 (40%)
1066	25	1/9 (10%)	3/8 (38%)	2/8 (25%)
1075	35	2/13 (15%)	6/11 (55%)	5/11 (45%)
All Five Centers	160	5/55 (9%)	18/52(35%)	18/53(34%)

Centers 1053, 1060, 1064 and 1076 enrolled 10 or more patients per center. These centers had repetitive sequences but without a definite pattern. The 4 week healing rate of these centers and the healing rate of centers with low enrollment is shown in the following table.

Reviewer Table 2c
Four Week Healing in Centers 1053, 1060, 1064, 1076 and Centers with Low Enrollment. All Patients Included

Centers	Enrollment	Placebo	Carafate	Sucralfate
1053	20	1/7(14%)	3/6(50%)	1/7(14%)
1060	12	2/4(50%)	1/4(25%)	1/4(25%)
1064	10	1/4(25%)	2/3(67%)	2/3(67%)
1076	26	4/9(44%)	6/8(75%)	6/9(67%)
1074	7	0/2(0%)	0/2(0%)	1/3(33%)
1063	7	2/3(67%)	0/2(0%)	0/2(0%)
1049	6	0/2(0%)	1/2(50%)	1/2(50%)
1059	6	0/2(0%)	1/2(50%)	0/2(0%)
1051	5	0/2(0%)	0/1(0%)	0/2(0%)
1054	4	0/1(0%)	1/2(50%)	0/1(0%)
1057	3	0/1(0%)	0/1(0%)	1/1(100%)
1068	3	0/1(0%)	0/1(0%)	0/1(0%)
1067	2		1/1(100%)	0/1(0%)
1061	1		1/1(100%)	
1050	1		0/1(0%)	
Total	113	10/38(26%)	17/37(46%)	13/38(34%)

d. Comments:

1. Inconsistencies.

a. In the database filed with the statistician reviewer, carafate patient 187/1066 was included as having a second 2 cm ulcer at week four which made this patient unhealed. This patient was included as healed at week four in the database filed to the statistician reviewer on April 16 and July 5, 1990. The second ulcer was not included in the database of July 5, 1990. No explanation was given for this apparent discrepancy.

b. Patient 188/1066 was declared healed in the database of April 16, 1990 and unhealed in the database of July 5, 1990.

c. Patient 275/1075 had one ulcer at baseline in the April 16, 1990 database and two ulcers at baseline in the July 5, 1990.

Appendix 4

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exb	Comments
4/25/88	Y	4/25/88	001	4/28/88	001	006	Bio	Inv		01	Initial Study Medication Shipment
4/29/88	Y	4/29/88	005	5/ 3/86	025	030	Bio	Inv		05	Initial study medication shipment.
4/29/88	Y	4/29/88	002	5/ 3/88	007	012	Bio	Inv		02	Initial Study Medication Shipment
4/29/88	Y	4/29/88	003	5/ 3/88	013	018	Bio	Inv		03	Initial Study Medication Shipment.
4/29/88	Y	4/29/88	004	5/ 3/88	019	024	Bio	Inv		04	Initial study medication shipment.
4/29/88	Y	4/29/88	006	5/ 3/88	031	036	Bio	Inv		06	Initial study medication shipment.
5/05/88	Y	5/05/88	007	5/ 6/88	037	042	Bio	Inv		07	Initial study medication shipment.
5/06/88	Y	5/06/88	008	5/11/88	043	048	Bio	Inv		08	Initial study medication shipment.
5/13/88	Y	5/13/88	009	5/18/88	049	054	Bio	Inv		09	Initial study medication shipment.
5/13/88	Y	5/13/88	011	5/18/88	055	060	Bio	Inv		10	Initial study medication shipment.
5/16/88	N	5/16/88	010	5/16/88	000	000	Bio	Inv		00	No study drug dispensed. Requisition used to send empty bottle of Maalox for video tape production. See submission of 05/07/93.
5/17/88	Y	5/17/88	012	5/19/88	061	072	Bio	Inv		11	Initial study medication shipment. Report of Telephone Contact of 07/08/88 with addenda states that #061-#066 went to VAMC, and #067-#072 went to Tulane University.
5/23/88	Y	5/23/88	013	5/24/88	073	078	Bio	Inv		12	Initial study medication shipment.
5/24/88	Y	5/24/88	014	5/24/88	079	084	Bio	Inv		13	Initial study medication shipment. No patients were enrolled at this site.
5/24/88	Y	5/24/88	015	5/25/88	085	090	Bio	Inv		14	Initial study medication shipment.

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exh	Comments
5/25/88	Y	5/25/88	016	5/26/88	019	024	Bio	Inv		15	Initial study medication shipment. Patient packs #019 - #024 had originally been distributed to site had been terminated on May 12, 1988, at which time pt. packs #019 - #024 were packaged and returned to Biocraft.
6/07/88	Y	6/07/88	017	6/ 8/88	091	096	Bio	Inv		16	Initial study medication shipment.
6/13/88	Y	6/13/88	018	6/13/88	097	102	Bio	Inv		17	Initial study medication shipment.
6/28/88	N	6/28/88	019	6/29/88	103	108	Bio	Inv		18	On 06/28/88, P.I. would have had only two (2) unassigned patient packs remaining after having dispensed Pt. #010 on that day. Letter from CRA to P.I. of 06/28/88 implies that P.I. had contacted the CRA.
6/29/88	Y	6/29/88	020	6/29/88	109	114	Bio	Inv		19	Initial study medication shipment.
7/05/88	N	7/05/88	021	7/ 7/88	115	120	Bio	Inv		20	Report of telephone contact of 07/05/88 implies that CRA was responding to a request for more drug. By 07/05/88, P.I. had exhausted all of his supply of study medication.
7/18/88	Y	7/18/88	022	7/20/88	121	126	Bio	Inv		21	Initial study medication shipment.
7/20/88	N	7/20/88	023	7/21/88	127	132	Bio	Inv		22	Letter of 07/20/88 from CRA to clinical site implies that site must have contacted her about very active enrollment. On 07/20/88, P.I. would have had only 3 unassigned patient packs remaining.
8/18/88	Y	8/18/88	024	8/18/88	133	138	Bio	Inv		23	Initial study medication shipment.
8/22/88	Y	8/22/88	025	8/23/88	139	144	Bio	Inv		24	Initial study medication shipment.
8/25/88	Y	8/26/88	026	8/29/88	145	150	Bio	Inv		25	Initial study medication shipment.

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exb	Comments
8/29/88	N	8/29/88	027	8/30/88	151	156	Bio	Inv		26	P.I. would only have had two patient packs left on 08/29/88.
9/14/88	N	9/14/88	028	9/19/88	157	162	Bio	Inv		27	Letter from CRA to site of 09/14/88 implies that CRA knew site's drug supplies were getting low. On 09/14/88, P.I. would have had only 2 unassigned patient packs left.
10/10/88	Y	10/10/88	029	10/12/88	163	168	Bio	Inv		28	
10/18/88	Y	10/18/88	031	10/18/88	175	180	Bio	Inv		30	
10/18/88	N	10/18/88	030	10/18/88	169	174	Bio	Inv		29	P.I. had dispensed all previously assigned pt. packs by 10/17/88
10/19/88	N	10/19/88	032	10/20/88	181	186	Bio	Inv		31	P.I. was actively entering pts. during this period, and would have had only 4 unassigned patient packs left after 10/19/88.
10/20/88	Y	10/21/88	033	10/25/88	187	192	Bio	Inv		32	
10/24/88	N	10/24/88	034	10/25/88	193	198	Bio	Inv		33	P.I. only had 2 patient packs left on 10/24/88, and was actively entering patients.
10/25/88	Y	10/25/88	035	10/25/88	199	204	Bio	Inv		34	
10/27/88	N	10/27/88	036	10/27/88	205	216	Bio	Inv		35	On 10/27/88, P.I. would have had only 3 unassigned patient packs remaining after dispensing #199-#201.
11/04/88	Y	11/04/88	038	N/A	223	228	Bio	Inv		37	This shipment was canceled on 11/08/88, and was never sent to P.I.
11/04/88	Y	11/04/88	037	11/7/88	217	222	Bio	Inv		36	Initial study medication shipment.
11/07/88	N	11/07/88	039	11/8/88	229	234	Bio	Inv		38	On 11/07/88, P.I. would have had only two (2) unassigned patient packs, and was actively

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	Pt	Exb	Comments
											entering patients. Shipped in lieu of patient packs #223-#228 in response to request of 11/04/88.
11/07/88	N	11/07/88	040	11/ 8/88	235	240	Bio	Inv		39	On 11/07/88, P.I. would have had only 3 unassigned patient packs, and was actively entering patients.
11/18/88	Y	11/18/88	041	11/21/88	241	246	Bio	Inv		40	
11/30/88	Y	11/30/88	042	12/ 2/88	247	252	Bio	Inv		41	
12/07/88	N	12/07/88	043	12/ 8/88	253	258	Bio	Inv		42	P.I. would only have had 2 unassigned patient packs on 12/7/88.
12/12/88	Y	12/12/88	044	12/15/88	259	264	Bio	Inv		43	
12/28/88	N	12/28/88	045	12/30/88	265	270	Bio	Inv		44	P.I. would only have had 2 unassigned patient packs remaining as of 12/28/88.
1/09/89	N	1/09/89	046	1/12/89	271	276	Bio	Inv		45	P.I. would only have had 2 unassigned pt. packs remaining as of 01/09/89.
1/10/89	N	1/10/89	047	1/12/89	277	282	Bio	Inv		46	On 01/10/89, P.I. would have had only one (1) unassigned patient pack remaining.
1/23/89	Y	1/24/89	049	1/26/89	289	294	Bio	Inv		48	
1/24/89	N	1/24/89	048	1/26/89	283	288	Bio	Inv		47	On 01/24/89, P.I. would have had only one (1) unassigned patient pack remaining.
1/27/89	N	1/27/89	050	1/30/89	295	300	Bio	Inv		49	Shipment CANCELED. On 01/27/89, P.I. would have had only one (1) unassigned patient pack remaining.
1/27/89	N	1/27/89	051	1/30/89	037	042	Bio	Inv		50	Report of Telephone Contact of 01/23/89 shows very active screening underway; P.I. would have had only 4 unassigned patient packs left.

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exb	Comments
											Investigator's Clinical Supply Verification (top) was dated 01/27/89, as was Clinical Supply Requisition
2/02/89	N	2/02/89	052	2/ 6/89	079	084	Bio	Inv		51	As of 02/02/89, P.I. was still screening, and would have had only 3 unassigned patient packs left (one of which was dispensed on 02/02/89).
2/03/89	N	2/03/89	**	2/ 3/89	259	264	Inv	Inv		65	Sent by CRA from On 02/03/89, would have had only two (2) unassigned patient packs remaining, and was still entering patients.
2/03/89	Y	2/03/89	**	2/ 3/89	277	282	Inv	Inv		66	CRA shipped drug directly from
2/13/89	Y	2/14/89	053	2/14/89	295	297	Bio	Inv		52	
2/15/89	(N)	2/15/89	054	2/17/89	298	300	Bio	Inv		53	On 02/15/89, P.I. would have had only two (2) unassigned patient packs remaining after dispensing #268.
2/17/89	Y	2/17/89	055	2/17/89	301	303	Bio	Inv		54	
2/17/89	Y	2/24/89	058	2/27/89	160	162	Bio	Inv		57	On 02/10/89, patient packs #160-#162 were packaged by CRA at site for shipment to Biocraft (Exhibit #27).
2/22/89	N	2/22/89	056	2/23/89	075	078	Bio	Inv		55	As of 02/22/89, P.I. was still actively screening, and would have had only 3 unassigned patient packs left (one of which was dispensed on 02/22/89). On 2/9/89, site was terminated; #075-#078 were packaged by CRA for shipment to Biocraft (Exb. #12)
2/22/89	(N)	2/22/89	057	2/23/89	106	108	Bio	Inv		56	On 02/22/89, PI would have had only 6 unassigned patient packs remaining after

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exb	Comments
											dispensing #062. P.I. was very actively screening. See Exb. #56. On 2/9/89, #106-#108 were packaged by CRA at (site for shipment to Biocraft (Exb. #18)
3/01/89	Y	3/09/89		3/ 9/89	157	159	Inv	Inv		67	CRA shipped drug directly from to (
3/03/89	Y	3/03/89	059	3/ 3/89	286	288	Bio	Inv		58	On 02/07/89, patient packs #286-#288 were packaged by CRA at site for shipment to Biocraft (Exhibit #47).
3/03/89	N	3/03/89	060	3/ 3/89	208	210	Bio	Inv		59	On 03/03/89, P.I. would have had only two (2) unassigned patient packs left. On 01/19/89, patient packs #208 - #216 were packaged by CRA at site for shipment to Biocraft (Exb. #35).
3/08/89	N	3/08/89	061	3/ 9/89	211	213	Bio	Inv		60	On 03/08/89, P.I. would have had only one (1) unassigned patient pack left after he dispensed #287. On 01/19/89, patient packs #208-#216 were packaged by CRA a site for shipment to Biocraft (Exhibit #35).
3/09/89	Y	3/09/89	062	3/11/89	134	138	Bio	Inv		61	E-Mail of 03/10/89 documents an earlier conversation with site on date of requisition. On 02/09/89, patient packs #134-#138 were packaged by CRA at site for shipment to Biocraft (see Exhibit #23).
3/13/89	N	3/14/89		3/14/89	103	104	Inv	Inv		68	CRA shipped drug directly from On 03/13/89, P.I. would have had only two (2) unassigned patient packs left after dispensing Pt. #211.
3/20/89	Y	3/20/89	063	3/21/89	098	100	Bio	Inv		62	On 02/22/89, patient packs #098 - #102 were packaged by CRA site for shipment to

Initial Contact	Req	Req Date	Num	Packed	Start	End	From	To	PI	Exb	Comments
											Biocraft.
3/23/89	N	3/23/89	**	3/23/89	284	285	Inv	Inv		69	CRA shipped drug directly from On 03/23/89, P.I. would have had only two (2) unassigned patient packs remaining.
4/13/89	Y	4/14/89	064	4/14/89	101	102	Bio	Inv		63	On 02/22/89, patient packs #098 - #102 were packaged by CRA at site for shipment to Biocraft.
4/19/89	N	4/19/89	065	4/19/89	214	216	Bio	Inv		64	On 04/19/89, P.I. would have had only one (1) unassigned patient pack left. On 01/19/89, patient packs #208 - #216 were packaged by CRA at site for shipment to Biocraft (Exhibit #35).
4/20/89	N	4/20/89	**	4/20/89	083	084	Inv	Inv		70	On 04/20/89, P.I. would have had only one (1) unassigned patient pack remaining. CRA shipped drug directly from:

Appendix 5

Biocraft Laboratories, Inc.

MEMORANDUM

March 7, 1989

To: Files

From: Debi Parker DP

Re: Sucralfate Return Drug

Unused patient packs returned to stock:
- ~~99~~-102
- 134-138

98
NSA
03/09/89
per
D. Parker

Used patient packs returned to Biocraft (left in quarantine):

97
- Week 1, 9 tablets returned
- Week 2, 12 tablets returned
- Week 3, 8 tablets returned
- Week 4, 8 tablets returned
- Week 5-6, unopened
- Week 7-8, unopened

To date, we have the following patient packs in stock:

Unused patient packs returned to Biocraft and placed in stock

99, 100, 101, 102, 134, 135, 136, 137,
138, 211, 212, 213, 214, 215, 216

Used patient packs returned to Biocraft

31, 32, 33, 34, 35, 36, 97, 145, 146, 147, 148,
149, 150, 193, 194, 195, 196, 197, 198

Patient packs in stock and never shipped

305, 306, 307, 309, 310, 311, 313, 315, 316, 318,
320, 321, 323, 324, 325, 326, 328, 330, 331, 332,
(223, 224, 225, *, 227, 228)

*226 missing QC retain - entire shipment cancelled.

Exhibit 10, Page 30

3/11/93-4/6/93
DAD

Biocraft Laboratories, Inc.

MEMORANDUM TO FILES

Re: Sucralfate Return Drug Inventory

Date: February 21, 1989

Unused Patient Packs Returned To Biocraft:

75, 76, 77, 78, 106,107, 108, 160, 161, 162,
208, 209, 210, 211, 212, 213, 214, 215, 216

Total of 19

Used Patient Packs Returned To Biocraft:

31, 32, 33, 34, 35, 36, 145, 146, 147, 148,
149, 150, 193, 194, 195, 196, 197, 198

Total of 18

The nineteen (19) unused patient packs were returned to stock.

43 x 6 unused Maalox Lot 78178 were returned to stock.

Debi Parker DP

DP/lp

cc: N. Maselli
H. Richards
M. Adamcio
B. Graber

Exhibit 10, Page 31

3/11/93-4/6/93
DAD

Appendix 6

Sucralfate drug substance was in limited supply when Biocraft manufactured the clinical batch of tablets, lot 12715. The theoretical batch size was [illegible] tablets. After manufacturing losses and removing samples for testing and stability, [illegible] of bulk tablets, equivalent to [illegible] tablets, were sent to [illegible] for packaging the clinical supplies. A summary of the amount of product sent for clinical packaging is summarized below.

Batch Number	Product	Amount sent to	Equivalent Number of Tabs *
12715	Sucralfate		
X1715	Placebo		
N7257	Carafate		

* based on target weight of tablets:

Sucralfate Tablets = 1.22 grams
Placebo Tablets = 1.07 grams

During April 12-14, 1988, [illegible] blister packed the clinical supplies of Carafate, sucralfate and placebo tablets. The accountability is as follows:

	Qty Recd by	Tablets Blistered	# Tablets Rejected	# Tablets Sampled	Accountability (%)
Sucralfate					
Placebo					
Carafate					

During April 21-25, 1988, [illegible] assembled the blister cards into the patient packs. Each blister card contained 36 tablets for each week and each patient pack contained 8 blister cards for the 8 week study. Therefore, each patient pack contained 8 x 36 = 288 tablets.

	# Tablets Blistered	# Complete Patient Packs
Sucralfate		
Placebo		
Carafate		

The last two complete sucralfate patient packs were used as QC retains and therefore 101 patient packs were available for each of the three study legs.

Appendix 7

The later requisitions cited, 051 to 065, preserve the shipping order which had been established with the previous shipments. Biocraft allocated drug to investigators who required it on an as-needed basis while maintaining an ascending numerical sequence. Where drug supplies were sufficient, and enrollment was adequate, a set of two consecutive randomization blocks of three patients each was sent in a shipment. Requisition 050 (which was canceled before leaving Biocraft) represented the last of these groups of six patient packs available to Biocraft from the original inventory - patient packs 301-303 remained in inventory after requisition 050 but did not represent a block of six. Since it was still possible to ship blocks of six patient packs at this stage of the study using unused blocks returned by inactive investigators, Biocraft held the remaining block of three in inventory. The shipping of blocks 051 to 065 then proceeded as follows (summarized as Table 3):

requested and Biocraft allocated randomization blocks to investigators in numerical sequence from supplies which were on hand (either from original or returned inventory). If a lower number block was returned, it was held until the end of the current numerical sequence.

- Block 037-042 which had been returned to Biocraft on 10/26/88 was shipped to investigator on 1/30/89 [req. 051].

- Block 079-084 which had been returned to Biocraft on 12/12/89 was shipped to investigator on 2/6/89 [req. 052].

At this point in the shipments, clinical supplies were in sufficiently short supply to necessitate the beginning of shipments of a single randomization block of three patient packs rather than the previously allocated set of two blocks. The study randomization was unaffected because it was designed with these blocks of three patients. Block 295-300 was available to Biocraft because requisition 050 had been canceled and the shipment never left Biocraft. Continuing in ascending numerical order but switching to single blocks of three, the shipments were:

- Block 295-297 was shipped to investigator on 2/14/89 [req. 053].

- Block 298-300 was shipped to investigator on 2/17/89 [req. 054].

- Block 301-303 could now be properly allocated since shipping had switched to a single block of three. This block was sent to investigator Cass on 2/17/89 [req. 055]. This was the last block in the randomization and therefore completed an ascending sequence.

TABLE 3

Shipment Date	Req Num	Block	Returned To BioCraft	Comment
01/30/89	050	295 - 300		Last block of six in inventory. This shipment was canceled.
Beginning of cited requisitions				
01/30/89	051	037 - 042	10/26/88	Lowest numbered block of six available.
02/06/89	052	079 - 084	12/12/89	Last returned block of six in inventory.
02/14/89	053	295 - 297		Part of shipment for requisition 050
02/17/89	054	298 - 300		Part of shipment for requisition 050.
02/17/89	055	301 - 303		Original inventory.
End of ascending numerical sequence, lowest available now selected				
02/23/89	056	075 - 078	02/09/89	
02/23/89	057	106 - 108	02/09/89	
02/27/89	058	160 - 162	02/27/89	
03/03/89	059	286 - 288	02/07/89	
Block 286-288 incorrectly shipped for req 059. Sequence restarts				
03/03/89	060	208 - 210	01/19/89	Note[1]
03/09/89	061	211 - 213	01/19/89	Note[1]
Following block sent due to heavy enrolling investigator				
03/11/89	062	134 - 138	02/09/89	
Numerical sequence resumes				
03/21/89	063	098 - 100	02/22/89	Note[2]
04/14/89	064	101 - 102	02/22/89	
04/19/89	065	214 - 216	01/19/89	Note[1]

[1] Patient packs 208-216 were returned as a group. The original shipment consisted of four randomization groups: packs 205-216. The original investigator assigned patients 205-207. This return was comprised of three complete randomization groups: 208-210, 211-213 and 214-216.

[2] Patient packs 098-102 were returned as a group. Patients 099-100 were never assigned.

- Block 075-078 had been returned to Biocraft on 2/9/89. A shipment of his block as requisition 053 would have broken the ascending numerical order. This block was shipped to investigator on 2/23/89 [req. 056]. This shipment began the next ascending sequence.

- Block 106-108 had been returned to Biocraft on 2/9/89. This block was shipped to investigator on 2/23/89 [req. 057].

- Block 160-162 had been returned to Biocraft on 2/27/89. This block was shipped to investigator . on 2/27/89 [req. 058].

All shipments to investigators to this point had maintained a correct, ascending numerical sequence given the supplies available to Biocraft from either the original inventory or from returns of unused patient packs from investigators, coupled with a desire to maintain shipments of two randomization blocks for as long as practical. In particular, shipments for requisitions 051 and 056 represented the maintenance of a consistent procedure rather than a departure from that procedure. Shipments then continued as follows:

- Block 286-288 had been returned to Biocraft on 2/7/89. This block was shipped to investigator on 3/3/89 [req. 059].

- Block 208-216 had been returned to Biocraft on 1/19/89. Block 208-210 was shipped to investigator on 3/3/89 [req. 060].

- Block 211-213, part of return discussed under requisition 060, was shipped to investigator on 3/9/89 [req. 061].

- Block 134-138 was returned to Biocraft on 2/9/89. This represents a block of five patient packs; two patient packs from block 133-135 and the entire block 136-138. These packs were shipped to investigator on 3/11/89. enrolled all of these patients. This shipment allowed an original set of two randomization blocks to be kept together and used by a single investigator with the exception of patient 133. Patient 133 was the only patient enrolled by investigator [req. 062].

- Block 098-102 was returned to Biocraft on 2/22/89. This represents a block of five patient packs. Block 098-100 was shipped to investigator on 3/21/89 [req. 063].

FEB 15 1994

STATISTICAL REVIEW & EVALUATION

ANDA #: 70-848 Date: February 10, 1994

Applicant: Biocraft

Drug Name: Biocraft Sucralfate's 1 gm tablet
(Generic Drug)

Indication: Duodenal Ulcer

Statistical Review Request Date: December 10, 1993

This review addresses issues raised by the medical officer Robert Prizont, M.D. These issues are concerning randomization and treatment allocation of the clinical trial which was designed and conducted as a 3-arm trial with treatments sucralfate, carafate and placebo. The trial purpose was to show that the generic sucralfate is bioequivalent to carafate having shown that carafate and sucralfate are effective in the trial. The Week 4 healing rate of acute duodenal ulcer was the main clinical endpoint. The trial was to be conducted as a double-blind randomized multi-center trial.

Randomization for the Trial

In this trial, patients were claimed to be randomized in blocks of 3 patients, and within each block, patients were to be assigned to treatments A=placebo, B=carafate, and C=sucralfate on using an appropriate sequence of random numbers. Exhibit #10 (attached) shows sponsor's documentation of the prospective (i.e., pre-established) randomization plan (chart) for the trial.

1. Concerns Regarding Prospective Randomization

If the treatment assignments use proper random number sequence, then within-block first-patient treatment assignments should follow a statistical random order. However, the medical officer noted that this may not be the case

because of the following observations:

(1). In the early part of the randomization plan (see Reviewer Table 4 attached), long runs (of length 4 and more) of treatment assignments of A (placebo) and B (carafate) occurred in the first position of the contiguous randomization blocks. This is captured in the following sequence (labelled as Sequence 1) derived from the 1st assignments of blocks 1-38.

Sequence 1: AA CC A BB C AAAAA CC A C BBB A B CC B AAAAA BBBBBBB C

The medical officer conjectured that if treatment assignments A's and B's in the above sequence followed random order then A's and B's should have alternated more frequently. Therefore, a statistical test for randomness of this sequence with respect to treatments A and B was called for.

(2). In addition, in the end part, for blocks 77-113, long runs (of length 4 or more) of treatment assignments of C (sucralfate) and B occurred in the first position of the contiguous randomization blocks. This is seen in the following sequence:

Sequence 2: A B CCCCCCC A BBBB A CCCC B AA C B A C A B AA CC AAA B C

This sequence of treatment allocations also called for a statistical test of randomness with respect to assignments of C and B.

Unusual Patterns at Centers #1052, 1055 and #1059

Randomization blocks used for shipment of medications to centers #1052, 1055 and #1059 exhibited unusual first patient assignment patterns (see Reviewer Table 1 on the next page):

Reviewer Table 1

Centers with Repetitive Treatment Assignments

Center 1052 Patient #s	Assignments	Center 1055 Patient #s	Assignments	Center 1059 Patient #s	Assignments
(1, 2, 3)	A C B	(67, 68, 69)	C A B	(31, 32, 33)	A B C
(4, 5, 6)	A B C	(70, 71, 72)	C A B	(34, 35, 36)	A C B
(115, 116, 117)	A C B	(277, 278, 279)	C A B	(241, 242, 243)	C B A
(118, 119, 120)	C A B	(61, 62, 63)	A C B	(244, 245, 246)	C B A
(127, 128, 129)	A C B	(64, 65, 66)	B C A	(265, 266, 267)	B A C
(130, 131, 132)	C B A	(280, 281, 282)	C A B	(268, 269, 270)	B A C
(164, 163, 165) switching of patient order	A B C	(106, 107, 108)	B A C	(298, 299, 300)	B C A
(166, 167, 168)	B A C	(134, 135) did not ship the B of BCA	C A	(286, 287, 288)	B C A
(175, 176, 177)	A B C	(136, 137, 138)	C A B	(211, 212)	B A
(178, 179, 180)	A B C	(157) 1st assignment of Block # 53 (CAB)	C	(103, 213)	B C
(181, 182, 183)	A B C				
(184, 185, 186)	C A B				
(199, 200, 201)	A C B				
(202, 203, 204)	C B A				
(205, 206, 207)	C B A				

As seen in the above table, within-block first-patient assignments were dominated by A in Center 1052, by C in Center 1055, and by B in Center 1059. Also, in Center 1055, the pattern 'CAB' (i.e., the first patient receiving C, the second A and the third B), occurred in 6 out of the total 10 blocks used for this center. The medical officer therefore has raised the point: Could these unusual patterns have occurred by the chance factor alone?

REVIEWER'S COMMENTS

I. Sponsor's Prospective Randomization

This reviewer applied the statistical run test methodology to test for the randomness of occurrences of assignments A and B in Sequence 1 and of B and C in Sequence 2. Both these sequences are listed above. The run test methodology is described in the book by E. L. Lehman ("Nonparametrics", pages 313-315, published by Holden-Day, Inc., 1975). These pages are attached. The methodology is also discussed in a paper by A. M. Mood (Ann. Math. Statist., 11: 367-392; 1940).

This run test is based on the concept that, if either the treatment assignments alternate too frequently (e.g., in a systematic assignment ABABAB ...) or alternates too slowly resulting in long sequences of treatments (e.g., in the above Sequence 1 with respect to treatments A and B), then non-randomness of treatment assignments are suspected.

The results of the analyses performed by this reviewer were as follows:

Reviewer Table 2
Run Test Results for Treatment Assignments

Allocation Blocks	Treatment Assignments Tested[1]	2-sided P-Value
1 - 38	A and B	.016
77 - 113	B and C	.083

[1] These within-block first-patient treatment assignments of the prospective randomization plan were tested because they exhibited unusually long runs than expected under random assignment.

These results, suggest the possibility of a defective randomization in the prospective randomization plan, at least for the early the portion of the plan.

The sponsor's randomization document (see Exhibit 10) also gave a randomization seed number, which was read with difficulty by this reviewer as

#58566422, indicating that a seed number was used to generate the random number sequence for treatment assignments. One of the purposes for documenting and reporting such a seed number for a given trial is that one would be able to generate the original random number sequence and verify the random allocation used for the trial.

Verification of the sponsor's planned random allocation in Exhibit 10 has not been possible, because the sponsor's document did not contain the actual random number sequence used and did not describe the method applied to it in arriving at the planned treatment allocation claimed in the table given in Exhibit 10.

This reviewer did several experiments: 1) generated the random number sequence with the above seed number using the random number generator software "RANUNI" of SAS (Statistical Analysis System), 2) and used various commonly used approaches for arriving at the treatment allocations from this random number sequence. However, this reviewer was not able to replicate the sponsor planned treatment allocations as given in Exhibit 10.

As some statistical software generate "pseudo-random" numbers. The sponsor may have used a correct approach of randomization, but inadvertently generated an inappropriate pseudo-random number sequence and went ahead with treatment allocation.

II. Unusual Patterns at Centers 1052, 1055, and 1059

Center 1052

As seen in the Reviewer Table 1, within-block first-patient assignments occurred in the following sequence:

AAA C A C A B AAA C A CC.

Thus, with regard to within-block first-patient assignments, A occurred 9 times as compared to B which occurred only once and C which occurred 5 times. For a single randomization block of size 3, there are 6 equally likely assignments: ABC, ACB, BAC, BCA, CAB, CBA. This means that the

probability of occurring assignment A in the first position of a single block is 2/6 or 1/3. Therefore, the probability that assignment A would occur by chance in at least 9 times in the first position in 15 independent randomization blocks can then be calculated by the exact binomial probability calculations. This probability on using the function PROBBNML of the statistical software SAS comes out to be

$$\text{Probability}\{\ \text{A occurs} \geq 9 \ /\ \text{given } n=15,\ p_A = 1/3\} = .0085.$$

Center 1055

As seen in the Reviewer Table 1, there were at least 5 allocation blocks where 'ABC' replicated. Again, for a single randomization block of 3, there are 6 equally likely assignments: ABC, ACB, BAC, BCA, CAB, CBA. This means that the probability of occurring assignment 'CAB' in a single block is 1/6. Therefore, the probability that this particular allocation would replicate by chance at least 5 times in 10 independent allocation blocks shipped to this center is

$$\text{Probability}\{\ \text{'CAB' occurs} \geq 5\ /\ \text{given } n=10,\ p_{(CAB)} = 1/6\} = .0024.$$

Center 1059

As seen in the Reviewer Table 1, the first-patient within block assignments for this center had the following sequence:

AA CC BBBBBB

Thus, with regard to first-patient within-block assignments, B occurred 6 times as compared to A and C which occurred each twice. The probability of occurring B by chance at least 6 times is

$$\text{Probability}\{\ \text{B occurs} \geq 6\ /\ \text{given } n=10,\ p_B = 1/3\} = .0197.$$

Reviewer Table 3 given below summarizes exact binomial probability calculations for unusual repetitive assignments for centers #1052, #1055, and #1059

Reviewer Table 3
Exact Binomial Probability Calculations for
Unusual Repetitive Assignments at Some Centers

Center	Total Blocks Allocated	---Repetitive Assignments---- 1st Patient Allocation	Block Allocation	Binomial Event	Probability of the Event by Chance
#1052	15	'A' occurred 9 times	-	# of 'A' ≥ 9	.0085
#1055	10	'C' occurred 7 times	'CAB' occurred 5 times	# of 'C' ≥ 7 # of 'CAB' ≥ 5	.0034 .0024
#1059	10	'B' occurred 6 times	-	# of 'B' ≥ 6	.0197

Low probabilities of repetitive assignments as shown in the last column of the above table do not support the hypothesis that these repetitive assignments to incoming patients at centers #1052, #1055, and #1059 occurred by the chance factor alone. These complications for this trial could have been avoided if the pr-established randomization was blocked by center.

III. Influence of Centers #1052, #1055, and #1059

Given that there were unusual patterns in randomization blocks used at centers #1052, 1055 and at 1059, the medical officer has raised the questions: Are results in these 3 centers influencing or biasing in a direction that if the results for these centers were similar to those observed for the remaining centers then

the claimed results of bio-equivalence of sucralfate versus carafate and/or of effectiveness of sucralfate and carafate would not occur? To answer this question, the sponsor needs to provide appropriate statistical analyses including some sensitivity analyses at least for the Week 4 healing rate.

FINAL COMMENTS

This reviewer's run test results detected the possibility of a defective randomization in the prospective randomization plan, at least for early the portion of the plan.

Therefore, the sponsor should provide the following details to further assess the validity of the claimed randomization plan:

1. Please regenerate the original random number sequence using the randomization seed number provided in Exhibit 10.

2. Describe the method used to arrive at treatment allocations in blocks of 3 as claimed in Exhibit 10.

3. Please provide computer outputs and details of each step for review and verification purpose.

Treatment allocation blocks for patient enrollment exhibited unusual patterns at some centers. In Center 1052, first-patient allocations were 'A' in 9 out of the total 15 treatment allocation blocks. In Center 1055, pattern 'CAB' (i.e., the first patient receiving C, the second A and the third B), occurred in 6 out of the total 10 blocks used for this center. In Center 1059 also first-patient allocations were B in 6 out of the total 10 treatment allocation blocks. Statistical evaluation did not support the hypothesis that these unusual patters were due to chance factor alone.

4. To evaluate the impact of problem centers #1052, 1055 and 1059, please provide appropriate statistical analyses including some

sensitivity analyses at least for the Week 4 healing rate to answer the question: Are results in these 3 centers influencing or biasing in a direction that if the results for these centers were similar to those observed for the remaining centers then the claimed results of bio-equivalence of sucralfate versus carafate and/or of effectiveness of sucralfate and carafate would not occur?

M. F. Huque, Ph. D.
Mathematical Statistician

Concur: Dr. Dubey 2-15-94.

[This review contains 9 pages of texts and 6 pages of attachments.]

cc: Orig. ANDA 70-848
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Ms. Walsh
HFD-713/Dr. Dubey [File: DRU 1.3.2] generics
HFD-713/Dr. Huque
Chron.
Dr. Huque/X34594/1-25-95

Reviewer Table 4*

Prospective (Pre-Established) Randomization Plan
Derived from Exhibit 10 by Biocraft-Almedica

BLK #s	Treat. Codes	Patients #s	BLK #s	Treat. Codes	Patients #s	BLK #s	Treat. Codes	Patients #s
1.	ACB	1, 2, 3	39.	ACB	115, 116, 117	77.	ACB	229, 230, 231
2.	ABC	4, 5, 6	40.	CAB	118, 119, 120	78.	BCA	232, 233, 234
3.	CAB	7, 8, 9	41.	ABC	121, 122, 123	79.	CAB	235, 236, 237
4.	CBA	10, 11, 12	42.	CAB	124, 125, 126	80.	CBA	238, 239, 240
5.	ABC	13, 14, 15	43.	ACB	127, 128, 129	81.	CBA	241, 242, 243
6.	BCA	15, 17, 18	44.	CBA	130, 131, 132	82.	CBA	244, 245, 246
7.	BCA	19, 20, 21	45.	BCA	133, 134, 135	83.	CAB	247, 248, 249
8.	CBA	22, 23, 24	46.	CAB	136, 137, 138	84.	CBA	250, 251, 252
9.	ABC	25, 25, 27	47.	ACB	139, 140, 141	85.	CBA	253, 254, 255
10.	ACB	28, 29, 30	48.	ACB	142, 143, 144	86.	ABC	256, 257, 258
11.	ABC	31, 32, 33	49.	CAB	145, 146, 147	87.	BAC	259, 260, 261
12.	ACB	34, 35, 36	50.	BAC	148, 149, 150	88.	BCA	262, 263, 264
13.	ACB	37, 38, 39	51.	CBA	151, 152, 153	89.	BAC	265, 266, 267
14.	CBA	40, 41, 42	52.	BAC	154, 155, 156	90.	BAC	268, 269, 270
15.	CAB	43, 44, 45	53.	CAB	157, 158, 159	91.	ACB	271, 272, 273
16.	ABC	46, 47, 48	54.	CBA	160, 161, 162	92.	CAB	274, 275, 276
17.	CBA	49, 50, 51	55.	BAC	163, 164, 165	93.	CAB	277, 278, 279
18.	BCA	52, 53, 54	56.	BAC	166, 167, 168	94.	CAB	280, 281, 282
19.	BAC	55, 56 57	57.	BCA	169, 170, 171	95.	CBA	283, 284, 285
20.	BCA	58, 59, 60	58.	CAB	172, 173, 174	96.	BCA	286, 287, 288
21.	ACB	61, 62, 63	59.	ABC	175, 176, 177	97.	ACB	289, 290, 291
22.	BCA	64, 65, 66	60.	ABC	178, 179, 180	98.	ACB	292, 293, 294
23.	CAB	67, 68, 69	61.	ABC	181, 182, 183	99.	CAB	295, 296, 297
24.	CAB	70, 71, 72	62.	CAB	184, 185, 186	100.	BCA	298, 299, 300
25.	BCA	73, 74, 75	63.	BAC	187, 188, 189	101.	ABC	301, 302, 303
26.	ABC	76, 77, 78	64.	ABC	190, 191, 192	102.	CBA	304, 305, 306
27.	ACB	79, 80, 81	65.	BCA	193, 194, 195	103.	ACB	307, 308, 309
28.	ABC	82, 83, 84	66.	CAB	196, 197, 198	104.	BAC	310, 311, 312
29.	ACB	85, 86, 87	67.	ACB	199, 200, 201	105.	ACB	313, 314, 315
30.	ACB	88, 89, 90	68.	CBA	202, 203, 204	106.	ACB	316, 317, 318
31.	BAC	91, 92, 93	69.	CBA	205, 206, 207	107.	CBA	319, 320, 321
32.	BAC	94, 95, 96	70.	ACB	208, 209, 210	108.	CAB	322, 323, 324
33.	BAC	97, 98, 99	71.	BAC	211, 212, 213	109.	ABC	325, 326, 327
34.	BCA	100, 101, 102	72.	ACB	214, 215, 216	110.	ACB	328, 329, 330
35.	BCA	103, 104, 105	73.	BAC	217, 218, 219	111.	ABC	331, 332, 333
36.	BAC	106, 107, 108	74.	ACB	220, 221, 222	112.	BAC	334, 335, 336
37.	BCA	109, 110, 111	75.	BCA	223, 224, 225	113.	CBA	337, 338, 339
38.	CAB	112, 113, 114	76.	BAC	226, 227, 228			

A = placebo, B = caratate, C = sucralfate

(*Table modified from the medical officer's review Table 2, page 9, 1994)

[redacted] / RIDECRAFT

[redacted]

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PAGE NO. 1

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TREATMENT CHOICES
A B C .....

BLOCK SIZE
3

T.S.

DESCRIPTIONS

A PLACEBO
B CHEMOTHERAPY (VINCRISTINE)
C RADIOTHERAPY (RIDECRAFT)

TREATMENT GROUPS SEED #: 3856A22

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100	[redacted]	[redacted]	[redacted]

Exhibit 10, Page 19

3/11/93-4/6/93
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BY:.....

DATE:.....

C

NAME OF STUDY
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/ BIOCRAFT
NDIB 143907
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PATIENT TREATMENT GROUP ASSIGNMENT REPORT

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TREATMENT GROUP(S)
A B C 3

BLOCK SIZE

TREATMENT GROUPS   SEED #: 30844422

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178	179	180
182	181	183
185	184	186
188	187	189
190	191	192
195	193	194
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301	303	302
306	304	305
307	308	309
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313	315	314
316	318	317
321	320	319
323	324	322
325	326	327
328	330	329
331	[illegible]	[illegible]
333	[illegible]	[illegible]
335	338	337

91   48

Exhibit 10, Page 20

3/11/93-4/6/93
DAD

E.L. Lehman, Nonparametrics, pages 313-315, Holden-Day, Inc., 1975

were proposed by Theil (1950), who also suggested the median of the slopes $(Z_j - Z_i)/(j-i)$ as a point estimate of β. Some extensions of Theil's result and references to other estimation methods for β are given by Sen (1968). It is interesting to note, as is done by Bhattacharyya (1968), that the same point estimate of β is obtained by applying the method of Chap. 2, Sec. 6, to the test statistic D instead of to B. The estimate is also derived from a completely different point of view by Beran (1971).

When one suspects a linear trend and hence a model of the form (7.37), it may be of interest to test the appropriateness of this model. Two simple tests for this purpose are proposed by Olshen (1967).

Important problems also arise in the comparison of several regression coefficients when one is dealing with more than one series of observations for each of which one assumes a model of the form (7.37) with common distribution function F. This situation is considered, for example, by Sen (1969), Hollander (1970), Adichie (1974), and Potthoff (1974).

For further work on inference concerning regression parameters, including multiple regression and other approaches to robust estimation, see Adichie (1967), Bickel (1971), Jureckova (1971), and Koul (1969).

5C. Tests of Randomness Based on Runs

The alternatives of an upward or downward trend considered in Sec. 2 are not the only alternatives to randomness that may be of interest. Instead, a trend might be cyclical (for example, seasonal, or following some other pattern), or successive observations may be dependent, as is the case in model (7.38). The problem of testing for randomness against these or other less clearly specified alternatives arises, for example, in quality control if one wishes to know whether the quality of successively produced items behaves like a sequence of identically, independently distributed random variables, in the study of economic time series, or when considering a sequence of physiological or psychological measurements taken on the same individual over a period of time.

Although the alternatives to randomness are often not clearly defined, a common feature of a large class of alternatives is a tendency toward clustering so that high (or low) values tend to occur together. This can be exploited by considering various kinds of runs of like elements exhibited by the series of observations and rejecting the hypothesis of randomness when the number of runs is too small, or when too many long runs occur.

Consider first the important special case in which the response is dichotomous, so that each observation represents either a success or a failure. If these two outcomes are denoted by 1 and 0, respectively, the N observations form a sequence of ones

and zeros. The hypothesis of randomness states that this sequence constitutes a sequence of N binomial trials with unknown success probability, say, p. A natural test statistic to test this hypothesis against the alternatives of clustering is the total number R of runs of ones and zeros. For example, in the series

$$1 \quad 0 \quad 0 \quad 0 \quad 1 \quad 1 \quad 0 \quad 0 \quad 1 \quad 1$$

there are three runs of ones (of lengths 1, 2, and 2) and two runs of zeros (of lengths 3 and 2), so that $R = 5$.

The null distribution of R depends on p; however, the conditional null distribution, given that the number of zeros is m and the number of ones is n, does not, since the conditional probability of any particular arrangement of the m zeros and n ones is $1 \Big/ \binom{N}{n}$. The conditional distribution of R has in fact the simple expression

$$P(R = 2k) = \frac{2\binom{m-1}{k-1}\binom{n-1}{k-1}}{\binom{N}{n}} \tag{7.43}$$

and

$$P(R = 2k+1) = \frac{\binom{m-1}{k-1}\binom{n-1}{k} + \binom{m-1}{k}\binom{n-1}{k-1}}{\binom{N}{n}} \tag{7.44}$$

As m and n tend to infinity with m/n tending to γ, it is shown by Wald and Wolfowitz (1940) that the distribution of

$$\frac{R - 2m(1+\gamma)}{\sqrt{4\gamma m(1+\gamma)^3}}$$

tends to the Standard Normal distribution. (Wald and Wolfowitz discuss R in the context of the two-sample problem. For this problem, the R-test is now known to be very inefficient.) Tables of the null distribution of R are given by Swed and Eisenhart (1943). As pointed out by David (1947) and Lehmann (1959, pp. 155–156), the R-test has certain optimum properties against the alternatives that the observations come from a stationary Markov chain. For further work on the application of run tests to Markov chains, see Goodman (1958) and a survey paper by Billingsley (1961).

Other run statistics that have been considered for testing randomness in a sequence of zeros and ones are the number of runs of length greater than l and the length of the longest run. For a discussion of some interesting early applications of runs, see von Mises (1931, Sec. 4.2). A systematic account of the theory of runs of

two kinds of elements and its
Mood (1940). Additional mat
(1962).

Let us now return to the
hypothesis of randomness (in t
identically and independently
clustering of like values. A pr
by a zero if it falls below and
by taking as test statistic the r
zeros. The statistic R clearly c
when $N = 2n + 1$ and when N
$m = n$ and N replaced by $2n$.

A class of run statistics c
the median is obtained by cons
$Z_3 - Z_2, \ldots, Z_N - Z_{N-1}$. This
(a plus sign if $Z_i - Z_{i-1} > 0$, a
up (i.e., runs of plus signs) and
null distribution. A simple tes
which is essentially the number
considered by Wallis and Moo
Edgington (1961). The distrib
joint distribution of numbers of
among others, Kermack and M
Wolfowitz (1944), and Olmstea
problem of choosing a test that
is discussed by Levene (1952).

5D. Other Tests of Independen

The statistic $B = \sum_{(i<j)} U_{ij}$ discuss
an upward or downward tren
independence against positive
pairs of observations $(X_1, Y_1), \ldots$
B counts the number of pairs (
first ordered, it follows that B
$Y_i < Y_j$. Thus, in general, B is
$X_j - X_i$ and $Y_j - Y_i$ have the same

(7.45)

Such pairs are said to be *concor*

two kinds of elements and its extension to the case of more than two is given by Mood (1940). Additional material can be found in the book by David and Barton (1962).

Let us now return to the general problem of a series $Z_1, \ldots, Z_N$ for which the hypothesis of randomness (in the population model, the hypothesis that the Z's are identically and independently distributed) is to be tested against the alternative of clustering of like values. A possible test is obtained by replacing each observation by a zero if it falls below and by a one if it falls above the median of the Z's and by taking as test statistic the number R of runs in the resulting series of ones and zeros. The statistic R clearly depends only on the ranks of the observations. Both when $N = 2n + 1$ and when $N = 2n$, the null distribution of R is given by (7.43) with $m = n$ and N replaced by $2n$.

A class of run statistics different from those based on runs above and below the median is obtained by considering the signs of the successive differences $Z_2 - Z_1$, $Z_3 - Z_2, \ldots, Z_N - Z_{N-1}$. This again constitutes a sequence of two kinds of elements (a plus sign if $Z_i - Z_{i-1} > 0$, a minus sign if $Z_i - Z_{i-1} < 0$) but the associated runs up (i.e., runs of plus signs) and runs down (i.e., of minus signs) have a quite different null distribution. A simple test statistic is the total number of runs up and down, which is essentially the number of turning points or of peaks and troughs in the series, considered by Wallis and Moore (1941). A table of the null distribution is given by Edgington (1961). The distribution of the number of runs of given length and the joint distribution of numbers of runs of several different lengths has been studied by, among others, Kermack and McKendrick (1937a, b), Levene and Wolfowitz (1944), Wolfowitz (1944), and Olmstead (1946). The power of the associated tests and the problem of choosing a test that is appropriate against a specified class of alternatives is discussed by Levene (1952).

5D. Other Tests of Independence

The statistic $B = \sum_{(i,j)} U_{ij}$ discussed in Sec. 5B above for testing randomness against an upward or downward trend can also be adapted to the problem of testing independence against positive or negative association of two variables. If the N pairs of observations $(X_1, Y_1), \ldots, (X_N, Y_N)$ are arranged in increasing order of the X's, B counts the number of pairs (i,j) with $i < j$ for which $Y_i < Y_j$. If the X's are not first ordered, it follows that B is the number of pairs (i,j) with $X_i < X_j$ for which $Y_i < Y_j$. Thus, in general, B is the number of pairs (i,j) for which the differences $X_j - X_i$ and $Y_j - Y_i$ have the same sign, or equivalently, the number of pairs for which

$$(X_j - X_i)(Y_j - Y_i) > 0 \tag{7.45}$$

Such pairs are said to be *concordant*. The probability p of the event (7.45), which is

STATISTICAL REVIEW & EVALUATION

Date: March 15, 1994

ANDA #: 70-848

Applicant: Biocraft

Drug Name: Biocraft Sucralfate's 1 gm tablet (Generic Drug)

Indication: Duodenal Ulcer

This review is an **addendum** to the statistical review of the ANDA dated February 10, 1994. This review addresses some new analyses results.

The medical officer's recent review indicated randomization and randomization related concerns for study centers #1052, 1055, 1059, 1066, and 1075. The statistical review of February 10, 1994 indicated similar concerns for centers #1052, 1055, and 1059. This review, therefore, examined some results for the following subgroups of centers:

(1) Centers #1052, 1055, 1059, 1066, 1075 vs. the remaining Centers 15 centers; 13 of these 15 remaining centers had sample sizes of less than 6 patients per treatment arm.

(2) Centers #1052, 1055, 1059 vs. the remaining 17 centers. These 3 centers had randomization related concerns and are addressed in the stat review of February 10, 1994.

The analyses (1) and (2) above were requested in January 1994 by the Medical Officer, Robert Prizont, M.D. In addition to these, this reviewer did the large vs. small centers analyses. The subgroup of centers with less than 6 patients per treatment arms was called 'small centers.'

Reviewer's Analyses Methods

For these subgroupings, this reviewer calculated the following for the primary endpoint (week 4 healing rate):

1. Sucralfate vs placebo comparison 2-sided p-values using Fisher's exact test.

2. 90% confidence intervals for the sucralfate minus carafate healing rates using the formula given at the bottom of Table B1. Such confidence intervals, if they fell within ± 20 percent clinical bio-equivalence limits, satisfies the given ± 20 percent clinical bio-equivalence criteria for such trials.

3. The Breslow Day test for the center by treatment interaction. In this test, because of low power, only extreme cases would be detected for the sample sizes observed in the two groups of centers examined.

Tables (A1, B1) through (A3, B3) provide results of the above analyses for the respective subgroups of the centers. Tables C and D (attached), provided by the medical officer, give the week 4 healing rates by treatment group and center. Note that in the latter tables total healing rate for the sucralfate group is 33/91 as compared to 31/91 considered in the original stat review of July 12, 1992.

Table A1
Results: Centers 1052, 1055,1059, 1066,1075 Vs. Remaining
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2-sided p by Exact Test
5 Centers *	5/55 9.1%	20/53 37.7%	6.1	28.6%	< 0.001
Remaining-Centers **	10/38 26.3%	13/38 34.2%	1.5	7.9%	0.618
All Centers	15/93 16.1%	33/91 36.3%	3.0	20.2%	0.002

Interaction Test: Breslow Day Chi-Square = 3.771, 1 df
2-sided p = .052

Note: In this interaction test the sucralfate versus placebo effect of the 5 centers is compared with that of the remaining centers.

Table B1

Results: Centers 1052, 1055,1059, 1066,1075 Vs. Remaining
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	@90 Percent Confidence Interval*
The 5 Centers#	18/52 34.6%	20/53 37.7%	+3.0%	(-12.3%, 18.4%)
The Remaining Centers##	17/37 46.0%	13/38 34.2%	-11.8%	(-30.3%, 6.7%)**
All Centers	35/89 39.3%	33/91 36.3%	-3.0%	(-13.9%, 8.9%)

Interaction Test: Breslow Day Chi-Square = 1.01, 1 df
2-sided p = 0.316

Note: In this interaction test the sucralfate versus placebo effect of the 5 centers is compared with that of the remaining centers.

#See Table C, ##See Table D

@This 90% confidence interval being within 20 percent limits on each side establishes clinical bio-equivalence between the test and the reference drugs with 5% risk of being not clinically bio-equivalent.

* Confidence intervals were calculated using the formula:

$$95\%\ CI = (p_1 - p_2) \pm 1.645\sqrt{(p_1(1-p_1)/n_1 + p_2(1-p_2)/n_2}$$

where p_1 and p_2 are sucralfate and carafate rates and n_1 and n_2 are corresponding sample sizes.

**This wide confidence interval indicating non-equivalence for this subgroup of centers could be due to small sample sizes.

Table A2

Results: Centers 1052, 1055, 1059 Vs. Remaining Centers
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2-sided p by Exact Test
Centers 1052, 1055, 1059	2/33 6.1%	13/34 38.2%	9.6	-32.1%	0.001
Remaining Centers	13/60 21.7%	20/57 35.1%	2.0	-13.4%	0.728
Interaction Test: Breslow Day Chi-Square = 3.269, 1 df **2-sided p = .0706**					

Table B2

Results: Centers 1052, 1055, 1059 Vs. Remaining Centers
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	90 Percent Confidence Interval
Centers 1052, 1055, 1059	9/33 27.3%	13/34 38.2%	10.9%	(-7.7%, 29.9%)
Remaining Centers	26/56 46.4%	20/57 35.1%	-11.3%	(-26.5%, 3.8%)

Interaction Test: Breslow Day Chi-Square = 2.242, 1 df
2-sided p = .134

Table A3
Results: Large Vs. Small Centers
2-Sided P-values and the Interaction Test Result
(Week 4 healing Rate, All Randomized Patients)

Center Groupings	Placebo Rate	Sucralfate Rate	Odds Ratio	(Sucralfate - Placebo) Difference	2-sided p by Exact Test
Large Centers #	10/71 14.1%	27/69 39.1%	3.9	25.0%	0.001
Small Centers	5/22 22.7%	6/22 27.3%	1.3	4.6%	0.728
Interaction Test: Breslow Day Chi-Square = 1.938, 1 df **2-sided p = .164**					

Table B3
Results: Large Vs. Small Centers
Test - Reference 90% Confidence Intervals
(Week 4 Healing Rate, All Randomized Patients)

Center Groupings	Carafate Rate	Sucralfate Rate	(Sucralfate - Carafate) Difference	90 Percent Confidence Interval
Large Centers#	27/66 40.9%	27/69 39.1%	-1.8%	(-15.7%, 12.1%)
Small Centers	8/23 34.8%	6/22 27.3%	-7.5%	(-30.1%, 15.1%)

#Centers which had 6 or more patients in each treatment arm.

Reviewer's Comments

The above analyses are post-hoc subgroup analyses and as such have limitations. However, these analyses are driven by the randomization and randomization related concerns and provide following insights to the week 4 healing data of this trial.

1. The interaction test result for the sucralfate versus placebo comparison indicates

cc: Orig. ANDA 70-848
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Prizont
HFD-180/Ms. Walsh
HFD-713/Dr. Dubey [File DRU 1.3.2] generic
HFD-713/Dr. Huque
Chron.

Dr. Huque/x34594/3-14-94

Table C (Medical Officer's Table)

Four Week Healing Rate of Centers 1052, 1055, 1059, 1066 and 1075. All Patients

Center	Number Pts	Placebo	Carafate	Sucralfate
1052	48	1/15 (7%)	3/15 (20%)	4/18 (22%)
1055	37	0/9 (0%)	2/8 (25%)	5/10 (50%)
1059	28	1/9 (10%)	4/10 (40%)	4/9 (40%)
1066	25	1/8 (10%)	3/8 (38%)	2/8 (25%)
1075	36	2/13 (15%)	6/11 (55%)	5/11 (45%)
All Five Centers	160	5/55 (9%)	18/52(35%)	20/64 (31%) 10 8

APPEARS THIS WAY
ON ORIGINAL

Table D (Medical Officers Table)

Four Week Healing in Centers 1053, 1060, 1064, 1076 and Centers with Low Enrollment. All Patients Included

Centers	Enrollment	Placebo	Carafate	Sucralfate
1053	20	1/7(14%)	3/8(50%)	1/7(14%)
1060	12	2/4(50%)	1/4(25%)	1/4(25%)
1064	10	1/4(25%)	2/3(67%)	2/3(67%)
1076	28	4/9(44%)	6/8(75%)	6/8(67%)
1074	7	0/2(0%)	0/2(0%)	1/3(33%)
1068	7	2/3(67%)	0/2(0%)	0/2(0%)
1048	6	0/2(0%)	1/2(50%)	1/2(50%)
1066	6	0/2(0%)	1/2(50%)	0/2(0%)
1061	5	0/2(0%)	0/1(0%)	0/2(0%)
1054	4	0/1(0%)	1/2(50%)	0/1(0%)
1067	3	0/1(0%)	0/1(0%)	1/1(100%)
1063	3	0/1(0%)	0/1(0%)	0/1(0%)
1069	2		1/1(100%)	0/1(0%)
1071	1		1/1(100%)	
1080	1		0/1(0%)	
Total	113	10/38(26%)	17/37(46%)	13/38(34%)

APPEARS THIS WAY
ON ORIGINAL

NDA
70848

DIV

ANDA 70-848

Biocraft Laboratories, Inc.
Attention: Maurice Bordoni
18-01 Rover Road
P.O. Box 948
Fair Lawn, NJ 07410

Dear Sir:

This is in reference to your abbreviated new drug application dated November 8, 1985, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sucralfate Tablets USP, 1 gram.

Reference is also made to your amendments dated April 16 and July 5, 1990, September 28, 1994, August 23, and October 16, 1995 and January 4, and March 19, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sucralfate Tablets USP, 1 gram, to be bioequivalent and, therefore, therapeutically equivalent to those of listed drug (Carafate Tablets, 1 gram, of Blue Ridge Laboratories, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

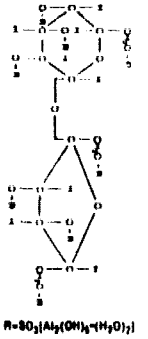
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

SUCRALFATE TABLETS USP

DESCRIPTION

Sucralfate is an α-D-glucopyranoside, β-D-fructofuranosyl, octakis-(hydrogen sulfato), aluminum complex.



$R=SO_3[Al_2(OH)_5(H_2O)_2]$

Tablets for oral administration contain 1 gram of sucralfate.

Inactive Ingredients

Corn Starch, Magnesium Stearate and Microcrystalline Cellulose.

Therapeutic Category: antiulcer

CLINICAL PHARMACOLOGY

Sucralfate is only minimally absorbed from the gastrointestinal tract. The small amounts of the sulfated disaccharide that are absorbed are excreted primarily in the urine.

Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action. The following observations also appear pertinent:

1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site.
2. *In vitro*, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions.
3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32%.
4. *In vitro*, sucralfate adsorbs bile salts.

These observations suggest that sucralfate's antiulcer activity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14-18 mEq of acid-neutralizing capacity per 1-gram dose of sucralfate.

CLINICAL TRIALS

Acute Duodenal Ulcer

Over 900 patients have participated in well-controlled clinical trials worldwide. Multicenter trials conducted in the United States, both of them placebo-controlled studies with endoscopic evaluation at two and four weeks, showed:

ity is the result of formation of an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. There are approximately 14-16 mEq of acid-neutralizing capacity per 1-gram dose of sucralfate

CLINICAL TRIALS

Acute Duodenal Ulcer

Over 600 patients have participated in well-controlled clinical trials worldwide. Multicenter trials conducted in the United States, both of them placebo-controlled studies with endoscopic evaluation at two and four weeks, showed

STUDY 1

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	37/105 (35.2%)	82/109 (75.2%)
Placebo	26/106 (24.5%)	68/107 (63.9%)

STUDY 2

Treatment Groups	Ulcer Healing/No. Patients	
	2 wk	4 wk (Overall)
Sucralfate	8/24 (33%)	22/24 (92%)
Placebo	4/31 (13%)	18/31 (58%)

The sucralfate-placebo differences were statistically significant in both studies at four weeks but not at two weeks. The poorer result in the first study may have occurred because sucralfate was given two hours after meals and at bedtime rather than one hour before meals and at bedtime, the regimen used in international studies and in the second United States study. In addition, in the first study liquid antacid was utilized as needed, whereas in the second study antacid tablets were used

Maintenance Therapy After Healing of Duodenal Ulcer

Two double-blind randomized placebo-controlled U.S. multicenter trials have demonstrated that sucralfate (1 g bid) is effective as maintenance therapy following healing of duodenal ulcers.

In one study, endoscopies were performed monthly for 4 months. Of the 254 patients who enrolled, 239 were analyzed in the intention-to-treat life table analysis presented below

Duodenal Ulcer Recurrence Rate (%)					
	Months of Therapy				
Drug	n	1	2	3	4
Sucralfate	122	20*	30*	38**	42**
Placebo	117	33	46	55	63

*p<0.05, **p<0.01
Prn antacids were not permitted in this study

In the other study, scheduled endoscopies were performed at 6 and 12 months, but for cause, endoscopies were permitted as symptoms dictated. Median symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results.

Duodenal Ulcer Recurrence Rate (%)			
Drug	n	6 Months	12 Months
Sucralfate	48	19*	27*
Placebo	46	54	65

*p<0.002
Prn antacids were permitted in this study.
Data from placebo-controlled studies longer than 1 year are not available

INDICATIONS AND USAGE

Sucralfate is indicated in:

• Short-term treatment (up to

Drug	Duodenal Ulcer Recurrence Rates (%)				
	Months of Follow-up				
	1	2	3	4	
Sucralfate	20*	26*	38**	42**	
Placebo	33	46	55	63	

*p<0.05, **p<0.01
Pre antacids were not permitted in this study

In the other study, scheduled endoscopies were performed at 6 and 12 months, but for cause, endoscopies were permitted as symptoms dictated. Mean symptom scores between the sucralfate and placebo groups were not significantly different. A life table intention-to-treat analysis for the 94 patients enrolled in the trial had the following results:

Drug	Duodenal Ulcer Recurrence Rate (%)		
	6 Months	12 Months	
Sucralfate	48	27*	
Placebo	42	85	

*p<0.002
Prn antacids were permitted in this study. Data from placebo-controlled studies longer than 1 year are not available.

INDICATIONS AND USAGE
Sucralfate is indicated in:

•Short-term treatment (up to 8 weeks) of active duodenal ulcer. While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

•Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate.

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the posthealing frequency or severity of duodenal ulceration.

Special Populations: Chronic Renal Failure and Dialysis Patients

When sucralfate is administered orally, small amounts of aluminum are absorbed from the gastrointestinal tract. Concomitant use of sucralfate with other products that contain aluminum, such as aluminum-containing antacids, may increase the total body burden of aluminum. Patients with normal renal function receiving the recommended doses of sucralfate and aluminum-containing products adequately excrete aluminum in the urine. Patients with chronic renal failure or those receiving dialysis have impaired excretion of absorbed aluminum. In addition, aluminum does not cross dialysis membranes because it is bound to albumin and transferrin plasma proteins. Aluminum accumulation and toxicity (aluminum osteodystrophy, osteomalacia, encephalopathy) have been described in patients with renal impairment. Sucralfate should be used with caution in patients with chronic renal failure.

Drug Interactions

Some studies have shown that simultaneous sucralfate administration in healthy volunteers reduced the extent of absorption (bioavailability) of single doses of the following: cimetidine, digoxin, fluoroquinolone antibiotics, ketoconazole, l-thyroxine, phenytoin, quinidine, ranitidine, tetracycline, and theophylline. Subtherapeutic prothrombin times with concomitant warfarin and sucralfate therapy have been reported in spontaneous and published case reports. However, two clinical studies have demonstrated no change in either serum warfarin concentrations or prothrombin time with the addition of sucralfate to chronic warfarin therapy.

The mechanism of these interactions appears to be nonsystemic in nature, presumably resulting from sucralfate binding to the concomitant agent in the gastrointestinal tract. In all cases studied to date (cimetidine, ciprofloxacin, digoxin, ranitidine, and warfarin), dosing the concomitant medication 2 hours before sucralfate eliminated the interaction. Because of the potential of sucralfate to alter the absorption of some drugs, sucralfate should be administered separately from other drugs when alterations in bioavailability are felt to be critical. In these cases, patients should be monitored appropriately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 g/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 30 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy

Teratogenic Effects. Pregnancy Category B.

Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,700 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system.

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash

[illegible] System: dizziness

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,780 patients treated with sucralfate tablets, adverse effects were reported in 129 (4.7%).

Constipation was the most frequent complaint (2%). Other adverse effects reported in less than 0.5% of the patients are listed below by body system.

Gastrointestinal: diarrhea, nausea, vomiting, gastric discomfort, indigestion, flatulence, dry mouth.

Dermatological: pruritus, rash.

Nervous System: dizziness, insomnia, sleepiness, vertigo.

Other: back pain, headache.

Postmarketing reports of hypersensitivity reactions, including urticaria (hives), angioedema, respiratory difficulty, rhinitis, laryngospasm, and facial swelling have been reported in patients receiving sucralfate tablets. Similar events were reported with sucralfate suspension. However, a causal relationship has not been established.

Bezoars have been reported in patients treated with sucralfate. The majority of patients had underlying medical conditions that may predispose to bezoar formation (such as delayed gastric emptying) or were receiving concomitant enteral tube feedings.

Inadvertent injection of insoluble sucralfate and its insoluble excipients has led to fatal complications, including pulmonary and cerebral emboli. Sucralfate is not intended for intravenous administration.

OVERDOSAGE

Due to limited experience in humans with overdosage of sucralfate, no specific treatment recommendations can be given. Acute oral toxicity studies in animals, however, using doses up to 12 g/kg body weight, could not find a lethal dose. Sucralfate is only minimally absorbed from the gastrointestinal tract. Risks associated with acute overdosage should, therefore, be minimal. In rare reports describing sucralfate overdose, most patients remained asymptomatic. Those few reports where adverse events were described included symptoms of dyspepsia, abdominal pain, nausea, and vomiting.

DOSAGE AND ADMINISTRATION

Active Duodenal Ulcer

The recommended adult oral dosage for duodenal ulcer is 1 gram four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

Maintenance Therapy

The recommended adult oral dosage is 1 gram twice a day.

HOW SUPPLIED

Sucralfate Tablets USP are supplied as white, scored, capsule-shaped tablets containing 1 gram of sucralfate. Available in bottles of 30 (NDC 0332-2210-04), 100 (NDC 0332-2210-00) and 500 (NDC 0332-2210-13). Tablets are debossed BROCRAFT on one side and 105 on the other.

Dispense in a tight container as defined in the USP/NF.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
Brocraft Laboratories, Inc.
Elmwood Park, New Jersey 07407

October 1994

D. V

ANDA 70-848

1. CHEMIST'S REVIEW NO. 11

2. ANDA # 70-848

3. NAME AND ADDRESS OF APPLICANT

Biocraft Laboratories, Inc.
92 Route 46, P.O. Box 200
Elmwood Park, NJ 07407

6. NAME OF DRUG

Sucralfate, USP

9. AMENDMENTS AND OTHER DATES:

Firm:

1) 11-8-85 with original application.
2) 11-25-85 with manufacturing site of for active ingredient, sucralfate
3) 12-16-85 with DMF # for active ingredient
4) 3-18-86 with 1st responding letter
5) 9-9-86 with 2nd responding letter
6) 2-13-87 with amendment for Bio's protocol
7) 2-10-87 with amendment for Bio's protocol
8) 5-15-87 with Bio study
9) 1-13-88 with amendment for meeting
10) 2-1-88 with amendment on new supplier/manufacturer of active ingredient
11) 4-27-88 and 4-28-88 with method validation for active ingredient and the finished product (The source of the active ingredient was from later was withdrawn)
12) 5-4-88 with COA from
13) 5-12-88 with a meeting request
14) 6-20-88 with reformulation, manufacturing and control revision
15) 8-16-88 with 3rd responding letter
15a) 5-18-89 with 4th responding letter
16) 8-18-89 with the revised method validation for both drug substance and the finished product
17) 11-1-89 with draft labeling
18) 11-3-89 with second source and stability data
19) 2-15-90 with Bio material (Vol. 3.3-3.5)
20) 3-5-90 with responding to HFD-180 letter dated 2-14-90
21) 3-14-90 with NC
22) 3-16-90 with 5th responding to chemistry

deficiency letter dated 2-13-90
23) 4-16-90 with Bio amendment
24) 11-14-90 with amendment
25) 1-17-92 with 6th responding to chemistry deficiency letter dated 3-28-91
26) 8-20-92 with amendment
27) 10-23-92 with amendment
28) 2-10-93 with amendment
29) 7-6-93 with amendment
30) 10-27-93 with labeling amendment
31) 7-7-95 with amendment
32) 7-26-95 with fax
33) 7-28-95 with fax
34) 10-16-95 with amendment

FDA:

1) 11-13-85 with acknowledgement
2) 6-11-86 with developing a protocol for Bio
3) 2-13-86 with 1st deficiency letter
4) 8-18-86 with 2nd deficiency letter and deficiency letter to DMF#
5) 9-30-86 with 3rd deficiency letter
6) 12-9-86 with 4th deficiency letter
7) 3-6-87 with acknowledgement and ok for protocol
8) 5-13-88 with Bio protocol comments
9) 4-11-89 with 5th deficiency letter
10) 1-10-90 & 1-19-90 with deficiency letters to DMF# and DMF #
11) 1-25-90 with Bio deficiency letter from mathematical statistician
12) 2-13-90 with 5th deficiency letter
13) 2-14-90 With Bio deficiency letter from HFD-180
14) 4-17-90 with deficiency letter from HFD-180
15) 6-5-90 with clarifications
16) 3-28-91 with 6th deficiency letter
17) 6-24-92 with 7th deficiency letter
18) 10-19-92 with method validation for both drug substance and finished product (OK)
11) 9-2-93 with 8th deficiency letter
12) 6-22-94 with 9th deficiency letter
13) 9-26-95 with 10th deficiency letter

10. PHARMACOLOGICAL CATEGORY — 11. HOW DISPENSED

Antiulcer or Duodenal Ulcer — Rx

13. DOSAGE FORM — 14. POTENCY

Tablets — 1 gram

15. CHEMICAL NAME AND STRUCTURE

Sucralfate USP
$Al_8(OH)_{16}(C_{12}H_{14}O_{35}S_8)[Al(OH)_3]_x[H_2O]_y$ in which
x=8 to 10, and y=22 to 31.

α-D-Glucopyranoside, ß-D-fructofuranosyl, octa-kis(hydrogen sulfate), aluminum complex.
Sucrose octakis(hydrogen sulfate) aluminum complex.

17. COMMENTS

The formulation has been changed since the site was used as the source of the drug substance on 8-20-88.

The finished products are manufactured using the source drug substance.

The revised formulation (composition)

The indication for maintenance therapy (in healed duodenal ulcer patients at dose of 1 gram twice daily) is covered by exclusivity.

Comments:

Q: 1. The drug product is now an article in USP 23. Please revise the testing specifications accordingly, if applicable. If the drug product does not meet the compendial standards, please address the specific issues.

A: OK (see attached comment 1).

Status:

a. EER status: **Pending**

Requested for updated for applicant (Biocraft),

b. Method Validation status: **satisfactory**

Samples for the raw materials and the finished product have been validated by St. Louis Lab and Philadelphia District and found acceptable on October 19, 1992 and July 12, 1993. Samples for the raw materials and the finished product from lot 16046 were used for the method validation. The special **Chemical Structure Elucidation Work** was performed by St Louis (DDA) and found acceptable. Now Sucralfate is USP product.

c. Bio-review and clinical studies review: **Satisfactory**

Satisfactory per J Henderson reviewed on 1-31-96. Bio and clinical studies found satisfactory per Dr. Stephen Fredd, MD/Gastrointestinal & Coagulation Drug Products and Paula Boststein, MD on 12-8-95.

Clinical studies is from lot 12715. The batch size for lot 12715 is tablets. The raw material used for lot 12715 is from
Sucralfate as the stability indicating assay method is used for stability studies on lot 12715.

d. Labeling review status: **satisfactory**

Satisfactory per C Hoppes reviewed on 12-13-94 and per A Vezza on 2-21-96.

E. DMF **Satisfactory**

DMF have been reviewed and found satisfactory on 9-22-95.

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable - Pending EER and Bio-study.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 2-21-96

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #70-848 SPONSOR: BIOCRAFT
DRUG: SUCRALFATE
DOSAGE FORM: TABLET
STRENGTHS/(s): 1 g
TYPE OF STUDY: COMPARATIVE CLINICAL TRIAL
STUDY SITE: CONDUCTED BY

STUDY SUMMARY:

On 8/16/89 the sponsor submitted the results of a comparative clinical trial conducted from 5/13/88 to 6/26/89 as a three-treatment, randomized, parallel design comparing the test product sucralfate 1 g tablets (Biocraft lot #12715, assay 100.3%) with the reference listed drug (RLD) Carafate® 1 g tablets (MMD lot #N7257, assay 94.3%) and placebo in the treatment of duodenal ulcer disease. The lot of test product used in clinical studies was manufactured (2/16/88, batch size units) prior to the implementation of OGD PPG #22-90 (applicable to applications submitted after 9/1/89).

The clinical trial results were reviewed by the Division of Gastrointestinal and Coagulation Drug Products, HFD-180, and the Division of Biometrics, HFD-713. The clinical end point was duodenal ulcer healing at four weeks. The statistician's original conclusion was that Biocraft sucralfate was more effective than placebo and bioequivalent to Carafate®. The original medical review raised questions concerning the conduct of the trial (randomization and blinding) and clinical significance of low healing rates. Dr. Stephen Fredd, Director, HFD-180, commented on these findings and an inspection was conducted by the Division of Scientific Investigations concerning these issues (randomization, patient assignment, distribution of test drugs, blinding).

These inspection results were reviewed by HFD-180 and their (medical reviewer and Dr. Fredd) resulting comments transmitted to the firm in a deficiency letter issued from the Division of Bioequivalence on 7/27/94. The firm's response was submitted 9/28/94, reviewed by Dr. Fredd, and additional information was requested regarding the databases (letter issued 7/31/95). The firm's response was submitted 8/23/95. Dr. Fredd's final review was completed 11/27/95 and he recommended approval of Biocraft's sucralfate as bioequivalent to Carafate®. Because Dr. Fredd believed that the original medical reviewer and the field inspector considered the application not approvable, he requested concurrence from the Director, ODE III. Dr. Paula Botstein, Director, ODE III, concurred with Dr. Fredd's recommendation on 12/8/95. There was one further

communication to the firm to clarify certain statements made in the 8/23/95 regarding corrections to the databases. The firm's response on 1/4/96 was acceptable to Dr. Fredd and the 7/5/90 database is the basis for approval. The test product is deemed bioequivalent to the RLD

WAIVER/DISSOLUTION: N/A

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL: JH DATE 1-24-96

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL: RNP DATE 1/24/96

DIRECTOR, DIVISION OF BIOEQUIVALENCE:
Keith K. Chan, Ph.D.
INITIAL: KKC DATE 1/30/96

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: N/A DATE