CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

APPROVAL LETTER

ANDA 74-555

SEP 30

Copley Pharmaceutical, Inc.
Attention: I. Nudelman
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated October 3, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cholestyramine for Oral Suspension, USP (Light), 4 g Resin/Packet.

Reference is also made to your amendments dated August 23, 1996; November 19, 1997; and February 26, and July 1, 6, and 28, 1998.

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 Cholestyramine for Oral Suspension, USP (Light), 4 g resin per packet to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (Questran Powder, 4 g resin per packet, of Bristol Myers Co.). The binding capacity assay described in USP 23 should be incorporated into your stability and quality control program.

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 is set forth in 21 CFR 314.80-81 and 314.98. 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-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9-28-88

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

DRAFT FINAL PRINTED LABELING

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT)

LEA505004

Revised: May 1998

505004

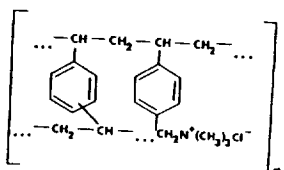
APPROVED

SEP 30 1998

℞ Only

DESCRIPTION

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT), the chloride salt of a basic anion exchange resin, a cholesterol-lowering agent, is intended for oral administration. Cholestyramine resin is quite hydrophilic, but insoluble in water. The cholestyramine resin in Cholestyramine for Oral Suspension (light) is not absorbed from the digestive tract. Five grams of Cholestyramine for Oral Suspension (light) contain 4 grams of anhydrous cholestyramine resin. It is represented by the following structural formula:



Representation of structure of main polymeric groups

This product contains the following inactive ingredients: aspartame, citric acid (anhydrous), D&C Yellow No. 10, FD&C Red No. 40, flavor (natural and artificial), propylene glycol alginate, colloidal silicon dioxide, sucrose, and xanthan gum.

CLINICAL PHARMACOLOGY

Cholesterol is probably the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestines. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. Only very small amounts of bile acids are found in normal serum.

Cholestyramine resin adsorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption.

The increased fecal loss of bile acids due to cholestyramine resin administration leads to an increased oxidation of cholesterol to bile acids, a decrease in beta lipoprotein or low density lipoprotein plasma levels, and a decrease in serum cholesterol levels. Although in man, cholestyramine resin produces an increase in hepatic synthesis of cholesterol, plasma cholesterol levels fall.

In patients with partial biliary obstruction, the reduction of serum bile acid levels by cholestyramine resin reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Clinical Studies

In a large, placebo-controlled, multi-clinic study, LRC-CPPT[1], hypercholesterolemic subjects treated with cholestyramine resin had mean reductions in total and low-density lipoprotein cholesterol (LDL-C) which exceeded those for diet and placebo treatment by 7.2% and 10.4%, respectively. Over the seven-year study period the cholestyramine resin group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% cholestyramine resin and 8.6% placebo). The subjects included in the study were men aged 35 to 39 with serum cholesterol levels above 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to females and other segments of the hypercholesterolemic population. (See also PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility.)

Two controlled clinical trials have examined the effects of cholestyramine monotherapy upon coronary atherosclerotic lesions using coronary arteriography. In the NHLBI Type II Coronary Intervention Trial[2], 116 patients (80% male) with coronary artery disease (CAD) documented by arteriography were randomized to cholestyramine resin or placebo for five years of treatment. Final study arteriography revealed progression of coronary artery disease in 49% of placebo patients compared to 32% of the cholestyramine resin group ($p<0.05$).

In the St. Thomas Atherosclerosis Regression Study (STARS)[3], 90 hypercholesterolemic men with CAD were randomized to three blinded treatments: usual care, lipid-lowering diet, and lipid-lowering diet plus cholestyramine resin. After 36 months, follow-up coronary arteriography revealed progression of disease in 46% of usual care patients, 15% of patients on lipid-lowering diet and 12% of those receiving diet plus cholestyramine resin ($p<0.02$). The mean absolute width of coronary segments decreased in the usual care group, increased slightly (0.003 mm) in the diet group and increased by 0.103 mm in the diet plus cholestyramine group ($p<0.05$). Thus in these randomized controlled clinical trials using coronary arteriography, cholestyramine resin monotherapy has been demonstrated to slow progression[2,3] and promote regression[3] of atherosclerotic lesions in the coronary arteries of patients with coronary artery disease.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or intensive combination therapy using diet plus colestipol (an anion exchange resin with a mechanism of action and an effect on serum lipids similar to that of Cholestyramine for Oral Suspension (Light)) plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.

disease.

INDICATIONS AND USAGE

1. Cholestyramine for Oral Suspension (light) is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoprotein [LDL] cholesterol) who do not respond adequately to diet. Cholestyramine resin may be useful to lower LDL cholesterol in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

   Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

   Prior to initiating therapy with cholestyramine resin, secondary causes of hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

   LDL-C = Total cholesterol - [(TG/5) + HDL-C]

   For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases cholestyramine resin may not be indicated.

   Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm initial and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of cholestyramine resin therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of cholestyramine resin or adding other lipid-lowering agents in combination with cholestyramine resin should be considered.

   Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

		LDL-Cholesterol mg/dL (mmol/L)	
Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

   *Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

   **Other risk factors for coronary heart disease (CHD) include: age (males ≥ 45 years; females: ≥ 55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥ 60 mg/dL (≥ 1.6 mmol/L).

   Cholestyramine resin monotherapy has been demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis.

2. Cholestyramine for Oral Suspension (light) is indicated for the relief of pruritus associated with partial biliary obstruction. Cholestyramine resin has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit an elevated cholesterol as part of their disease.

CONTRAINDICATIONS

Cholestyramine resin is contraindicated in patients with complete biliary obstruction where bile is not secreted into the intestine and in those individuals who have shown hypersensitivity to any of its components.

WARNING

PHENYLKETONURICS: CHOLESTYRAMINE FOR ORAL SUSPENSION (LIGHT) CONTAINS 18.81 mg PHENYLALANINE PER 5-GRAM DOSE.

PRECAUTIONS

General

Chronic use of cholestyramine resin may be associated with increased bleeding tendency due to hypoprothrombinemia associated with Vitamin K deficiency. This will usually respond promptly to parenteral Vitamin K_1 and recurrences can be prevented by oral administration of Vitamin K_1. Reduction of serum or red cell folate has been reported over long term administration of cholestyramine resin. Supplementation with folic acid should be considered in these cases. There is a possibility that prolonged use of Cholestyramine for Oral Suspension (light), since it is a chloride form of anion exchange resin, may produce hyperchloremic acidosis. This would especially be true in younger and smaller patients where the relative dosage may be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

Cholestyramine resin may produce or worsen preexisting constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with preexisting constipation, the starting dose should be 1 packet or 1 scoop once daily for 5 to 7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4 to 6 weeks apart. Increased fluid intake and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by one dose/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at one to six doses/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with cholestyramine resin may aggravate hemorrhoids.

Information for Patients

Inform your physician if you are pregnant or plan to become pregnant or are breastfeeding. Drink plenty of fluids and mix each 5-gram dose of Cholestyramine for Oral Suspension (light) in at least 2 to 3 ounces of fluid before taking. Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

Laboratory Tests

Serum cholesterol levels should be determined frequently during the first few months of therapy and periodically thereafter. Serum triglyceride levels should be measured periodically to detect whether significant changes have occurred.

The LRC-CPPT showed a dose-related increase in serum triglycerides of 10.7%-17.1% in the cholestyramine-treated group, compared with an increase of 7.9%-11.7% in the placebo group. Based on the mean values and adjusting for the placebo group, the cholestyramine-treated group showed an increase of 5% over pre-entry levels the first year of the study and an increase of 4.3% the seventh year.

Drug Interactions

Cholestyramine resin may delay or reduce the absorption of concomitant oral medication such as phenylbutazone, warfarin, thiazide diuretics (acidic), or propranolol (basic), as well as tetracycline, penicillin G, phenobarbital, thyroid and thyroxine preparations, estrogens and progestins, and digitalis. Interference with the absorption of oral phosphate supplements has been observed with another positively-charged bile acid sequestrant. Cholestyramine resin may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance of cholestyramine resin could pose a hazard to health if a potentially toxic drug such as digitalis has been titrated to a maintenance level while the patient was taking cholestyramine resin.

Because cholestyramine resin binds bile acids, cholestyramine resin may interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E and K. When cholestyramine resin is given for long periods of time, concomitant supplementation with water-miscible (or parenteral) forms of fat-soluble vitamins should be considered.

SINCE CHOLESTYRAMINE RESIN MAY BIND OTHER DRUGS GIVEN CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS TAKE OTHER DRUGS AT LEAST ONE HOUR BEFORE OR 4 TO 6 HOURS AFTER CHOLESTYRAMINE RESIN (OR AT AS GREAT AN INTERVAL AS POSSIBLE) TO AVOID IMPEDING THEIR ABSORPTION.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In studies conducted in rats in which cholestyramine resin was used as a tool to investigate the role of various intestinal factors, such as fat, bile salts and microbial flora, in the development of intestinal tumors induced by potent carcinogens, the incidence of such tumors was observed to be greater in cholestyramine resin-treated rats than in control rats.

The relevance of this laboratory observation from studies in rats to the clinical use of cholestyramine resin is not known. In the LRC-CPPT[5] study referred to above, the total incidence of fatal and nonfatal neoplasms was similar in both treatment groups. When the many different categories of tumors are examined, various alimentary system cancers were somewhat more prevalent in the cholestyramine resin group. The small numbers and the multiple categories prevent conclusions from being drawn. However, in view of the fact that cholestyramine resin is confined to the GI tract and not absorbed, and in light of the animal experiments referred to above, a six-year post-trial follow-up of the LRC-CPPT[5] patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

Pregnancy: Teratogenic Effects, Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. The use of cholestyramine in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. Cholestyramine is not absorbed systemically, however, it is known to interfere with absorption of fat-soluble vitamins; accordingly, regular prenatal supplementation may not be adequate (see PRECAUTIONS: Drug Interactions).

Nursing Mothers

Caution should be exercised when cholestyramine resin is administered to a nursing mother. The possible lack of proper vitamin absorption described in the "Pregnancy" section may have an effect on nursing infants.

Pediatric Use

Although an optimal dosage schedule has not been established, standard texts[6-7] list a usual pediatric dose of 240 mg/kg/day of anhydrous cholestyramine resin in two to three divided doses, normally not to exceed 8 g/day with dose titration based on response and tolerance.

In calculating pediatric dosages, 80 mg of anhydrous cholestyramine resin are contained in 100 mg of Cholestyramine for Oral Suspension, USP (light).

The effects of long-term drug administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients, are unknown. Also see "ADVERSE REACTIONS".

ADVERSE REACTIONS

The most common adverse reaction is constipation. When used as a cholesterol-lowering agent, predisposing factors for most complaints of constipation are high dose and increased age (more than 60 years old). Most instances of constipation are mild, transient, and controlled with conventional therapy. Some patients require a temporary decrease in dosage or discontinuation of therapy.

Less Frequent Adverse Reactions: Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, eructation, anorexia, steatorrhea, bleeding tendencies due to hypoprothrombinemia (Vitamin K deficiency) as well as Vitamin A (one case of night blindness reported) and D deficiencies, hyperchloremic acidosis in children, osteoporosis, rash and irritation of the skin, tongue and perianal area. Rare reports of intestinal obstruction, including two deaths, have been reported in pediatric patients.

Occasional calcified material has been observed in the biliary tree, including calcification of the gallbladder, in patients to whom cholestyramine resin has been given. However, this may be a manifestation of the liver disease and not drug related.

One patient experienced biliary colic on each of three occasions on which he took a cholestyramine for oral suspension product. One patient diagnosed as acute abdominal symptom complex was found to have a "pasty mass" in the transverse colon on x-ray.

Other events (not necessarily drug-related) reported in patients taking cholestyramine resin include:

Gastrointestinal - GI-rectal bleeding, black stools, hemorrhoidal bleeding, bleeding from known duodenal ulcer, dysphagia, hiccups, ulcer attack, sour taste, pancreatitis, rectal pain, diverticulitis.

Laboratory test changes - Liver function abnormalities.

Hematologic - Prolonged prothrombin time, ecchymosis, anemia.

Hypersensitivity - Urticaria, asthma, wheezing, shortness of breath.

Musculoskeletal - Backache, muscle and joint pains, arthritis.

Neurologic - Headache, anxiety, vertigo, dizziness, fatigue, tinnitus, syncope, drowsiness, femoral nerve pain, paresthesia.

Eye - Uveitis.

Renal - Hematuria, dysuria, burnt odor to urine, diuresis.

Miscellaneous - Weight loss, weight gain, increased libido, swollen glands, edema, dental bleeding, dental caries, erosion of tooth enamel, tooth discoloration.

OVERDOSAGE

Overdosage with cholestyramine resin has not been reported in a patient taking 150% of the maximum recommended daily dosage for a period of several weeks. No ill effects were reported. Should an overdosage occur, the chief potential harm would be obstruction of the gastrointestinal tract. The location of such potential obstruction, the degree of obstruction, and the presence or absence of normal gut motility would determine treatment.

DOSAGE AND ADMINISTRATION

The recommended starting adult dose for Cholestyramine for Oral Suspension (light) is one packet or one level scoopful (5 grams of Cholestyramine for Oral Suspension (light) contains 4 grams of anhydrous cholestyramine resin) once or twice a day. The recommended maintenance dose for Cholestyramine for Oral Suspension (light) is 2 to 4 packets or scoopfuls daily (8-16 grams anhydrous cholestyramine resin) divided into two doses. It is recommended that increases in dose be gradual with periodic assessment of lipid/lipoprotein levels at intervals of not less than 4 weeks. The maximum recommended daily dose is six packets or scoopfuls of Cholestyramine for Oral Suspension (light) (24 grams of anhydrous cholestyramine resin). The suggested time of administration is at mealtime but may be modified to avoid interference with absorption of other medications. Although the recommended dosing schedule is twice daily, Cholestyramine for Oral Suspension (light) may be administered in 1-6 doses per day.

Cholestyramine for Oral Suspension (light) should not be taken in its dry form. Always mix the dry powder with water or other fluids before ingesting. See Preparation Instructions.

Concomitant Therapy

Preliminary evidence suggests that the lipid-lowering effects of cholestyramine resin on total and LDL-cholesterol are enhanced when combined with a HMG-CoA reductase inhibitor, e.g., pravastatin, lovastatin, simvastatin and fluvastatin. Additive effects on LDL-cholesterol are also seen with combined nicotinic acid/cholestyramine resin therapy. See the Drug Interactions subsection of the PRECAUTIONS section for recommendations on administering concomitant therapy.

Preparation

The color of Cholestyramine for Oral Suspension (light) may vary somewhat from batch to batch but this variation does not affect the performance of the product. Place the contents of one single-dose packet or one level scoopful of cholestyramine resin in a glass or cup. Add at least 2 to 3 ounces of water or the beverage of your choice. Stir to a uniform consistency.

Cholestyramine for Oral Suspension (light) may also be mixed with highly fluid soups or pulpy fruits with a high moisture content such as applesauce or crushed pineapple.

HOW SUPPLIED

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT) is available in cartons of sixty 5-gram packets and in cans containing 210 grams with a scoop. Five grams of Cholestyramine for Oral Suspension (light) contain 4 grams of anhydrous cholestyramine resin.

NDC 38245-300-28	210 g cans, 42 doses
NDC 38245-300-80	Cartons of 60, 5 g packets

The scoop is not interchangeable with scoops from other products.

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

References

1. The Lipid Research Clinics Coronary Primary Prevention Trial Results: (I) Reduction in Incidence of Coronary Heart Disease; (II) The Relationship of Reduction in Incidence of Coronary Heart Disease to Cholesterol Lowering. *JAMA*. 1984; 251:351-374.
2. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. Circulation 1984;69:313-24.
3. Watts, GF, Lewis B, Brunt JNH, Lewis ES, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St. Thomas Atherosclerosis Regression Study (STARS). Lancet 1992; 339:563-69.
4. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994 Mar;89 (3):1333-445.
5. The Lipid Research Clinics Investigators. The Lipid Research Clinics Coronary Primary Prevention Trial: Results of 6 Years of Post-Trial Follow-up. Arch Intern Med 1992; 152:1399-1410.
6. Behrman RE et al (eds): *Nelson, Textbook of Pediatrics*, ed 15. Philadelphia, PA, WB Saunders Company, 1996.
7. Takemoto CK et al (eds): *Pediatric Dosage Handbook*, ed 3. Cleveland/Akron, OH, Lexi-Comp, Inc., 1996/1997.

Copley Pharmaceutical, Inc.
Canton, MA 02021

Revised: May 1998
LEA505004
MG #11205

NDC 38245-300-80

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP LIGHT

4 grams cholestyramine resin, USP, per packet*

with NUTRASWEET® BRAND SWEETENER
This product also contains sucrose.

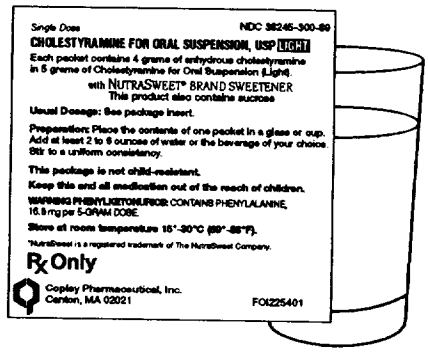
*Each packet contains 4 grams of anhydrous cholestyramine in 5 grams of Cholestyramine for Oral Suspension (Light).

USUAL DOSAGE: See package insert.

℞ Only

60 SINGLE-DOSE PACKETS

Copley Pharmaceutical, Inc.
Canton, MA 02021



NutraSweet is a registered trademark of the NutraSweet Company.

Single Dose NDC 38245-300-89

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP LIGHT

This packet contains 4 grams of cholestyramine resin in 5 grams of Cholestyramine for Oral Suspension.

with NUTRASWEET*BRAND SWEETENER
This product also contains sucrose.

Usual Dosage: See package insert.

Preparation: Place the contents of one packet in a glass or cup. Add at least 2-3 ounces of water or the non-carbonated beverage of your choice. Stir to a uniform consistency.

This package is not child-resistant.

Keep this and all medication out of the reach of children.

WARNING PHENYLKETONURICS: CONTAINS PHENYLALANINE 18.81 mg PER 5-GRAM DOSE.

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

*NutraSweet is a registered trademark of The NutraSweet Company.

CAUTION: Federal law prohibits dispensing without prescription.

Copley Pharmaceutical, Inc.
Canton, MA 02021

FOI225401

SEP 30 1989

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NDC 98245-300-28

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP LIGHT

4 grams cholestyramine resin, USP, per scoopful*

SCOOP ENCLOSED

with NUTRASWEET® BRAND SWEETENER
This product also contains sucrose

CONTENTS 210 G (168 G ANHYDROUS CHOLESTYRAMINE)

CAUTION: Federal law prohibits dispensing without prescription.

42 MEASURED DOSES

NutraSweet is a registered trademark of The NutraSweet Co.

Copley Pharmaceutical, Inc.
Canton, MA 02021

LAB701703

USUAL DOSAGE:
One level scoop one to six times daily.

*Each level scoopful supplies 4 grams of anhydrous Cholestyramine in 5 grams of Cholestyramine for Oral Suspension.

Preparation

1. A scoop is enclosed to help you measure accurately. The scoop is not interchangeable with scoops from other products. Do not force or pack the powder into the scoop.
2. Place one level scoopful of Cholestyramine for Oral Suspension in a glass or cup.
3. Add at least 2-3 ounces of water or the non-carbonated beverage of your choice.
4. Stir to a uniform consistency.

Always mix CHOLESTYRAMINE FOR ORAL SUSPENSION with water or other liquid before using.

WARNINGS
PHENYLKETONURICS:
CONTAINS PHENYLALANINE
18.81 mg per 5 g DOSE.

This package is not child-resistant. Keep this and all medication out of the reach of children. Always replace plastic lid after use.

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

See bottom of container for Lot Number and Expiration Date.

N 3 38245-300-28 0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

CHEMISTRY REVIEW(S)

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-555

FIRM: Copley Pharmaceutical Inc.

DOSAGE FORM: Powder For Suspension

STRENGTH: 4 g/dose

DRUG: Cholestyramine for Oral Suspension, USP (Light)

CGMP STATEMENT/EIR UPDATED STATUS:
EER for all the facilities listed below is found acceptable on 7-2-98.

1. Copley Pharmaceuticals, Inc.
   Canton Commerce Center
   25 John Road
   Canton, MA 02021
   (Manufacturer, processing and testing facility for finished dosage form).
2.

   (Manufacturer DMF
3.

4.

5.

6.

7.

BIO STUDY:
Acceptable based on OGD's Division of Bioequivalence letter signed off by D. Conner on 8-2-98.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?
Containers used in the stability studies are identical to those listed in container section.
Expiration dating period of 24 months for these drug products is acceptable based on the stability data.

LABELING:
FPL: Acceptable per review conducted by T. Watkins singed off 7-29-98.

STERILIZATION VALIDATION (IF APPLICABLE):
N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Size of the *in-vitro* biobatch is Lot # 300Z01 [size: kg unit dose)].

NDS Source: DMF **became adequate** per M. Shaikh's review completed on 6-5-96 after review of DMF amendment submitted on 5-7-96. DMF remains adequate per review conducted by this reviewer on 4-8-98 of annual update dated 4-18-98. No new information is submitted by the DMF holder since last review.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)
Bio/Stability Batch:
Cholestyramine for Oral Suspension USP, Exhibit batch (lot # 300Z01)
Batch Size: kg units)

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
Production batch size post-approval of this application are:
kg units).

Manufacturing process for intended production size batch is same as used for the bio/stability batch.

cc: ANDA 74-555
Division File
Field Copy

Endorsements:

/S/ 9/22/98

HFD-625/M.Shaikh/9/10/98
HFD-625/M.Smela/9/10/98
x:\new\firmsam\copley\ltrs&rev\74555app.sum
F/T by: gp/9/15/98

/S/ 9/22/98

Chemistry Closed

1. CHEMISTRY REVIEW NO. 5

2. ANDA# 74-555

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceutical Inc.
Canton Commerce Center
25 John Road
Canton, MA 02021

4. BASIS OF SUBMISSION
Acceptable per CR # 1 completed by this reviewer.

Listed drug product: Questran Light (eq 4 gm resin/packet) by Bristol Myers Pharmaceutical Laboratories and approved in NDA 19-669 (Questran Light)

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Cholestyramine Oral Powder, USP (Light)

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original submissions: 10-3-94
ONC: 11-24-94
ONC: 10-2-95 (Reference Product)
Amendment: 10-26-95 (To add testing facility)
Major Amendment: 4-8-96 (Response to NA letter dated 5-16-95)
NC (Bio): 8-23-96 (response to 7-5-96 bio deficiency letter)
Major Amendment: 11-1-96
Bio amendment: 11-19-97
Major Amendment: 12-11-97 (Response to NA letters dated April 8, and September 29, 1997)
Bio Amendment: 2-26-98 (Response to 2-19-98 bio deficiency letter)
* Bio amendment: 7-1-98
* Minor Amendment: 7-6-98 (Response to 5-4-98 NA letter)

FDA:
Accepted for filing by OGD: 11-16-94 (letter date)
ONC: 10-2-95
NA letter: 5-16-95
Bio deficiency letter: 7-5-96
NA letter: 8-1-96
Bio deficiency letter: 2-20-97

NA letter (Chemistry): 4-8-97
Labeling deficiencies letter: 9-29-97
Bio deficiency letter: 2-19-98
NA letter: 5-4-98

10. PHARMACOLOGICAL CATEGORY
1. Reduction of elevated serum cholesterol.
2. Relief of pruritus associated with partial biliary obstruction.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF
DMF
DMF

DMF
DMF

DMF
DMF

13. DOSAGE FORM
Powder (Oral)

14. POTENCY
4 g/dose

15. CHEMICAL NAME AND STRUCTURE
Cholestyramine is a synthetic anion ion-exchange polymer in which quaternary ammonium groups are attached to a copolymer of styrene and divinylbenzene.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Copley has submitted adequate information from chemistry point of view for drug substance and drug product. EER status for all the facilities listed in this ANDA is acceptable.

Copley's response in this amendment regarding labeling comments communicated to Copley on 5-4-98 is pending review.

Bio response dated 2-26-98 and 7-1-98 is pending review.

18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry closed.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
7-13-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

BIOEQUIVALENCY REVIEW(S)

ANDA # 74-555
Cholestyramine Light Powder, 4 g Resin
Reviewer: S. P. Shrivastava
WP 74555O.798

Copley Pharmaceutical, Inc.
Canton, MA
Submission Date:
~~**November 19, 1997**~~ — no original submn
2/19/98, 7/1/98, 7/28/98

REVIEW OF DEFICIENCY RESPONSE

I. BACKGROUND

The firm has responded to the deficiency cited by the Agency (see Review by SShrivastava, 2/2/98). In response to an earlier deficiency (see Review by SShrivastava, 1/31/97, 6/14/96), the firm had conducted second study (*in vitro* binding studies) to establish bioequivalence of its cholestyramine light, with Bristol Laboratories' Questran Light[R] powder preparations. However, the firm used the test Lot/Batch #300Z01, which had passed the proposed expiration date. In this submission, the firm has re-established the stability of the lot. The assay results showed a potency of 99.9% on June 24, 1998. Therefore, second study submitted on 11/19/97, is valid and data are reviewed here.

II. FIRM'S RESPONSE AND CONCLUSION

DEFICIENCY #1. *The firm has used an expired lot in the biostudy (Copley, Lot/Batch #300Z01). According to the records, the lot was packaged on 3/4/94 (manufacture date, 12/1/93); its 24 months' stability period expired on 3/4/96; and the biostudy was conducted in 1997. Results obtained from expired batches are not valid. The firm should demonstrate that the packaged product had the claimed stability at the time of the biostudy, or conduct another study on unexpired batches/lots.*

Response: The firm had determined the potency of the Lot # 300Z01 on 10/20/94 (prior to first *in vitro* biostudy) and 3/26/97 (prior to second biostudy) dates, and again recently on 6/24/98 (after the second biostudy). The potency of the biolot remained consistent throughout, and were 100.1, 99.5 and 99.9%, respectively, indicating no stability problems.

Conclusion: The second biostudy is valid, details of which are covered under deficiency #2.

DEFICIENCY #2. *In case of choletyramine light, the ratio of the mean of the total bile acid salt binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equation, are outside the ±20% of the reference. The firm should repeat the equilibrium binding study at 0.1-30 mM total bile salt concentrations, without acid pre-wash. The calculations should include the individual bile salt binding, total bile salts binding, basic statistics, affinity constants (linear and nonlinear K1), capacity constants (linear and nonlinear K2), test/reference ratios, and 90% confidence intervals (CI) for K2 parameter. The product must pass the 90% CI criteria of 80-120*

for K2 parameter, and maintain a 0.8-1.2 ratio for K1 parameter.

Response: The firm has conducted second biostudy as described below.

Protocol #11226. ***In vitro*** **Bioequivalence of Cholestyramine *(Light)* Resin Powder**

Laboratory/Site:

Products:	Test Drug:	A: Cholestyramine light 4 g anhydrous resin/5 g powder; Lot #300Z01; Potency: 99.5%; Lot size: kg, dose units.
	Ref. Drug:	B: Questran Light[R] Powder, 4 g anhydrous/5 g powder; Lot #L6K03B; Potency: 100.1%; Date of expiry: 11/99

Methods Validation

Results: **Equilibrium Binding Study, Without Acid Pre-treatment** (Tables 1-2, Attachments 1-8):

- The T/R ratios of means for total bile salts' binding ranged between 0.9-1.15 at 0.1-30 mM concentrations (Table 1).
- Using nonlinear model (Microsoft Excel 5.0), the means (range) of T/R ratios for affinity and capacity constants for cholestyramine light, were 1.02 (0.74-1.32) and 1.06 (0.94-1.22), respectively (Table 2). The T/R ratio for K1 passes the 0.8-1.2 point-estimate requirement.
- The 90% CI for K2 is within the 80-120% of reference as required.
- Individual and total bile salts binding data (amount/10 mg and % bound) are given in Attachments 1-8).

Conclusion: The study is acceptable.

III. RECOMMENDATION

1. The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine light, 4 g resin/5 g dose, Lot # 300Z01, comparing it with Bristol-Myers Squibb's Questran Light[R], 4 g resin/dose unit, Lot #L6K03B, has been found acceptable.

2. From the bioequivalence point of view, the firm has met the *in vitro* bioequivalence

requirements for its cholestyramine light, 4 g/5 g resin oral suspension powder. The study demonstrates, that Copley's cholestyramine light, 4 g resin, oral suspension formulation, is bioequivalent to Questran Light[R], 4 g resin, oral suspension, manufactured by Bristol Laboratories.

3. The binding capacity assay described in USP 23 should be incorporated into firm's manufacturing controls and stability program.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar /S/
FT INITIALED SNerurkar _____ Date 7/29/1998

Concur: /S/ Date: 8/4/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachments-8
SPS/sps/7-22-98/74555o.798

cc: ANDA #74555 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.

Table 1. Statistical Treatment for Total Bile Salts Binding (μmoles/10 mg Resin) at Equilibrium with Cholestyramine *Light*: *Without Acid Pretreatment*

Concentration (mM)	Test (mean)	Ref. (mean)	Ratio
0.1	0.7200	0.7600	0.95
0.3	1.6470	1.8330	0.90
1.0	5.6730	5.8820	0.96
2.0	11.6880	11.5240	1.01
3.0	16.8130	16.3100	1.03
5.0	21.8490	20.2970	1.08
7.0	25.7030	24.6580	1.04
8.5	27.9810	25.8690	1.08
10.0	28.7590	26.9330	1.07
15.0	35.2960	30.6200	1.15
20.0	36.4240	36.0700	1.01
30.0	39.0770	37.7270	1.04

Table 2. Affinity (K1) and Capacity (K2) Constants for Cholestyramine *Light* Powder: *Without Acid Pretreatment*, Non-Linear Models

Replicate	Test K1	Ref K1	T/R K1	Test K2	Ref K2	T/R K2
		Non-Linear Model				
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	0.4143	0.4251	1.02	4.1822	3.9687	1.06
SD	0.0867	0.1448	0.20	0.4335	0.5321	0.09
CV, %	20.9248	34.0585	19.69	10.3656	13.4068	8.62
90% CI	86.3 - 108.6*			101.2 - 109.6		

* For K1, a test/ref ratio of 0.8-1.2 point-estimate is required. 90% CI data for is for information only.

BIOEQUIVALENCY COMMENTS

ANDA: 74-555 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Cholestyramine Light, 4 g/dose

The Division of Bioequivalence has completed its review and has no further questions at this time.

The binding capacity assay described in USP 23 should be incorporated into firm's manufacturing controls and stability program.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Study #084-08-11226

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin

Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)

in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

Total Amount Bound (mmole/gram of Resin)

Drug = Copley

Added (mM)		0.1000	0.3000	1.0000	2.0000	3.0000	5.0000	7.0000	8.5000	10.0000	15.0000	20.0000	30.0000
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		.0720	0.1647	0.5673	1.1688	1.6813	2.1849	2.5703	2.7981	2.8759	3.5296	3.6424	3.9077
Std		–	0.0096	0.0219	0.0384	0.0743	0.1127	0.1839	0.2776	0.1667	0.2913	0.3540	0.3989
CV(%)		–	5.8	3.9	3.3	4.4	5.2	7.2	9.9	5.8	8.3	9.7	10.2

Drug = Bristol

Added (mM)		0.1000	0.3000	1.0000	2.0000	3.0000	5.0000	7.0000	8.5000	10.0000	15.0000	20.0000	30.0000
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		.0760	0.1833	0.5882	1.1524	1.6310	2.0297	2.4658	2.5869	2.6933	3.0620	3.6070	3.7727
Std		–	0.0104	0.0299	0.0684	0.1524	0.0873	0.1644	0.0953	0.2099	0.6760	0.3493	0.3945
CV(%)		–	5.7	5.1	5.9	9.3	4.3	6.7	3.7	7.8	22.1	9.7	10.5

Attachment - 1 3 5 3 6

Study #084-08-11226

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

Total Percent Bound

Drug = Copley

Added (mM)		0.1000	0.3000	1.0000	2.0000	3.0000	5.0000	7.0000	8.5000	10.0000	15.0000	20.0000	30.0000
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	54.90	56.73	58.44	56.04	43.70	36.72	32.92	28.76	23.53	18.21	13.03
Std		-	3.20	2.19	1.92	2.48	2.25	2.63	3.27	1.67	1.94	1.77	1.33
CV(%)		-	5.8	3.9	3.3	4.4	5.2	7.2	9.9	5.8	8.3	9.7	10.2

Drug = Bristol

Added (mM)		0.1000	0.3000	1.0000	2.0000	3.0000	5.0000	7.0000	8.5000	10.0000	15.0000	20.0000	30.0000
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	61.10	58.82	57.62	54.37	40.59	35.23	30.44	26.93	20.41	18.03	12.58
Std		-	3.46	2.99	3.42	5.08	1.74	2.35	1.12	2.10	4.51	1.75	1.32
CV(%)		-	5.7	5.1	5.9	9.3	4.3	6.7	3.7	7.8	22.1	9.7	10.5

Attachment - 2

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin , Study #084-08-11226
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

GCA Amount Bound (mmole/gram of Resin)

Drug = Copley

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		0.0147	0.0425	0.1345	0.2799	0.4016	0.4926	0.5918	0.6429	0.6548	0.8671	0.8836	0.9550
Std		0.0016	0.0030	0.0080	0.0144	0.0211	0.0364	0.0487	0.0718	0.0593	0.0755	0.1061	0.1487
CV(%)		11.0	7.1	6.0	5.1	5.3	7.4	8.2	11.2	9.1	8.7	12.0	15.6

Drug = Bristol

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		0.0188	0.0540	0.1559	0.2978	0.4170	0.4846	0.5600	0.6217	0.6422	0.7468	0.9386	0.9718
Std		0.0014	0.0040	0.0125	0.0214	0.0471	0.0295	0.1128	0.0384	0.0684	0.2324	0.1452	0.1322
CV(%)		7.5	7.4	8.0	7.2	11.3	6.1	20.1	6.2	10.6	31.1	15.5	13.6

000074

Attachment - 3

3 43

Study #084-08-11226
In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

GCA Percent Bound

Drug = Copley

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
	Mean	34.37	33.03	31.39	32.65	31.24	22.99	19.73	17.65	15.28	13.49	10.31	7.43
	Std	3.77	2.35	1.87	1.68	1.64	1.70	1.62	1.97	1.38	1.17	1.24	1.16
	CV(%)	11.0	7.1	6.0	5.1	5.3	7.4	8.2	11.2	9.1	8.7	12.0	15.6

Drug = Bristol

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
	Mean	43.80	42.03	36.38	34.74	32.43	22.61	18.67	17.07	14.98	11.62	10.95	7.56
	Std	3.30	3.10	2.91	2.49	3.66	1.37	3.76	1.05	1.60	3.62	1.69	1.03
	CV(%)	7.5	7.4	8.0	7.2	11.3	6.1	20.1	6.2	10.6	31.1	15.5	13.6

000027

Attachment 4

3 46

Study #084-08-11226
In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

GCDA Amount Bound (mmole/gram of Resin)

Drug = Copley

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	0.0902	0.3148	0.6427	0.9189	1.1943	1.3804	1.4964	1.5310	1.8350	1.8832	1.9943
Std		-	0.0050	0.0113	0.0203	0.0432	0.0620	0.1043	0.1577	0.0879	0.1638	0.1875	0.2002
CV(%)		-	5.5	3.6	3.2	4.7	5.2	7.6	10.5	5.7	8.9	10.0	10.0

Drug = Bristol

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	0.0963	0.3160	0.6189	0.8738	1.0916	1.3340	1.3699	1.4239	1.5946	1.8461	1.9171
Std		-	0.0053	0.0143	0.0386	0.0829	0.0450	0.0682	0.0510	0.1064	0.3353	0.1656	0.2018
CV(%)		-	5.5	4.5	6.2	9.5	4.1	5.1	3.7	7.5	21.0	9.0	10.5

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Attachment - 5

3 44

Study #084-08-11226
In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

GCDA Percent Bound

Drug = Copley

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		_	70.16	73.45	74.99	71.47	55.73	46.01	41.08	35.72	28.55	21.97	15.51
Std		_	3.86	2.63	2.37	3.36	2.89	3.48	4.33	2.05	2.55	2.19	1.56
CV(%)		_	5.5	3.6	3.2	4.7	5.2	7.6	10.5	5.7	8.9	10.0	10.0

Drug = Bristol

Added (mM)		0.0429	0.1286	0.4286	0.8571	1.2857	2.1429	3.0000	3.6429	4.2857	6.4286	8.5714	12.8571
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		_	74.87	73.74	72.21	67.96	50.94	44.47	37.61	33.22	24.81	21.54	14.91
Std		_	4.09	3.34	4.50	6.45	2.10	2.27	1.40	2.48	5.22	1.93	1.57
CV(%)		_	5.5	4.5	6.2	9.5	4.1	5.1	3.7	7.5	21.0	9.0	10.5

000078

Attachment - 6

3 47

Study #084-08-11226

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

TDCA Amount Bound (mmole/gram of Resin)

Drug = Copley

Added (mM)		0.0143	0.0429	0.1429	0.2857	0.4286	0.7143	1.0000	1.2143	1.4286	2.1429	2.8571	4.2857
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	0.0320	0.1180	0.2462	0.3608	0.4980	0.5981	0.6588	0.6901	0.8275	0.8756	0.9585
Std		-	0.0020	0.0030	0.0049	0.0117	0.0210	0.0409	0.0630	0.0354	0.0697	0.0727	0.0857
CV(%)		-	6.4	2.5	2.0	3.2	4.2	6.8	9.6	5.1	8.4	8.3	8.9

Drug = Bristol

Added (mM)		0.0143	0.0429	0.1429	0.2857	0.4286	0.7143	1.0000	1.2143	1.4286	2.1429	2.8571	4.2857
Bound (mmole/g)	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	0.0330	0.1163	0.2357	0.3402	0.4535	0.5718	0.5953	0.6273	0.7205	0.8224	0.8838
Std		-	0.0016	0.0036	0.0102	0.0241	0.0199	0.0314	0.0235	0.0423	0.1122	0.0534	0.0848
CV(%)		-	4.8	3.1	4.3	7.1	4.4	5.5	3.9	6.7	15.6	6.5	9.6

Attachment-7

3 45

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

Study #084-08-11226

TDCA Percent Bound

Drug = Copley

Added (mM)		0.0143	0.0429	0.1429	0.2857	0.4286	0.7143	1.0000	1.2143	1.4286	2.1429	2.8571	4.2857
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	74.71	82.57	86.16	84.18	69.73	59.81	54.26	48.31	38.62	30.65	22.36
Std		-	4.76	2.09	1.71	2.73	2.95	4.09	5.19	2.48	3.25	2.54	2.00
CV(%)		-	6.4	2.5	2.0	3.2	4.2	6.8	9.6	5.1	8.4	8.3	8.9

Drug = Bristol

Added (mM)		0.0143	0.0429	0.1429	0.2857	0.4286	0.7143	1.0000	1.2143	1.4286	2.1429	2.8571	4.2857
Percent Bound	1												
	2												
	3												
	4												
	5												
	6												
	7												
	8												
	9												
	10												
	11												
	12												
Mean		-	76.97	81.42	82.49	79.38	63.50	57.18	49.02	43.91	33.63	28.78	20.62
Std		-	3.71	2.53	3.58	5.62	2.78	3.14	1.94	2.96	5.24	1.87	1.97
CV(%)		-	4.8	3.1	4.3	7.1	4.4	5.5	3.9	6.7	15.6	6.5	9.6

000079

Attachment - 8

3 48

FEB 19 1998

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-555 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Cholestyramine Light[R] Powder, 4 gm Resin

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

1. You have used an expired lot in the biostudy (Copley, Lot/Batch #300Z01). According to the records, the lot was packaged on 3/4/94 (manufacturedate, 12/1/93); its 24 months' stability period expired on 3/4/96; and the biostudy was conducted in 1997. Results obtained from expired batches are not valid. Please demonstrate that the packaged product had the claimed stability at the time of the biostudy, or conduct another study on unexpired batches/lots.

Therefore, the *in vitro* study conducted on your cholestyramine light, 4 g resin/5 g dose, Lot# 300Z01, comparing it with Bristol-Myers Squibb's Questran Light[R], 4 g resin/dose unit, Lot #L6K03B, has been found unacceptable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA # 74-555
Cholestyramine Light Powder, 4 g Resin
Reviewer: S. P. Shrivastava
WP 74555O.N97

Copley Pharmaceutical, Inc.
Canton, MA
Submission Date:
November 19, 1997

REVIEW OF DEFICIENCY RESPONSE

I. BACKGROUND

The firm has responded to the deficiency cited by the Agency (see OGD letter, dated February 20, 1997; review by Shrivastava, 1/31/97), and has conducted another biostudy (*in vitro* binding studies) to establish bioequivalence of its cholestyramine powder with Bristol Laboratories' Questran Light^{R} powder.

II. DEFICIENCY

1 The firm has used an expired lot in the biostudy (Copley, Lot/Batch #300Z01). According to the records, the lot was packaged on 3/4/94 (manufacture date, 12/1/93); its 24 months' stability period expired on 3/4/96; and the biostudy was conducted in 1997. Results obtained from expired batches are not valid. The firm should demonstrate that the packaged product had the claimed stability at the time of the biostudy, or conduct another study on unexpired batches/lots.

III. RECOMMENDATION

1. The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine light, 4 g resin/5 g dose, Lot # 300Z01, comparing it with Bristol-Myers Squibb's Questran Light^{R}, 4 g resin/dose unit, Lot #L6K03B, has been found unacceptable, because of the deficiency #1.

The firm should be informed of the deficiency #1 and recommendation.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar /S/ Date 2/2/1998

JAN 3 1 1997

ANDA # 74-555
Cholestyramine Light Powder, 4 g Resin
Reviewer: S. P. Shrivastava
WP 74555O.896

Copley Pharmaceutical, Inc.
Canton, MA
Submission Date:
August 23, 1996

REVIEW OF DEFICIENCY RESPONSE

I. BACKGROUND

The firm has responded to the deficiencies cited in its *in vitro* studies conducted to establish bioequivalence of its cholestyramine powder with Bristol Laboratories' Questran Light[R] powder.

II. DEFICIENCY

1. *The ratio of the mean of the total bile acid salt binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equation, are outside the ±20% of the reference. The equilibrium binding study at 0.1-30 mM total bile salt concentrations, without acid pre-wash, will need to be repeated. The calculations should include the individual bile salt binding, total bile salts binding, basic statistics, affinity constants (linear and nonlinear K1), capacity constants (linear and nonlinear K2), test/reference ratios, and 90% confidence intervals (CI) for K2 parameter. The product must pass the 90% CI criteria of 80-120 for K2 parameter, and maintain a 0.8-1.2 ratio for K1 parameter.*

Response: The firm has quoted FDA data (Singh et al., 1993) showing 1.15 to 15-fold differences in K1 values of two replicates of the same product. It considers K1 values perhaps as an artifact of the estimation process, where binding at relatively high concentration tends to amplify the differences, when fitting to Langmuir binding equation. Therefore, the comparison of cholestyramine binding should be based on K2 parameter only.

Comment #1: The explanation is not acceptable. Singh et al. 1993 data (presented at AAPS Meeting, Orlando, FL), referred to by the firm were preliminary results. The investigators since then have obtained reproducible (within ±20%) K1 values. Additionally, the Agency has data that show consistent K1 values in studies.

III. RECOMMENDATION

1. The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine light, 4 g resin/5 g dose, Lot # 300Z01, comparing it with Bristol-Myers Squibb's Questran Light[R] , 4 g resin/dose unit, Lot #K3J21B, has been found unacceptable, because of the deficiency #1. The firm's response to the deficiency is not acceptable (see Comment #1).

The firm should be informed of the deficiency and comment #1 and recommendation.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED SNerurkar
FT INITIALED SNerurkar /S/ Date 1/15/1997

Concur: /S/ Date: 1/31/97

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

SPS/sps/11-25-96/74555o.896

cc: ANDA #74555 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File

JUN 14 1996

ANDA # 74-554; 74-555
Cholestyramine Powder, 4 g Resin (74-554)
Cholestyramine Light Powder, 4 g Resin (74-555)
Reviewer: S. P. Shrivastava
WP 74554S.994; 74555S.O94

Copley Pharmaceutical, Inc.
Canton, MA
Submission Date:
September 27, 1994
October 3, 1994

Review of Two *in vitro* Bioequivalence Studies

I. Objective

To compare the *in vitro* equilibrium and kinetic binding profiles of test and reference products, and establish the bioequivalence of:

1. Cholestyramine powder, 4 g resin with Questran^{R}, 4 g resin (Bristol Laboratories), and

2. Cholestyramine (light) powder, 4 g resin with Questran^{R} Light, 4 g resin (Bristol Laboratories).

II. Background

Cholestyramine resin was originally used to control pruritus in patients with elevated concentrations of plasma bile acid due to cholestasis. The resin is a bile acid sequestering anti-lipemic agent. It is used in as adjunct to dietary therapy to reduce elevated total and low-density lipoprotein (LDL) cholesterol levels in serum of patients with primary hypercholesterolemia when diet alone is not adequately effective. Cholestyramine may also lower plasma cholesterol levels in patients with hypertriglyceridemia.

In humans, cholesterol is oxidized to bile acids and converted to salts of glycine and taurine conjugates in the liver. They are stored in gall bladder for secretion into the intestine and used in the digestion of fats. Bile acids (90%) undergo reabsorption and enterohepatic circulation, and are returned to the liver. In the intestine, orally administered cholestyramine binds with bile acids, and is eliminated with feces. This causes 2 to 15-fold increase in the fecal excretion of bile acids, an increase in the oxidation of plasma cholesterol to bile acids in the liver, a decrease in the intestinal reabsorption of cholesterol, and an increase in the fecal excretion of neutral sterols. The net loss of bile acids and neutral sterol from liver leads to two compensatory changes in hepatic metabolism: an increase in the number of cell surface LDL-receptors, and an increase in the activity of HMG (3-hydroxy-3-methylglytaryl) CoA reductase, the rate-controlling enzyme in the synthesis of cholesterol. Both of these changes restore homeostasis in the liver by providing increased amounts of cholesterol for conversion to bile acids. Increased hepatic LDL-receptors leads to increased uptake of LDL from the plasma, resulting in a lower plasma LDL-cholesterol concentration.

The dosage of cholestyramine is expressed in grams resin/gram dry powder. The recommended starting dose is 4 g resin, once or twice a day, with a maximum dose of 24 g resin/day. Dosing is recommended with meals.

Cholestyramine is currently marketed as Powder for Oral Suspension containing 4 g resin/9 g powder (Questran^{R}) and 4 g resin/5 g powder (Questran^{R} Light) by Bristol Laboratories. Parke/Davis markets a Chewable Bar, 4 g resin (Cholybar^{R}).

Since the drug is not absorbed into the systemic circulation, pharmacokinetic data is not available.

III. Protocol # 10656. *In Vitro* Bioequivalence of Cholestyramine Resin Powder

Laboratory/Site:
Investigator(s):

Products

Test Drug: A: Cholestyramine 4 g resin/9 g powder; Lot #266Z01; Lot size: kg, dose units.
Ref. Drug: B: Questran^{R} Powder, 4 g/ 9 g powder; Lot #L3J71B; Date of expiry: 1/97

IV. Assay Methodology:

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secret and/or

confidential

commercial

information

V. Results for Cholestyramine Vs. Questran[R] *In Vitro* Studies

Equilibrium Binding Study, Without Acid Pre-treatment (See Tables 1-5, Attachments 1-6):

- The T/R ratios of mean binding for individual bile salts ranged between indicating little difference between the test and the reference products (Table 1, Attachments 1-6).

- Total bile salts' binding showed a T/R ratio of 1.0-1.1 at 0.1-30 mM concentrations (Table 2).

- The means of T/R affinity (K1) and capacity (K2) constants for cholestyramine powder using linear Langmuir Equation, were 1.09 and 1.08, respectively. However, inter-run variations (%CV) for K1 and K2 for the test were almost twice the reference, 79 and 17, respectively. The 90% CI calculations for K2 was 99-117 (Table 3).

- The means of T/R affinity and capacity constants for cholestyramine using nonlinear regression model (Microsoft Excel 5), were 1.00 and 1.05, respectively. Again inter-run variation for the test K1 values was slightly higher. The 90% CI was 99-109 (Table 4).

- The T/R ratios for K1 and K2 values for individual bile salts ranged between (Table 5).

Equilibrium Binding Study, With Acid Pre-treatment (See Tables 6-7c, Attachments 7-12):

- The T/R ratios for binding of individual bile salts ranged between respectively, for Low ratios are primarily at lower concentrations (Table 6, Attachments 7-12).

- The T/R ratios for K1 and K2 values for individual bile salts ranged between respectively (Table 7).

- The mean total bile salt bindings and T/R ratios are given in Table 7a. The average T/R ratio at all strengths was 0.93 (range . The individual test and reference data are given in Tables 7b and 7c.

Kinetics of Bile Salt Binding (Table 8-9, Attachments 13-17)

- The T/R ratios of binding at 0.3 mM at various time points ranged between with an average of 1.08 (Table 8). The amount of binding was uniform for each bile salt

throughout the incubation period. The kinetic binding curves for the test and reference products were parallel for the most part (Attachments 13-14).

- The T/R ratios of binding at 3 mM at various time points ranged between with an average of 0.96 (Table 9). The amount of binding was uniform for each bile salt throughout the incubation period. The kinetic binding curves for the test and reference products were parallel for the most part (Attachments 15-17).

- The kinetics of total bile salt binding at substrate concentration of 0.3 and 3mM are given in Tables 9a-9b. The average T/R ratios were 1.09 (range and 0.99 (range) for 0.3 and 3 mM substrate concentrations, respectively.

Table 1. Equilibrium Binding of Cholestyramine with Bile Acid Salts in SIF:
Without Acid Pretreatment

Bile Acid Salt	Init. Conc mM	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.0429	70.97	44.9	70.83	45.2	1.00
	0.1286	51.63	17.4	50.11	23.1	1.03
	0.4286	40.96	17.1	40.67	22.2	1.01
	1.2857	39.45	6.9	38.13	11.6	1.03
	3.0000	30.19	5.5	28.77	15.7	1.05
	4.2857	20.94	14.8	19.59	15.3	1.07
	8.5714	8.83	18.9	9.24	21.5	0.96
	12.8571	5.68	43.7	5.04	30.0	1.13
	0.0429	100	—	100	—	1.00
	0.1286	100	—	94.31	9.3	1.06
	0.4286	83.85	3.8	83.19	5.7	1.01
	1.2857	82.14	3.8	81.96	3.0	1.00
	3.0000	67.16	1.0	65.59	7.8	1.02
	4.2857	51.28	5.8	48.66	11.8	1.05
	8.5714	27.01	5.2	26.49	6.3	1.02
	12.8571	17.53	12.0	16.12	7.6	1.09
	0.0143	100	—	100	—	1.00
	0.0429	100	—	96.31	1	1.04
	0.1429	91.71	2.1	87.35	4.4	1.05
	0.4286	90.56	5.1	89.93	2.5	1.01
	1.0000	81.50	2.5	79.60	5.1	1.02
	1.4286	67.07	4.9	65.57	9.4	1.02
	2.8571	39.66	9.7	39.68	7.8	1.00
	4.2857	28.46	12.3	26.47	15.0	1.08

Table 2. Total Bile Salts Binding at Equilibrium:
Without Acid Pretreatment **(mmole/10 g resin)**

Concentration (mM)	Test (mean)	Ref. (mean)	Ratio
0.1	0.8763	0.8758	1.00
0.3	1.2218	1.1983	1.03
1.0	6.6445	6.5563	1.01
3.0	19.5138	19.2948	1.01
7.0	37.3555	36.2673	1.03
10.0	40.5303	38.6192	1.05
20.0	42.0440	41.9615	1.00
30.0	42.0417	38.5388	1.09

Table 3. Affinity (K1) and Capacity (K2) Constants for Cholestyramine Powder:
Without Acid Pretreatment**, Linear Langmuir Equation Models**

Replicate	Test K1	Ref K1	T/R K1	Test K2	Ref K2	T/R K2
		Langmuir Equation Model				
1						
2						
3						
4						
5						
6						
Mean	0.6097	0.5619	**1.19**	4.6889	4.3309	**1.08**
SD	0.4788	0.1820	0.88	0.7785	0.4225	0.11
CV, %	78.5222	32.3909	73.58	16.602	9.7555	10.23
90% CI				**99-117**		

Table 4. Affinity (K1) and Capacity (K2) Constants for Cholestyramine Powder: *Without Acid Pretreatment*, Non-Linear Models

Replicate	Test K1	Ref K1	T/R K1	Test K2	Ref K2	T/R K2
		Non-Linear Model				
1						
2						
3						
4						
5						
6						
Mean	0.7527	0.7510	1.04	4.7199	4.4962	1.05
SD	0.2040	0.1650	0.34	0.4794	0.3341	0.05
CV, %	27.1099	21.9676	32.91	10.1576	7.4311	4.46
90% CI				99-109		

Table 5. Equilibrium Binding for Individual Bile Salts in SIF: *Without Acid Pretreatment*; Estimates of Affinity (K2) and Capacity (K2) Constants

Bile Acid Salt	Constant	Test (T) Mean	CV % Test	Ref. (R) Mean	CV % Ref.	T/R
	K1	2.178	61.810	2.109	51.330	1.329
	K2	0.909	20.260	0.875	16.880	1.038
	K1	3.745	31.640	3.822	17.820	0.980
	K2*	2.435	7.480	2.301	7.680	1.058
	K1	11.963	39.620	10.367	27.020	1.154
	K2*	1.217	12.223	1.180	12.240	1.031

* Significant difference between test and reference, $p < 0.05$

Table 6. Equilibrium Binding of Cholestyramine with Bile Acid Salts in SIF:
With Acid Pretreatment

Bile Acid Salt	Init. Conc mM	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.0429	43.48	64.1	72.72	41.1	0.60
	0.1286	40.71	6.7	53.04	25.8	0.77
	0.4286	36.28	8.6	50.46	7.1	0.72
	1.2857	37.42	6.0	44.33	4.9	0.84
	3.0000	27.72	6.5	30.74	13.9	0.90
	4.2857	23.41	9.8	25.66	8.5	0.91
	8.5714	14.93	5.9	13.43	10.9	1.11
	12.8571	12.80	4.5	10.28	18.2	1.25
	0.0429	100	—	100	—	1.00
	0.1286	82.26	1.4	100	—	0.82
	0.4286	79.86	3.1	88.77	0.8	0.90
	1.2857	78.54	3.1	85.15	1.7	0.92
	3.0000	56.46	5.3	63.81	6.9	0.88
	4.2857	45.79	8.8	52.10	4.7	0.88
	8.5714	25.92	4.6	26.79	8.2	0.97
	12.8571	19.72	5.0	17.78	14.3	1.11
	0.0143	100	—	100	—	1.00
	0.0429	96.89	7.9	100	—	0.97
	0.1429	87.81	1.6	91.63	1.2	0.96
	0.4286	89.18	4.7	91.45	1.5	0.98
	1.0000	71.52	5.3	78.18	3.6	0.91
	1.4286	61.09	8.3	67.87	3.5	0.90
	2.8571	37.01	4.1	38.17	7.8	0.97
	4.2857	27.62	2.9	25.71	13.9	1.07

Table 7. Equilibrium Binding for Cholestyramine in SIF: *With Acid Pretreatment*
Estimates of Affinity (K2) and Capacity (K2) Constants

Bile Acid Salt	Constant	Test (T) Mean	CV % Test	Ref. (R) Mean	CV % Ref.	T/R
	K1	0.334*	21.72	0.979	41.01	0.341
	K2	1.987*	7.77	1.448	16.06	1.372
	K1	2.007*	21.02	4.416	17.40	0.454
	K2	2.489	4.46	3.383	6.64	1.044
	K1	7.352*	26.36	12.988	32.01	0.556
	K2	1.159	2.713	1.129	9.88	1.026

* Significant difference between test and reference, $p < 0.05$

Table 7a. Average Total Equilibrium Binding (mmole/10 g Resin) and Test vs Reference Ratios for *Acid Pretreated* Cholestyramine Resin

Concentration, mM	Test (T)	Reference (R)	T/R Ratio
0.10	0.7579	0.8832	0.86
0.30	1.9367	2.3962	0.81
1.00	6.2318	7.2759	0.86
3.00	18.7306	20.5654	0.91
7.00	32.4079	36.1835	0.90
10.00	38.3825	41.4054	0.93
20.00	45.5938	45.3789	1.00
30.00	53.6454	47.1062	1.14

Table 7b. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine Resin in SIF Copley (Test) Product (mmole/10 g Resin)

Conc., mM	Bile Salt	T-1	T-2	T-3	T-4	T-5	T-6	AVE	SD	%CV
0.1		0.4286	0.1157	0.1547	0.1359	0.1333	0.1500	0.1864	0.12	64.10
		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.00	0.00
		1.0001	0.6872	0.7262	0.7074	0.7048	0.7215	0.7579	0.12	15.76
	%	100.00	68.71	72.61	70.73	70.47	72.14	75.78	11.95	15.76
0.3		0.5786	0.5151	0.5241	0.5117	0.4714	0.5396	0.5234	0.04	6.74
		1.0654	1.0594	1.0706	1.0311	1.0530	1.0659	1.0576	0.01	1.35
		0.3571	0.3571	0.3571	0.3571	0.3571	0.3486	0.3557	0.00	0.98
		2.0011	1.9316	1.9518	1.8999	1.8815	1.9541	1.9367	0.04	2.20
	%	66.70	64.39	65.06	63.33	62.72	65.14	64.56	1.42	2.20
1		1.6534	1.6749	1.6569	1.4897	1.5240	1.3307	1.5549	0.13	8.63
		3.4611	3.5481	3.4697	3.4071	3.4204	3.2280	3.4224	0.11	3.14
		1.2366	1.2531	1.2453	1.2514	1.2461	1.2940	1.2544	0.02	1.61
		6.3511	6.4761	6.3719	6.1482	6.1905	5.8527	6.2318	0.22	3.56
	%	63.51	64.76	63.72	61.48	61.91	58.53	62.32	2.22	3.56
3		4.8896	4.4087	5.1617	4.8900	4.5219	4.9916	4.8106	0.29	5.98
		10.0706	9.6720	10.4589	10.1413	9.8293	10.4173	10.0982	0.31	3.10
		3.6941	3.5417	3.8999	3.8076	4.0296	3.9579	3.8218	0.18	4.72
		18.6543	17.6224	19.5205	18.8389	18.3808	19.3668	18.7306	0.69	3.70
	%	62.18	58.74	65.07	62.80	61.27	64.56	62.44	2.31	3.70

Table 7b. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine Resin in SIF Copley Product (mmole/10 g Resin), Continued,

Conc., mM	Bile Salt	T-1	T-2	T-3	T-4	T-5	T-6	AVE	SD	%CV
7		8.3447	8.4043	9.2190	7.8103	7.7006	8.4231	8.3170	0.54	6.52
		16.5394	16.9354	18.1449	15.6930	16.5394	17.7806	16.9388	0.90	5.30
		7.4524	7.1124	7.7009	6.6300	6.9451	7.0720	7.1521	0.38	5.29
		32.3365	32.4521	35.0648	30.1333	31.1851	33.2757	32.4079	1.70	5.25
	%	46.20	46.36	50.09	43.05	44.55	47.54	46.30	2.43	5.25
10		9.1427	9.2507	10.5171	10.7953	11.3606	9.1187	10.0309	0.98	9.79
		17.5834	18.5910	20.2526	20.8406	22.1194	18.3566	19.6239	1.73	8.81
		7.8866	8.2300	8.9920	9.1970	9.7964	8.2641	8.7277	0.72	8.27
		34.6127	36.0717	39.7617	40.8329	43.2764	35.7394	38.3825	3.42	8.90
	%	34.61	36.07	39.76	40.83	43.28	35.74	38.38	3.42	8.90
20		13.8553	11.8586	12.084	12.663	13.0689	13.265	12.7991	0.75	5.87
		23.3919	21.2644	21.177	21.933	23.5436	22.014	22.2209	1.02	4.61
		11.1529	10.2956	10.065	10.615	11.0209	10.294	10.5739	0.44	4.13
		48.4001	43.4186	43.326	45.212	47.6334	45.573	45.5938	2.10	4.61
	%	24.20	21.71	21.66	22.61	23.82	22.79	22.80	1.05	4.61
30		16.9633	17.424	16.646	15.752	16.5201	15.432	16.4562	0.75	4.53
		25.2883	27.1457	25.806	24.671	25.8266	23.388	25.3542	1.26	4.98
		12.0751	11.2933	12.212	11.869	11.5654	11.996	11.8351	0.34	2.91
		54.3267	55.863	54.663	52.292	53.9121	50.815	53.6454	1.81	3.37
	%	18.11	18.62	18.22	17.43	17.97	16.94	17.88	0.60	3.37

Table 7c. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine Resin in SIF Bristol Labs. (Reference) Product (mmole/10 g Resin)

Conc., mM	Bile Salt	R-1	R-2	R-3	R-4	R-5	R-6	AVE	SD	%CV
0.1		0.1873	0.4286	0.2019	0.4286	0.1950	0.4286	0.3117	0.13	41.13
		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.00	0.00
		0.7588	1.0001	0.7734	1.0001	0.7665	1.0001	0.8832	0.13	14.51
	%	75.87	100.00	77.33	100.00	76.64	100.00	88.31	12.82	14.51
0.3		0.7414	0.3240	0.7551	0.7444	0.7599	0.7667	0.6819	0.18	25.75
		1.2857	1.2857	1.2857	1.2857	1.2857	1.2857	1.2857	0.00	0.00
		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		2.4557	2.0383	2.4694	2.4587	2.4742	2.4810	2.3962	0.18	7.33
	%	81.86	67.94	82.31	81.96	82.47	82.70	79.87	5.85	7.33
1		2.1021	1.8823	2.2903	2.2701	2.1857	2.2449	2.1626	0.15	7.09
		3.7860	3.7920	3.8031	3.7963	3.7869	3.8619	3.8044	0.03	0.76
		1.3079	1.3080	1.3146	1.3247	1.3196	1.2790	1.3090	0.02	1.23
		7.1960	6.9823	7.4080	7.3911	7.2922	7.3858	7.2759	0.16	2.26
	%	71.96	69.82	74.08	73.91	72.92	73.86	72.76	1.65	2.26
3		5.9597	5.5161	5.9469	5.8813	5.2599	5.6306	5.6991	0.28	4.92
		10.9954	10.6564	11.0019	10.9933	10.8206	11.2157	10.9472	0.19	1.73
		3.8300	3.8813	3.9934	3.9553	3.9393	3.9153	3.9191	0.06	1.47
		20.7851	20.0538	20.9422	20.8299	20.0198	20.7616	20.5654	0.41	2.01
	%	69.28	66.85	69.81	69.43	66.73	69.21	68.55	1.38	2.01

Table 7c. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine Resin in SIF Reference Product (mmole/10 g Resin) Continued

Conc., mM	Bile Salt	R-1	R-2	R-1	R-4	R-5	R-6	AVE	SD	%CV
7		9.6951	9.9793	10.0239	10.2210	6.9429	8.4660	9.2214	1.28	13.89
		20.0383	19.5771	19.6496	20.2050	16.6731	18.7213	19.1441	1.32	6.87
		7.9541	7.9253	8.0541	8.0164	7.3384	7.6199	7.8180	0.28	3.59
		37.6875	37.4817	37.7276	38.4424	30.9544	34.8072	36.1835	2.85	7.88
	%	53.84	53.55	53.90	54.92	44.22	49.72	51.69	4.07	7.88
10		11.0576	10.8716	10.9650	11.6717	12.0853	9.3360	10.9979	0.94	8.55
		22.6581	20.9961	22.7961	22.6929	23.6760	21.1496	22.3281	1.04	4.67
		9.6953		9.7847	9.5350	10.1856	9.2759	9.6953	0.34	3.46
		43.4110	31.8677	43.5458	43.8996	45.9469	39.7615	41.4054	5.08	12.27
	%	43.41	31.87	43.55	43.90	45.95	39.76	41.41	5.08	12.27
20		10.0483	10.7263	12.9377	10.4413	12.1449	12.7676	11.5110	1.26	10.93
		25.4417	20.9816	24.5824	20.7793	23.2491	22.7469	22.9635	1.88	8.17
		11.9669	10.0103	11.2980	9.8207	11.4674	10.8630	10.9044	0.85	7.76
		47.4569	41.7182	48.8181	41.0413	46.8614	46.3775	45.3789	3.21	7.08
	%	23.73	20.86	24.41	20.52	23.43	23.19	22.69	1.61	7.08
30		13.3226	9.0973	12.4367	13.4280	14.9936	16.0586	13.2228	2.40	18.17
		22.8613	17.0876	22.4751	23.1969	24.6746	26.8941	22.8649	3.26	14.26
		12.3346	8.3133	10.4747	11.0570	11.4167	12.5146	11.0185	1.53	13.91
		48.5185	34.4982	45.3865	47.6819	51.0849	55.4673	47.1062	7.07	15.01
	%	16.17	11.50	15.13	15.89	17.03	18.49	15.70	2.36	15.01

Table 8. Kinetics of Binding of Cholestyramine with Bile Acid Salts:
Total Concentration 0.3 mM

Bile Acid Salt	Incub. Period, Hr	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.25	46.05	9.00	39.85	14.50	1.16
	0.50	45.21	5.70	39.21	13.10	1.15
	1.00	45.67	4.10	38.53	10.90	1.19
	2.00	45.01	5.60	38.44	10.50	1.17
	4.00	45.78	10.00	39.38	13.60	1.16
	8.00	44.76	16.10	43.47	11.90	1.03
	16.00	48.44	13.50	41.59	12.60	1.16
	24.00	48.94	8.70	40.04	13.70	1.22
	0.25	93.32	11.10	82.46	10.50	1.13
	0.50	94.17	9.60	86.60	12.10	1.09
	1.00	96.95	7.70	86.48	12.60	1.12
	2.00	96.79	8.10	81.55	11.50	1.19
	4.00	96.45	9.00	84.94	13.80	1.14
	8.00	89.08	13.60	89.42	13.40	1.00
	16.00	96.31	9.40	87.32	11.40	1.10
	24.00	97.09	7.30	87.29	11.30	1.11
	0.25	100.00	---	100.00	---	1.00
	0.50	100.00	---	100.00	---	1.00
	1.00	100.00	---	100.00	---	1.00
	2.00	100.00	---	100.00	---	1.00
	4.00	100.00	---	100.00	---	1.00
	8.00	100.00	---	96.52	8.80	1.04
	16.00	93.31	11.10	100.00	---	0.93
	24.00	90.36	26.10	100.00	---	0.90

Table 9. Kinetics of Binding of Cholestyramine with Bile Acid Salts: *Total Conc. 3.0 mM*

Bile Acid Salt	Incub. Period, Hr	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.25	27.66	6.80	28.84	9.90	0.96
	0.50	27.76	11.10	29.28	5.40	0.95
	1.00	28.61	6.90	29.75	7.20	0.96
	2.00	27.56	7.80	30.89	7.20	0.89
	4.00	27.66	10.90	29.79	5.60	0.93
	8.00	31.27	8.40	33.55	4.00	0.93
	16.00	28.08	8.45	30.11	5.90	0.93
	24.00	30.53	5.60	30.96	5.10	0.99
	0.25	69.19	2.40	70.76	3.20	0.98
	0.50	68.57	5.00	72.19	2.80	0.95
	1.00	70.53	3.40	73.47	2.80	0.96
	2.00	69.67	4.70	74.72	3.30	0.93
	4.00	69.68	5.40	74.99	4.70	0.93
	8.00	77.67	3.90	81.90	2.60	0.95
	16.00	71.76	3.10	75.54	3.20	0.95
	24.00	75.01	2.50	77.96	3.10	0.96
	0.25	81.53	1.30	81.90	2.10	1.00
	0.50	81.79	2.20	83.11	0.70	0.98
	1.00	82.60	2.40	84.24	0.90	0.98
	2.00	81.95	3.20	85.44	1.40	0.96
	4.00	81.83	3.70	86.01	2.70	0.95
	8.00	88.30	2.10	90.23	1.70	0.98
	16.00	83.32	1.90	85.74	1.80	0.97
	24.00	85.24	1.70	87.06	1.50	0.98

Table 9a. Kinetics of Total Bile Acid Salt Binding at *0.3 mM Conc.* to Cholestyramine (μmole/g Resin)

Time, Hrs	Test (T)	Reference (R)	Ratio, T/R
0.25	222.049	200.106	1.11
0.50	217.387	196.116	1.11
1.00	226.222	203.754	1.11
2.00	225.170	196.008	1.15
4.00	225.732	204.591	1.10
8.00	214.926	210.375	1.02
16.00	226.097	222.329	1.02
24.00	226.474	201.883	1.12

Table 9b. Kinetics of Total Bile Acid Salt Binding at *3 mM Conc.* to Cholestyramine (μmole/g Resin)

Time, Hrs	Test (T)	Reference (R)	Ratio, T/R
0.25	1594.552	1298.544	1.23
0.50	1588.962	1660.803	0.96
1.00	1628.636	1688.179	0.96
2.00	1601.296	1723.983	0.93
4.00	1602.224	1715.883	0.93
8.00	1779.102	1871.151	0.95
16.00	1640.709	1725.891	0.95
24.00	1722.257	1773.500	0.97

VI. Protocol #10741. *In vitro* Bioequivalence of Cholestyramine *(Light)* Resin Powder

Laboratory/Site:
Investigator(s):

Products

Test Drug:	A: Cholestyramine light 4 g anhydrous resin/5 g powder; Lot #300Z01; Lot size: kg, dose units.
Ref. Drug:	B: Questran^{R} Light Powder, 4 g anhydrous/9 g powder; Lot #K3J21B; Date of expiry: 12/96

VII. Assay Methodology:

VIII. Results for Cholestyramine Light Vs. Questran Light^{R} *In Vitro* Studies

Equilibrium Binding Study, Without Acid Pre-treatment (Tables 10-14, Attachments 18-23):

- The T/R ratios of mean binding for individual bile salts ranged between indicating little difference between the test and the reference products in majority of the cases (Table 10, Attachments 18-23). A higher percent binding of reference product at lower concentrations is observed for each bile salt, but the difference is negligible at higher concentrations (Attachments 21-23).

- The T/R ratios of means for total bile salts' binding ranged between at 0.1-30 mM concentrations (Table 11).

- Using linear Langmuir Equation, the means of T/R ratios for affinity (K1) and capacity (K2) constants for cholestyramine powder, were 0.38 and 1.06, respectively. The inter-run variations (%CV) for K1 and K2 for the test were almost 2 to 3 times the reference. The 90% CI calculations for and K2 was 105-122 (Table 12).

- Using nonlinear model (Microsoft Excel 5), the means of T/R ratios for affinity and capacity constants for cholestyramine, were 0.65 and 1.07, respectively. Again inter-run variation for the test K1 and K2 values were 2-3 times higher than the reference.

The 90% CI for K2 was 99.5-114.3 (Table 13).

- The T/R ratios for K1 and K2 values for individual bile salts ranged between (Table 14).

Equilibrium Binding Study, With Acid Pre-treatment (See Tables 15-16c, Attachments 24-29):

- The T/R ratios for binding of individual bile salts ranged between respectively, for GCA, GDCA and TDCA. A higher percent binding of reference product at lower concentrations is observed for each bile salt, but the difference is negligible at higher concentrations (Table 15, Attachments 27-29).

- The T/R ratios for K1 and K2 values for individual bile salts ranged between respectively (Table 16).

- The mean total bile salt binding and T/R ratios are given in Table 16a. The average ratio at all strengths was 0.92 (range . The individual test and reference data are given in Tables 16b-16c).

Kinetics of Bile Salt Binding (Tables 17-18, Attachments 30-33).

- The T/R ratios of binding at 0.3 mM at various times ranged between with an average of 0.91 (Table 17). The amount of binding was uniform for each bile salt throughout the incubation period. The kinetic binding curves for the test and reference products were parallel for the most part (Attachment 30).

- The T/R ratios of binding at 3 mM at various time points ranged between with an average of 0.96 (Table 18). The amount of binding was uniform for each bile salt throughout the incubation period. The kinetic binding curves for the test and reference products were parallel for the most part (Attachments 31-33).

- The kinetics of total bile salts' binding at substrate concentrations of 0.3 and 3 mM are given in Tables 18a and 18b. The average T/R ratios were 0.88 (range), and 0.96 (range) for 0.3 and 3 mM total bile salt concentrations.

IX. Adverse Reactions

Not applicable

X. Formulation

Qualitatively the composition of test and reference cholestyramine and cholestyramine light

products are similar, but quantitatively they differ significantly. The amounts of propylene glycol alginate in cholestyramine, and aspartame and colloidal silicon dioxide in cholestyramine light is much higher than listed in the IIG (Tables 19 and 20).

XI. *In Vitro* Dissolution

Not applicable. The comparative assay values for test and reference cholestyramine and cholestyramine light are tabulated below:

	Cholestyramine		**Cholestyramine, *Light***	
	Test	**Reference**	**Test**	**Ref**
Lot #	266Z01	3J71B	300Z01	K3J21B
Mean, (%)	97.0	97.7	101.1	101.8
R.S.D. (%)	1.5	1.4	0.3	0.5
Range				
n	3	3	3	3

XII. Comments

A. Cholestyramine

1. In pivotal equilibrium binding study, without acid wash, the binding capacity constant (K2) data for the total bile acid salts' binding to cholestyramine, obtained by Langmuir's linear equation or by best-fit nonlinear equation, meet the 90% confidence interval with 20% allowance between the test and reference products (Tables 3, 4).

2. The ratio of mean total bile acid salts' binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equations, are within ±20% of the reference product (Tables 3, 4).

3. The test/reference ratios of mean equilibrium bindings at 0.1-30 mM concentrations ranged between (Table 2).

4. In kinetic studies at both 0.3 and 3.0 mM total bile salts' concentrations, the extent of binding was fairly constant over the 24 hour period (Tables 8-9c).

B. Cholestyramine *Light*

1. In the pivotal equilibrium binding study without acid wash, the binding capacity constant (K2) data for the total bile acid salts' binding to cholestyramine light, passes

the 90% confidence interval by the best-fit nonlinear equation. However, it does not pass the 90% CI by Langmuir's linear equation (Tables 12, 13). This parameter passes the bioequivalence criteria.

2. The ratio of total bile acid salts' binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equation, are outside the ±20% of the reference (Tables 12, 13). Thus, this parameter fails the bioequivalenc criteria.

3. The test/reference ratios of mean equilibrium bindings at 0.1-30 mM concentrations ranged between (Table 11).

4. In kinetic studies at both 0.3 and 3.0 mM total bile salts' concentrations, the extent of binding was fairly constant throughout the 24 hour period (Tables 17-18c).

XIII. Deficiency

1. In case of choletyramine light, the ratio of the mean of the total bile acid salt binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equation, are outside the ±20% of the reference. The firm should repeat the equilibrium binding study at 0.1-30 mM total bile salt concentrations, without acid pre-wash. The calculations should include the individual bile salt binding, total bile salts binding, basic statistics, affinity constants (linear and nonlinear K1), capacity constants (linear and nonlinear K2), test/reference ratios, and 90% confidence intervals (CI) for K2 parameter. The product must pass the 90% CI criteria of 80-120 for K2 parameter, and maintain a 0.8-1.2 ratio for K1 parameter.

XIV. Recommendations

1. The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine, 4 g resin/9 g dose, Lot # 266Z01, comparing it with Bristol-Myers Squibb's Questan^{R}, 4 g resin/dose unit, Lot #3J71B, has been found acceptable.

2. From the bioequivalence point of view, the firm has met the *in vitro* bioequivalence requirements for its cholestyramine, 4 g resin oral suspension powder. The studies demonstrate, that Copley's cholestyramine, 4 g resin, oral suspension formulation, is bioequivalent to Questran^{R}, 4 g resin, oral suspension, manufactured by Bristol Laboratories.

3. The binding capacity assay described in USP 23 should be incorporated into firm's manufacturing controls and stability program.

4. The acceptance of cholestyramine bioequivalence is pending a satisfactory inspection report by the Scientific Investigations (HFD-340), Office of Compliance, FDA.

5. The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine light, 4 g resin/5 g dose, Lot # 300Z01, comparing it with Bristol-Myers Squibb's Questran Light[R] , 4 g resin/dose unit, Lot #K3J21B, has been found unacceptable, because of the deficiency #1.

The firm should be informed of the deficiency and recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK /S/ Date 6/13/96

Concur: /S/ Date: 6/14/96

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

Attachments-33

SPS/sps/11-9-95/74554S.994

cc: ANDA #74554, 74555 (Original, Duplicate) HFD-600 (DHare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Shrivastava), Drug File, Division File

Table 10. Equilibrium Binding of Cholestyramine *Light* with Bile Acid Salts in SIF: *Without Acid Pretreatment*

Bile Acid Salt	Init. Conc mM	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.0429	43.43	12.32	100.00	—	0.43
	0.1286	44.13	14.86	64.13	6.08	0.69
	0.4286	42.90	4.34	58.92	1.82	0.73
	1.2857	43.63	6.08	51.10	2.49	0.85
	3.0000	39.13	6.57	42.75	6.01	0.92
	4.2857	30.35	6.64	30.69	6.25	0.99
	8.5714	21.22	10.17	20.24	8.26	1.05
	12.8571	17.04	12.22	17.80	5.06	0.96
	0.0429	100.00	—	100.00	—	1.00
	0.1286	84.63	14.60	100.00	—	0.85
	0.4286	79.63	1.76	89.91	0.62	0.89
	1.2857	81.32	2.52	87.58	1.71	0.93
	3.0000	69.44	3.84	76.39	2.20	0.91
	4.2857	55.98	6.65	60.90	1.99	0.92
	8.5714	36.30	6.78	36.18	6.09	1.00
	12.8571	27.26	8.39	28.17	4.79	0.97
	0.0143	100.00	—	100.00	—	1.00
	0.0429	89.88	12.30	100.00	—	0.90
	0.1429	84.85	3.77	94.53	3.00	0.90
	0.4286	90.00	1.55	94.00	3.30	0.96
	1.0000	79.50	4.71	86.12	1.30	0.92
	1.4286	68.40	7.76	73.06	1.89	0.94
	2.8571	46.93	5.98	46.06	6.13	1.02
	4.2857	34.96	9.74	36.57	4.94	0.96

Table 11. Statistical Treatment for Total Bile Salts Binding (mmoles/10 g Resin) at Equilibrium with Cholestyramine *Light*: *Without Acid Pretreatment*

Concentration (mM)	Test (mean)	Ref. (mean)	Ratio
0.1	0.7349	1.0001	0.73
0.3	2.0045	2.5388	0.79
1.0	6.4456	7.7289	0.83
3.0	19.9229	21.8593	0.91
7.0	40.5221	44.3538	0.91
10.0	46.7694	49.6903	0.94
20.0	62.7110	62.0178	1.01
30.0	71.9490	74.7794	0.96

Table 12. Affinity (K1) and Capacity (K2) Constants for Cholestyramine *Light* Powder: *Without Acid Pretreatment*, Linear Langmuir Equation Models

Replicate	Test K1	Ref K1	T/R K1	Test K2	Ref K2	T/R K2
		Langmuir Equation Model				
1						
2						
3						
4						
5						
6						
Mean	**0.2237**	**0.5839**	**0.38**	**8.0677**	**7.6552**	**1.06**
SD	**0.0428**	**0.0432**	**0.06**	**1.5391**	**0.4173**	**0.21**
CV, %	**19.131**	**7.3945**	**16.63**	**19.077**	**5.4515**	**19.44**
90% CI				**104.8-121.5**		

Table 13. Affinity (K1) and Capacity (K2) Constants for Cholestyramine *Light* Powder: *Without Acid Pretreatment*, Non-Linear Models

Replicate	Test K1	Ref K1	T/R K1	Test K2	Ref K2	T/R K2
		Non-Linear Model				
1						
2						
3						
4						
5						
6						
Mean	0.3075	0.4764333	0.65	8.1174	7.59375	1.07
SD	0.07157	0.0414204	0.17	0.7945	0.339893	0.09
CV, %	23.2741	8.693853	26.08	9.7877	4.475952	8.27
90% CI				99.5 114.3		

Table 14. Equilibrium Binding for Cholestyramine *Light* in SIF: *Without Acid Pretreatment* Estimates of Affinity (K2) and Capacity (K2) Constants

Bile Acid Salt	Constant	Test (T) Mean	CV % Test	Ref.(R) Mean	CV % Ref.	T/R
	K1	0.368	33.947	0.511	14.416	0.720
	K2	2.754	15.866	2.482	6.705	1.110
	K1 *	1.366	22.463	2.651	13.321	0.515
	K2	3.664	7.758	3.482	5.649	1.052
	K1*	5.029	28.845	9.007	14.732	0.558
	K2	1.563	7.722	1.496	5.703	1.045

* Significant difference between test and reference, $p < 0.01$

Table 15. Equilibrium Binding of Cholestyramine *Light* with Bile Acid Salts in SIF: *With Acid Pretreatment*

Bile Acid Salt	Init. Conc mM	Test (T) Mean %	CV (%) Test	Ref. (R) Mean %	CV % Ref.	T/R Ratio
	0.0429	41.42	13.00	100.00	---	0.41
	0.1286	41.01	5.91	61.76	4.00	0.66
	0.4286	38.96	6.20	55.50	6.90	0.70
	1.2857	35.96	20.00	41.84	22.60	0.86
	3.0000	30.55	6.10	35.12	9.90	0.87
	4.2857	23.13	5.80	23.11	7.30	1.00
	8.5714	12.64	9.70	9.82	20.70	1.29
	12.8571	8.62	28.30	7.57	34.00	1.14
	0.0429	100.00	---	100.00	---	1.00
	0.1286	96.91	7.80	100.00	---	0.97
	0.4286	81.76	1.63	90.18	1.26	0.91
	1.2857	78.50	10.32	81.03	13.07	0.97
	3.0000	65.00	4.64	71.70	6.81	0.91
	4.2857	52.05	4.28	53.86	6.25	0.97
	8.5714	27.89	3.69	28.07	7.24	0.99
	12.8571	19.55	10.35	19.68	11.62	0.99
	0.0143	89.82	25.30	100.00	---	0.90
	0.0429	100.00	---	97.03	7.50	1.03
	0.1429	89.39	1.31	95.84	3.60	0.93
	0.4286	88.71	10.60	89.98	12.80	0.99
	1.0000	78.09	4.26	82.73	5.28	0.94
	1.4286	68.00	4.11	68.99	5.59	0.99
	2.8571	40.77	1.94	40.71	4.91	1.00
	4.2857	29.56	6.00	29.33	7.74	1.01

Table 16. Equilibrium Binding for Cholestyramine *Light* in SIF: *with Acid Pretreatment*
Estimates of Affinity (K2) and Capacity (K2) Constants

Bile Acid Salt	Constant	Test (T) Mean	CV % Test	Ref. (R) Mean	CV % Ref.	T/R
	K1	0.963*	40.80	2.314	43.71	0.42
	K2	1.386*	38.17	1.141	33.89	1.21
	K1	2.648*	34.36	4.209	38.99	0.63
	K2	2.657	11.25	2.652	12.10	1.00
	K1	7.924*	42.78	10.818	39.11	0.73
	K2	1.303	9.20	1.280	10.86	1.02

* Significant difference between test and reference, $p < 0.05$

Table 16a. Average Total Equilibrium Binding (mmole/10g Resin) and Test vs Reference Ratios for *Acid Pretreated* Cholestyramine *Light* Resin

Concentration, mM	Test (T)	Reference (R)	T/R Ratio
0.10	0.7349	1.0001	0.73
0.30	2.2017	2.4955	0.88
1.00	6.4508	7.6124	0.85
3.00	18.5065	19.6534	0.94
7.00	36.4752	40.3181	0.90
10.00	41.9320	42.7774	0.98
20.00	46.3882	44.1083	1.05
30.00	48.8913	47.6020	1.03

ble 16b. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine *Light* Resin in SIF Copley (Test) Product (mmole/10 g Resin)

Conc., mM	Bile Salt	T-1	T-2	T-3	T-4	T-5	T-6	AVE	SD	%CV
0.1		0.1617		0.1890	0.1911	0.1461	0.2006	0.1777	0.02	12.85
		0.4286		0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		0.1429		0.1429	0.1429	0.0714	0.1429	0.1286	0.03	24.86
		0.7332		0.7605	0.7626	0.6461	0.7721	0.7349	0.05	7.04
	%	73.31		76.04	76.25	64.60	77.20	73.48	5.17	7.04
0.3		0.5614	0.5331	0.5426	0.5267	0.5306	0.4689	0.5272	0.03	5.91
		1.2857	1.2857	1.2857	1.0470	1.2857	1.2857	1.2459	0.10	7.82
		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		2.2757	2.2474	2.2569	2.0023	2.2449	2.1832	2.2017	0.10	4.66
	%	75.86	74.91	75.23	66.74	74.83	72.77	73.39	3.42	4.66
1		1.5373	1.6187	1.6873	1.7850	1.7927	1.5977	1.6698	0.10	6.23
		3.4513	3.4534	3.4616	3.5906	3.5370	3.5301	3.5040	0.06	1.63
		1.2640	1.2757	1.2537	1.2797	1.2886	1.3004	1.2770	0.02	1.31
		6.2526	6.3478	6.4026	6.6553	6.6183	6.4282	6.4508	0.16	2.43
	%	62.53	63.48	64.03	66.55	66.18	64.28	64.51	1.57	2.43
3		4.9389	4.8673	2.7523	4.8904	5.0567	5.2359	4.6236	0.93	20.04
		10.4627	10.4773	7.9843	10.4293	10.7773	10.4259	10.0928	1.04	10.32
		3.7207	3.9939	3.1084	4.0009	4.2143	3.7024	3.7901	0.39	10.17
		19.1223	19.3385	13.8450	19.3206	20.0483	19.3642	18.5065	2.31	12.46
	%	63.74	64.46	46.15	64.40	66.83	64.55	61.69	7.69	12.46

ble 16b. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine *Light* Resin in SIF Copley Product (mmole/10 g Resin), Continued,

Conc., mM	Bile Salt	T-1	T-2	T-3	T-4	T-5	T-6	AVE	SD	%CV
7		9.1941	9.5580	8.0833	9.6137	9.2267	9.3154	9.1652	0.56	6.08
		20.0927	19.6941	17.6751	19.9431	19.8484	19.7507	19.5007	0.91	4.64
		7.9650	8.0371	7.1487	7.9990	7.8211	7.8847	7.8093	0.33	4.26
		37.2518	37.2892	32.9071	37.5558	36.8962	36.9508	36.4752	1.76	4.84
	%	53.22	53.27	47.01	53.65	52.71	52.79	52.11	2.52	4.84
10		8.8551	10.2244	9.6591	10.1880	10.1143	10.4241	9.9108	0.58	5.81
		20.7399	23.3837	21.6801	22.7867	22.3800	22.8746	22.3075	0.96	4.28
		9.1301	10.2827	9.4001	9.8211	9.8240	9.8239	9.7137	0.40	4.11
		38.7251	43.8908	40.7393	42.7958	42.3183	43.1226	41.9320	1.89	4.51
	%	38.73	43.89	40.74	42.80	42.32	43.12	41.93	1.89	4.51
20		10.3067	10.1031	12.846	10.067	10.6149	11.055	10.8321	1.05	9.72
		23.3233	23.577	25.425	23.262	23.3336	24.529	23.9082	0.88	3.69
		11.5213	11.7617	11.998	11.385	11.7366	11.485	11.6479	0.23	1.94
		45.1513	45.4418	50.268	44.714	45.6851	47.069	46.3882	2.06	4.44
	%	22.58	22.72	25.13	22.36	22.84	23.53	23.19	1.03	4.44
30		9.3741	10.9976	17.26	10.547	8.6477	9.6896	11.086	3.14	28.31
		23.3627	23.4146	30.143	24.25	23.9023	25.76	25.1387	2.60	10.35
		12.1223	11.9691	14.003	12.197	12.7301	12.977	12.6665	0.76	6.00
		44.8591	46.3813	61.406	46.994	45.2801	48.426	48.8913	6.26	12.81
	%	14.95	15.46	20.47	15.66	15.09	16.14	16.30	2.09	12.81

Table 16c. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine *Light* Resin in SIF Bristol Labs. (Reference) Product (mmole/10 g Resin)

Conc., mM	Bile Salt	R-1	R-2	R-3	R-4	R-5	R-6	AVE	SD	%CV
0.1		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.4286	0.00	0.00
		0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.1429	0.00	0.00
		1.0001	1.0001	1.0001	1.0001	1.0001	1.0001	1.0001	0.00	0.00
	%	100.00	100.00	100.00	100.00	100.00	100.00	100.00	0.00	0.00
0.3		0.8276	0.7551	0.7654	0.7787	0.8121	0.8250	0.7940	0.03	3.98
		1.2857	1.2857	1.2857	1.2857	1.2857	1.2857	1.2857	0.00	0.00
		0.4286	0.4286	0.4286	0.4286	0.4286	0.3521	0.4159	0.03	7.51
		2.5419	2.4694	2.4797	2.4930	2.5264	2.4628	2.4955	0.03	1.28
	%	84.73	82.31	82.66	83.10	84.21	82.09	83.18	1.07	1.28
1		2.5491	2.3036	2.1994	2.6117	2.3164	2.2903	2.3784	0.16	6.85
		3.9309	3.8430	3.8126	3.9154	3.8237	3.8640	3.8649	0.05	1.26
		1.4286	1.3569	1.3376	1.3531	1.3097	1.4286	1.3691	0.05	3.58
		7.9086	7.5035	7.3496	7.8802	7.4498	7.5829	7.6124	0.23	3.04
	%	79.09	75.04	73.50	78.80	74.50	75.83	76.12	2.31	3.04
3		6.0694	5.5509	3.0073	5.6829	5.5144	6.4513	5.3794	1.22	22.60
		11.0713	10.8981	7.6487	10.8493	10.8814	11.1583	10.4179	1.36	13.07
		3.7984	3.9231	2.9390	3.9054	4.2857	4.2857	3.8562	0.49	12.81
		20.9391	20.3721	13.5950	20.4376	20.6815	21.8953	19.6534	3.02	15.36
	%	69.80	67.91	45.32	68.13	68.94	72.98	65.51	10.06	15.36

Table 16c. Equilibrium Binding Of Bile Acid Salts to *Acid Pretreated* Cholestyramine *Light* Resin in SIF Reference Product (mmole/10 g Resin), Continued

Conc., mM	Bile Salt	R-1	R-2	R-1	R-4	R-5	R-6	AVE	SD	%CV
7		11.2551	10.0907	8.5959	11.0289	11.0949	11.1484	10.5357	1.04	9.87
		22.3470	20.8496	18.8730	21.6964	22.7734	22.5163	21.5093	1.47	6.81
		8.5237	8.2770	7.4266	8.4663	8.3011	8.6441	8.2731	0.44	5.28
		42.1258	39.2173	34.8955	41.1916	42.1694	42.3088	40.3181	2.90	7.19
	%	60.18	56.02	49.85	58.85	60.24	60.44	57.60	4.14	7.19
10		10.6783	10.0179	9.7731	9.9497	8.5933	10.4147	9.9045	0.72	7.30
		24.4721	23.3550	22.1306	22.9834	20.8886	24.2730	23.0171	1.35	5.87
		10.3383	9.8644	9.4914	9.8754	9.0271	10.5379	9.8558	0.55	5.59
		45.4887	43.2373	41.3951	42.8085	38.5090	45.2256	42.7774	2.60	6.07
	%	45.49	43.24	41.40	42.81	38.51	45.23	42.78	2.60	6.07
20		8.7887	5.9807	10.5741	8.5723	6.8027	9.7641	8.4138	1.74	20.70
		25.7627	21.7620	26.0169	23.8731	22.3719	24.5936	24.0634	1.74	7.24
		12.2526	10.6966	11.9791	11.5274	11.3229	12.0084	11.6312	0.57	4.91
		46.8040	38.4393	48.5701	43.9728	40.4975	46.3661	44.1083	3.94	8.92
	%	23.40	19.22	24.29	21.99	20.25	23.18	22.05	1.97	8.92
30		9.6317	8.7831	16.3076	7.9929	7.4503	8.2324	9.7330	3.31	33.96
		24.6887	23.2457	29.8710	23.6623	22.4207	27.9009	25.2982	2.94	11.62
		12.1886	11.4361	14.0497	11.9597	12.3794	13.4109	12.5707	0.97	7.74
		46.5090	43.4649	60.2283	43.6149	42.2504	49.5442	47.6020	6.72	14.12
	%	15.50	14.49	20.08	14.54	14.08	16.51	15.87	2.24	14.12

Table 17. Kinetics of Binding of Cholestyramine *Light* with Bile Acid Salts:
Total Concentration *0.3 mM*, Incubated with 0.1 M Sodium Chloride

Bile Acid Salt	Incub. Period, Hr	Test (T) Mean %	CV (%) Test	Ref (R) Mean %	CV % Ref.	T/R Ratio
	0.25	37.27	9.56	51.20	4.74	0.73
	0.50	42.03	23.74	53.57	6.35	0.78
	1.00	39.94	3.52	53.48	7.73	0.75
	2.00	49.41	16.45	39.70	7.65	1.24
	4.00	43.70	14.82	53.17	3.80	0.82
	8.00	42.95	4.87	55.74	5.72	0.77
	16.00	42.52	6.29	58.91	7.07	0.72
	24.00	43.46	8.59	58.53	2.49	0.74
	0.25	76.19	4.01	93.74	10.30	0.81
	0.50	78.96	13.80	97.00	7.60	0.81
	1.00	77.24	3.13	94.30	9.40	0.82
	2.00	92.78	12.20	76.10	2.73	1.22
	4.00	77.80	2.91	96.67	8.40	0.80
	8.00	87.15	11.50	100.00	—	0.87
	16.00	90.40	11.80	100.00	—	0.90
	24.00	87.31	11.30	100.00	—	0.87
	0.25	93.43	10.90	97.03	7.50	0.96
	0.50	92.12	13.30	100.00	—	0.92
	1.00	88.67	14.50	100.00	—	0.89
	2.00	96.92	7.80	84.64	9.10	1.15
	4.00	93.57	10.70	100.00	—	0.94
	8.00	96.83	8.00	100.00	—	0.97
	16.00	100.00	—	100.00	—	1.00
	24.00	85.98	20.80	100.00	—	0.86

Table 18. Kinetics of Binding of Cholestyramine *Light* with Bile Acid Salts: Total Concentration *3.0 mM*, Incubated with 0.1 M Sodium Chloride

Bile Acid Salt	Incub. Period, Hr	Test (T) Mean %	CV (%) Test	Ref (R) Mean %	CV % Ref.	T/R Ratio
	0.25	32.08	23.92	30.46	6.76	1.05
	0.50	26.67	7.03	30.07	7.10	0.89
	1.00	25.79	10.99	31.37	8.29	0.82
	2.00	27.67	7.42	32.59	2.88	0.85
	4.00	32.53	35.71	34.01	6.85	0.96
	8.00	36.78	4.58	39.36	6.58	0.93
	16.00	28.57	6.73	33.94	7.53	0.84
	24.00	34.06	8.82	39.16	9.10	0.87
	0.25	70.36	5.52	69.58	1.69	1.01
	0.50	66.99	2.96	68.78	2.96	0.97
	1.00	66.76	3.37	69.87	2.58	0.96
	2.00	67.85	2.35	70.63	2.74	0.96
	4.00	70.80	9.19	72.93	4.48	0.97
	8.00	77.53	0.73	79.53	2.14	0.97
	16.00	73.03	1.60	76.28	3.42	0.96
	24.00	75.55	1.75	78.48	3.11	0.96
	0.25	82.68	2.06	81.16	0.82	1.02
	0.50	80.94	2.25	81.01	1.31	1.00
	1.00	80.35	2.11	81.00	1.54	0.99
	2.00	80.81	1.98	81.94	2.19	0.99
	4.00	83.34	4.37	83.04	3.06	1.00
	8.00	87.39	0.51	88.10	1.59	0.99
	16.00	86.01	0.93	86.43	1.81	1.00
	24.00	86.42	1.28	87.11	1.50	0.99

Table 18a. Kinetics of Total Bile Acid Salt Binding at *0.3 mM Conc.* to Cholestyramine *Light* (μmole/g Resin)

Time, Hrs	Test (T)	Reference (R)	Ratio, T/R
0.25	185.906	227.940	0.82
0.50	195.034	236.445	0.82
1.00	188.658	231.633	0.81
2.00	224.241	185.159	1.21
4.00	196.311	235.509	0.83
8.00	208.769	243.092	0.86
16.00	213.746	247.164	0.86
24.00	204.982	246.678	0.83

Table 18b. Kinetics of Total Bile Acid Salt Binding at *3 mM Conc.* to Cholestyramine *Light* (μmole/g Resin)

Time, Hrs	Test (T)	Reference (R)	Ratio, T/R
0.25	1671.393	1634.031	1.02
0.50	1551.129	1618.035	0.96
1.00	1534.224	1648.784	0.93
2.00	1574.417	1678.376	0.94
4.00	1685.621	1730.778	0.97
8.00	1844.260	1906.185	0.97
16.00	1674.905	1787.631	0.94
24.00	1779.604	1885.917	0.94

TABLE 19. Comparison of Cholestyramine Formulations
(Lot Size - kg or dose units)

Ingredients	Test	Questran[R] Powder
	(Amount in g/9 g/Scoopful)	
Cholestyramine Resin, USP		
Propylene Glycol Alginate, NF		
Sucrose, NF		
Citric Acid, Anhydrous		
Flavor, Spray-Dried, Orange		
D&C Yellow #10, Al Lake (17%)		
FD&C Yellow #6, Al Lake (40%)		

* Includes 12% USP moisture equivalent to 4.0 gm cholestyramine resin anhydrous/dose.
** Listed as ingredient without quantitative or purity information.

TABLE 20. Comparison of Cholestyramine *Light* Formulations
(Lot Size - kg or dose units)

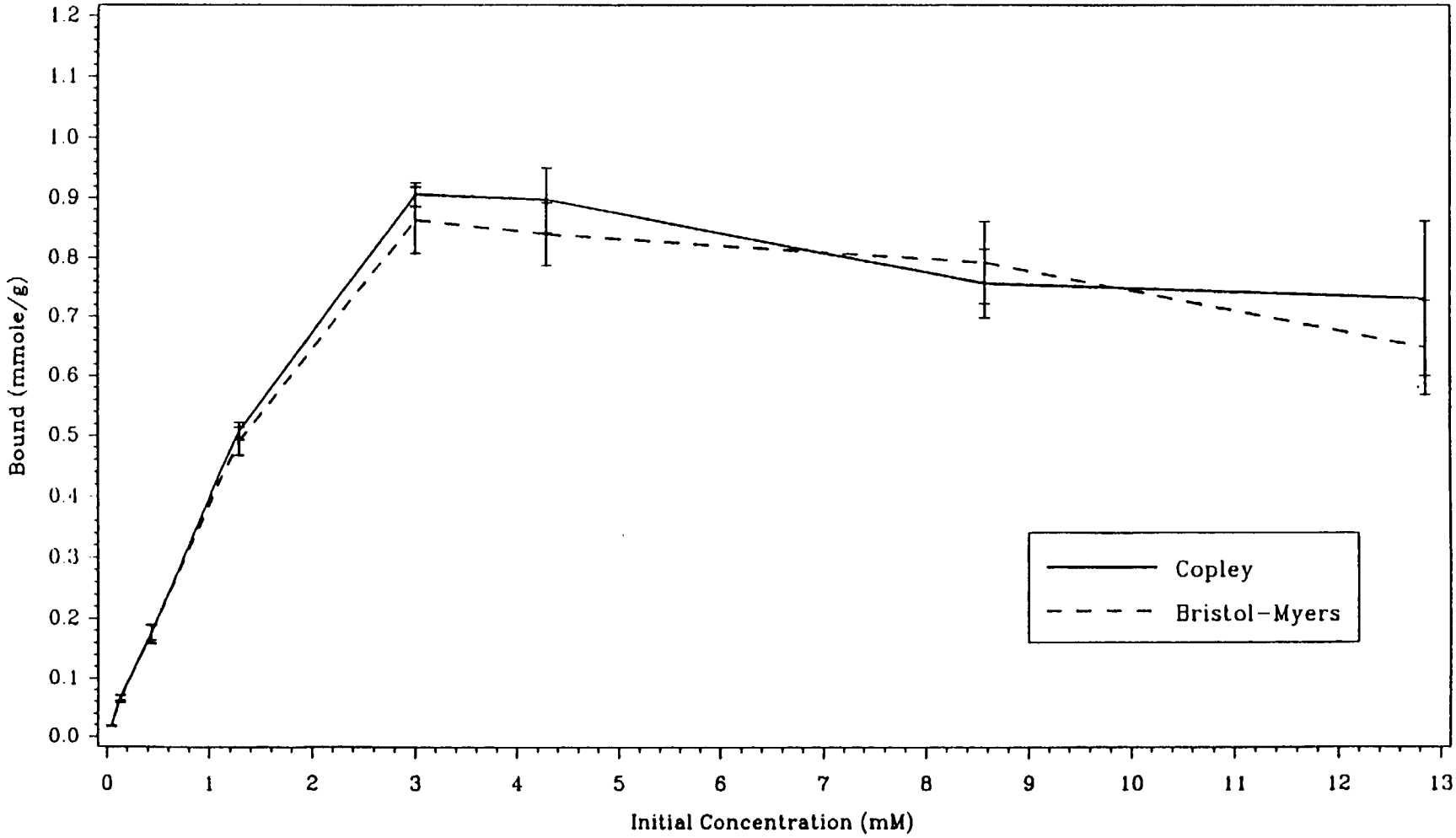
Ingredients	Test	Questran[R] Light
	(Amount in g/5 g/Scoopful)	
Cholestyramine Resin, USP		
Propylene Glycol Alginate, NF		
Xanthum Gum, NF		
Sucrose, NF		
Citric Acid, Anhydrous		
D&C Yellow #10, Lake (40%)		
FD&C Red #40, Lake (14-16%)		
Aspartame, NF (Neutasweet)		
Colloidal Silicon Dioxide, NF		

* Includes 12% moisture, equivalent to 4.0 gm cholestyramine resin anhydrous/dose.

Attachment - 1

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

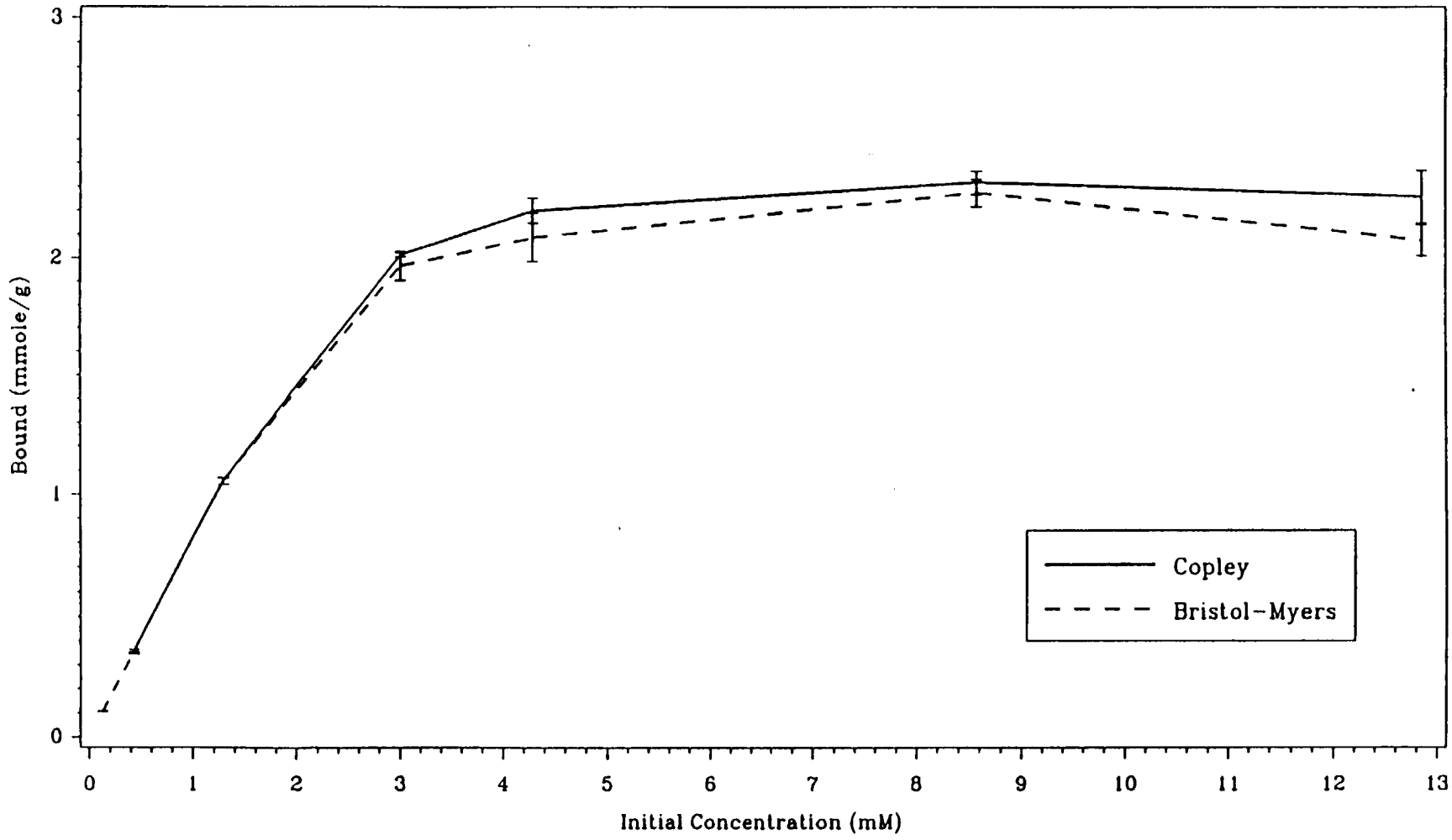
Figure 1-A: GCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment-2

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

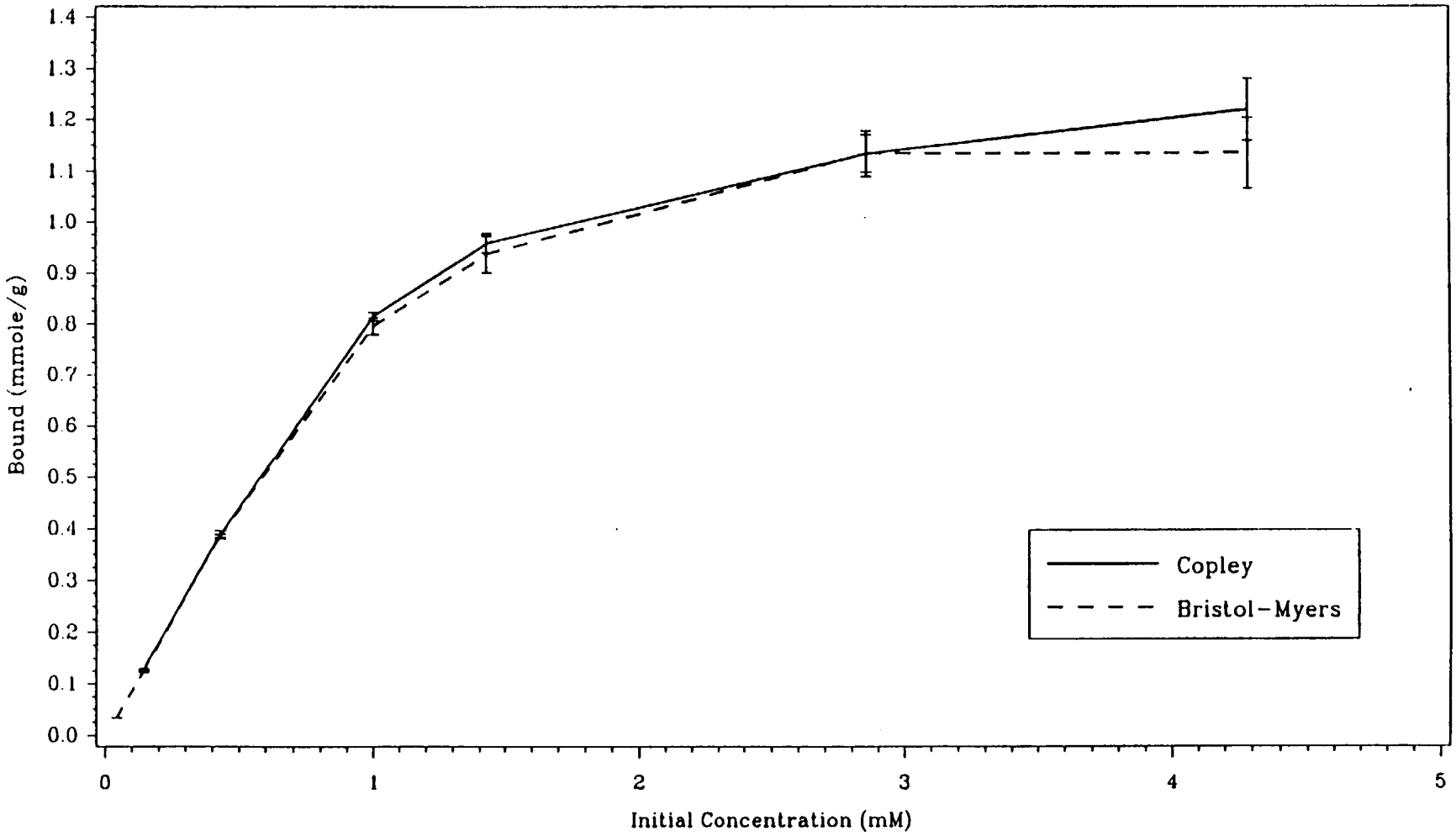
Figure 1-B: GCDA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 3

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

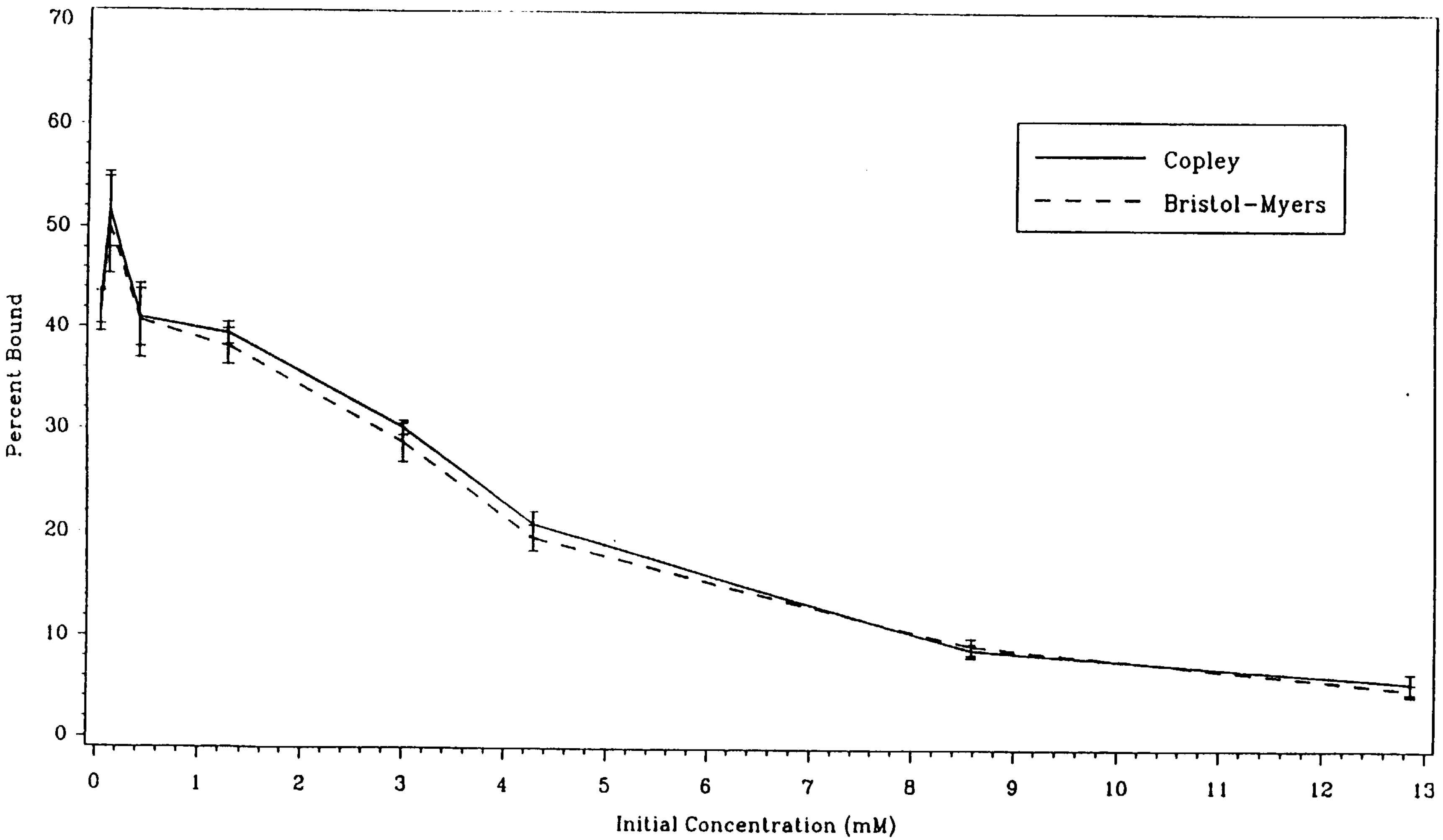
Figure 1-C: TDCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 4

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

Figure 2–A: GCA Percent Bound
Mean ± Standard Error (n = 6)



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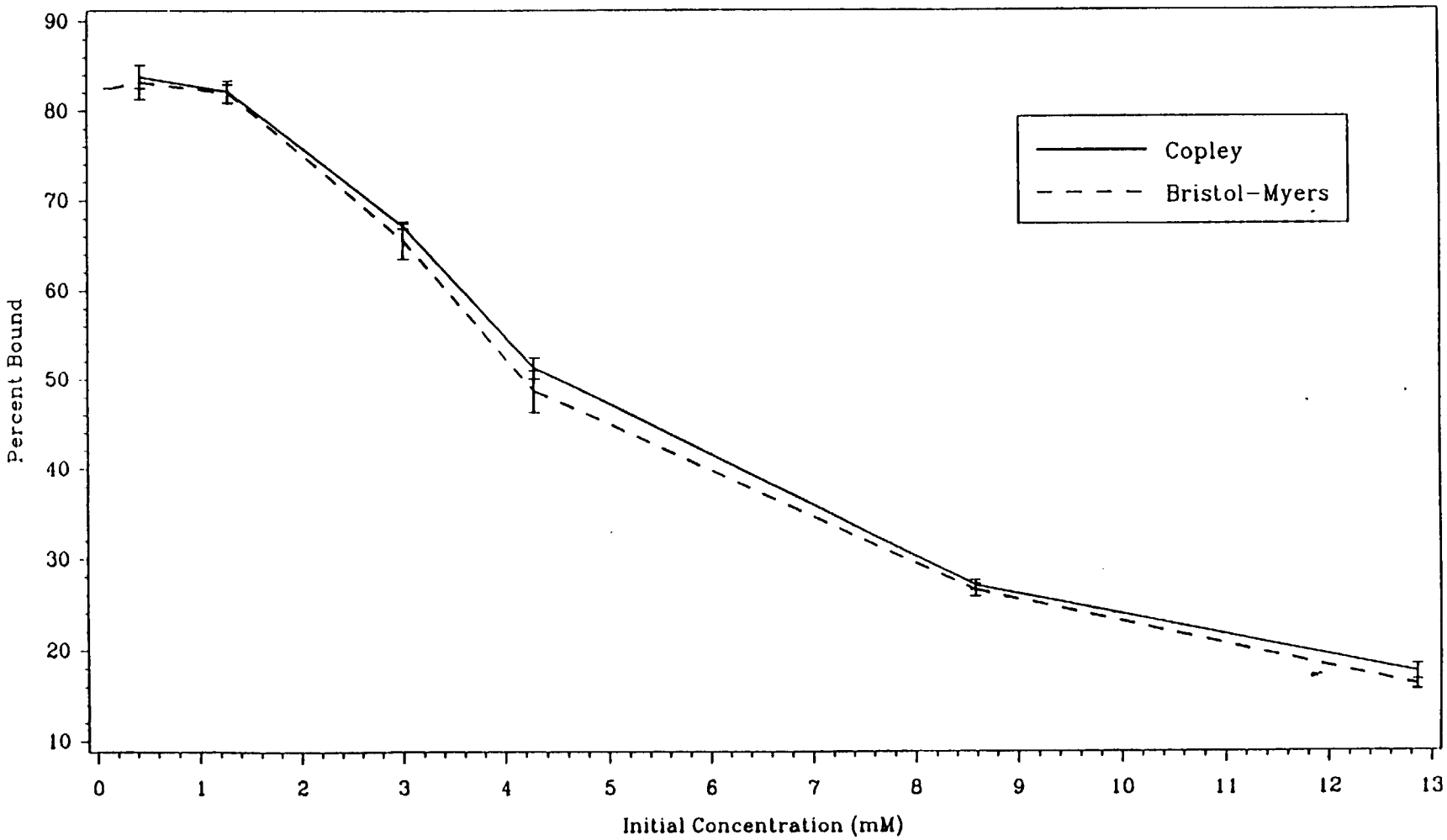
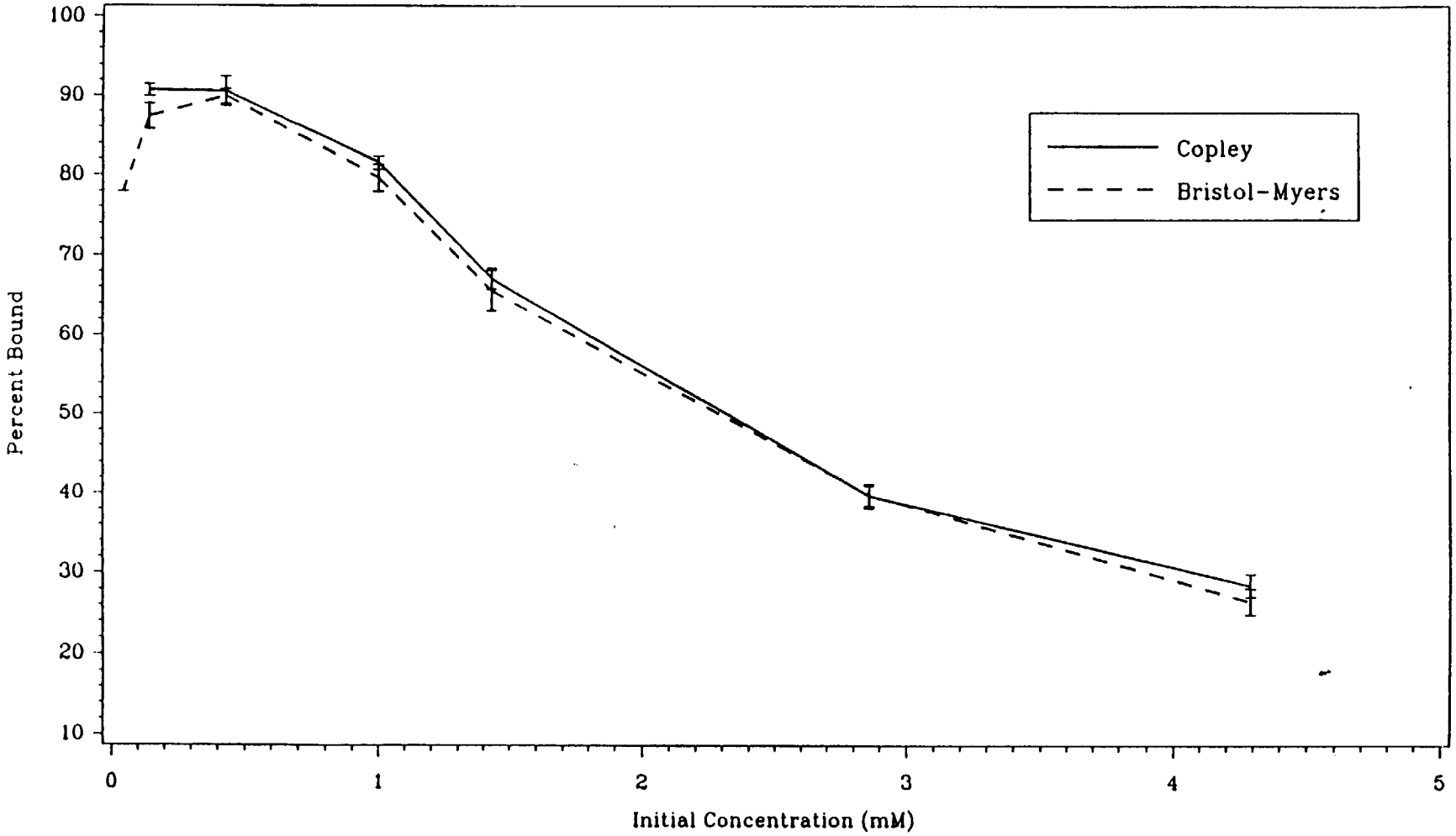
In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

Figure 2-B: GCDA Percent Bound
Mean ± Standard Error (n = 6)



In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

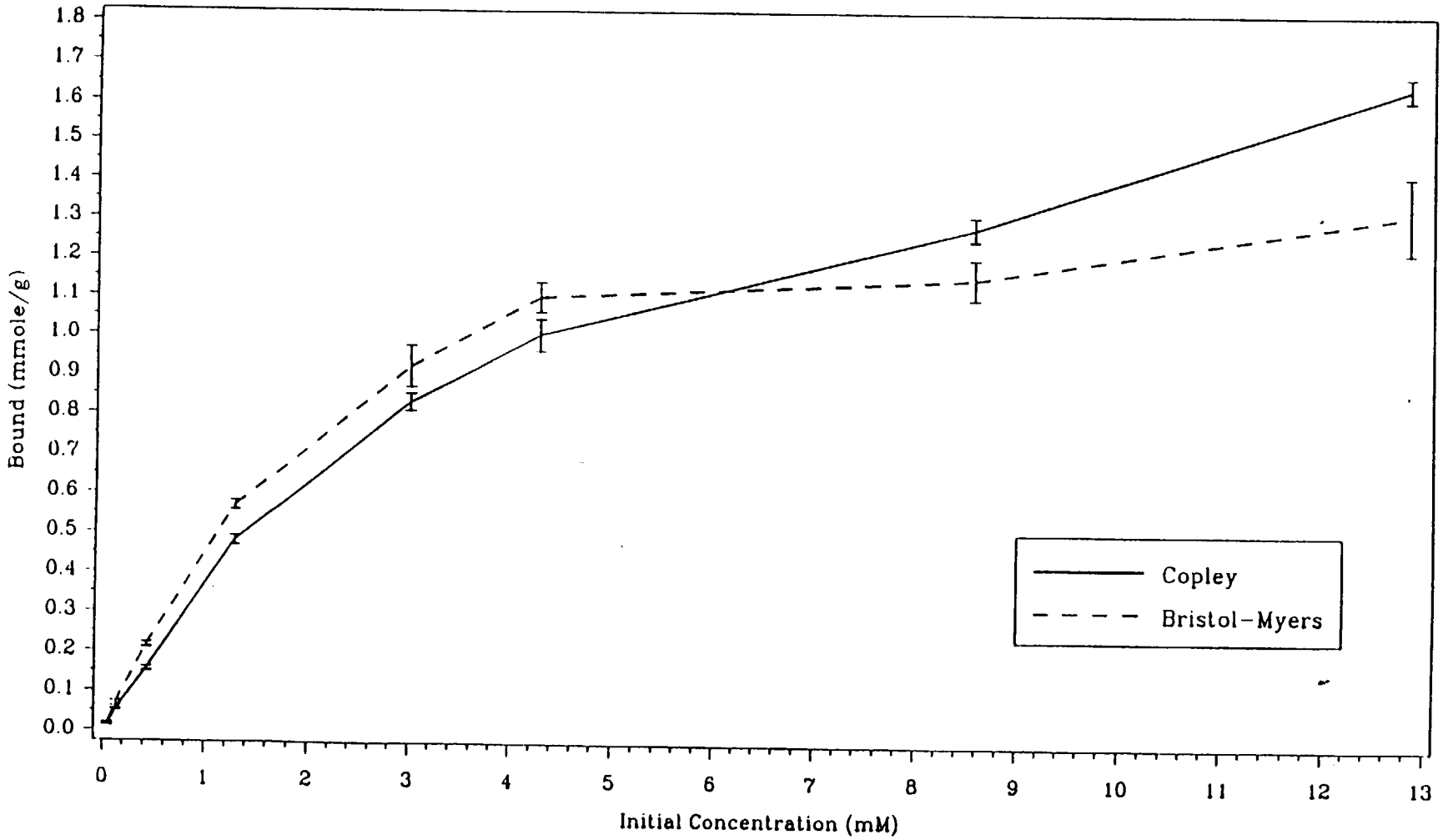
Figure 2-C: TDCA Percent Bound
Mean ± Standard Error (n = 6)



Attachment - 7

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

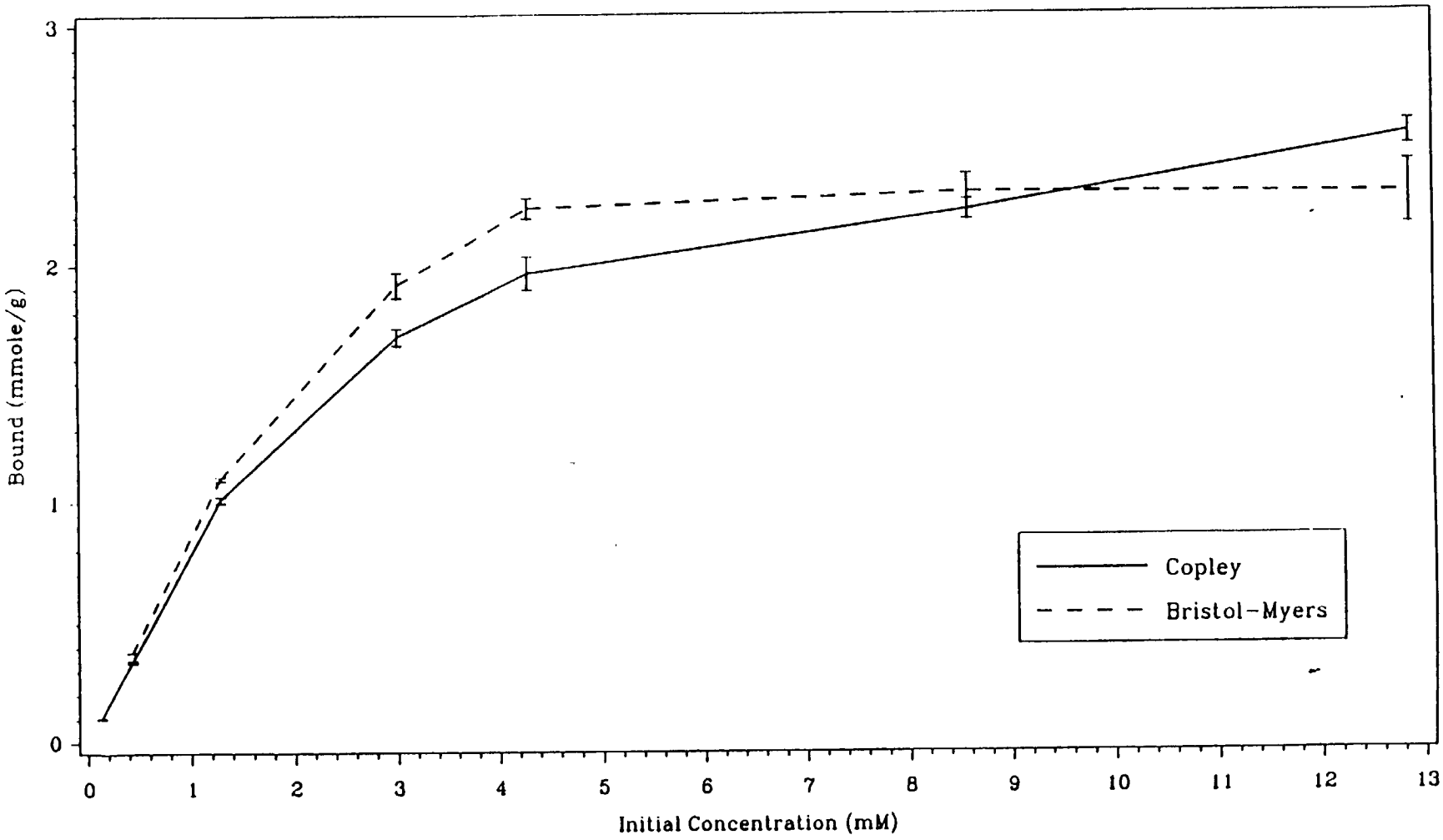
Figure 3-A: GCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 8

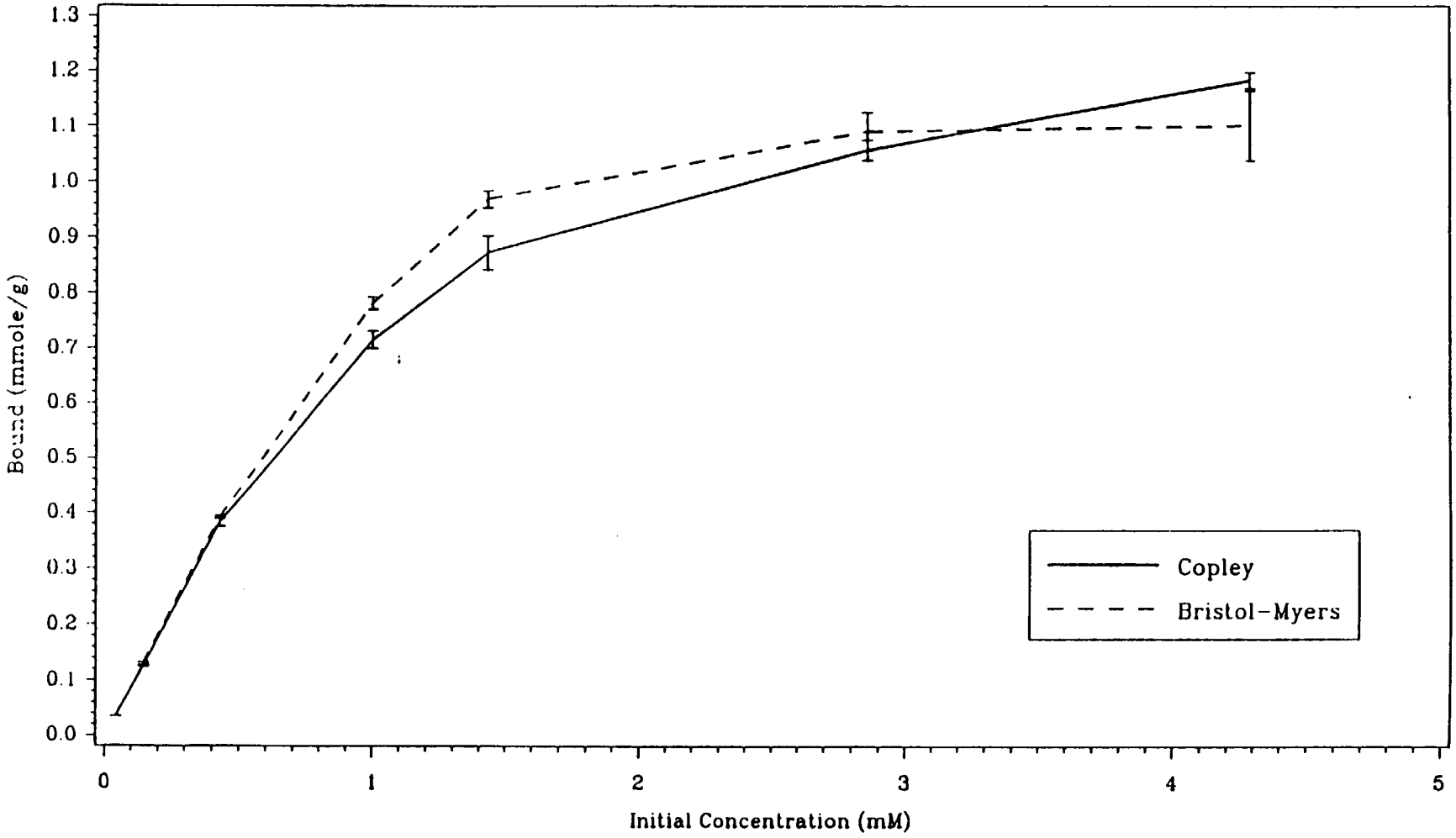
In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

Figure 3-B: GCDA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

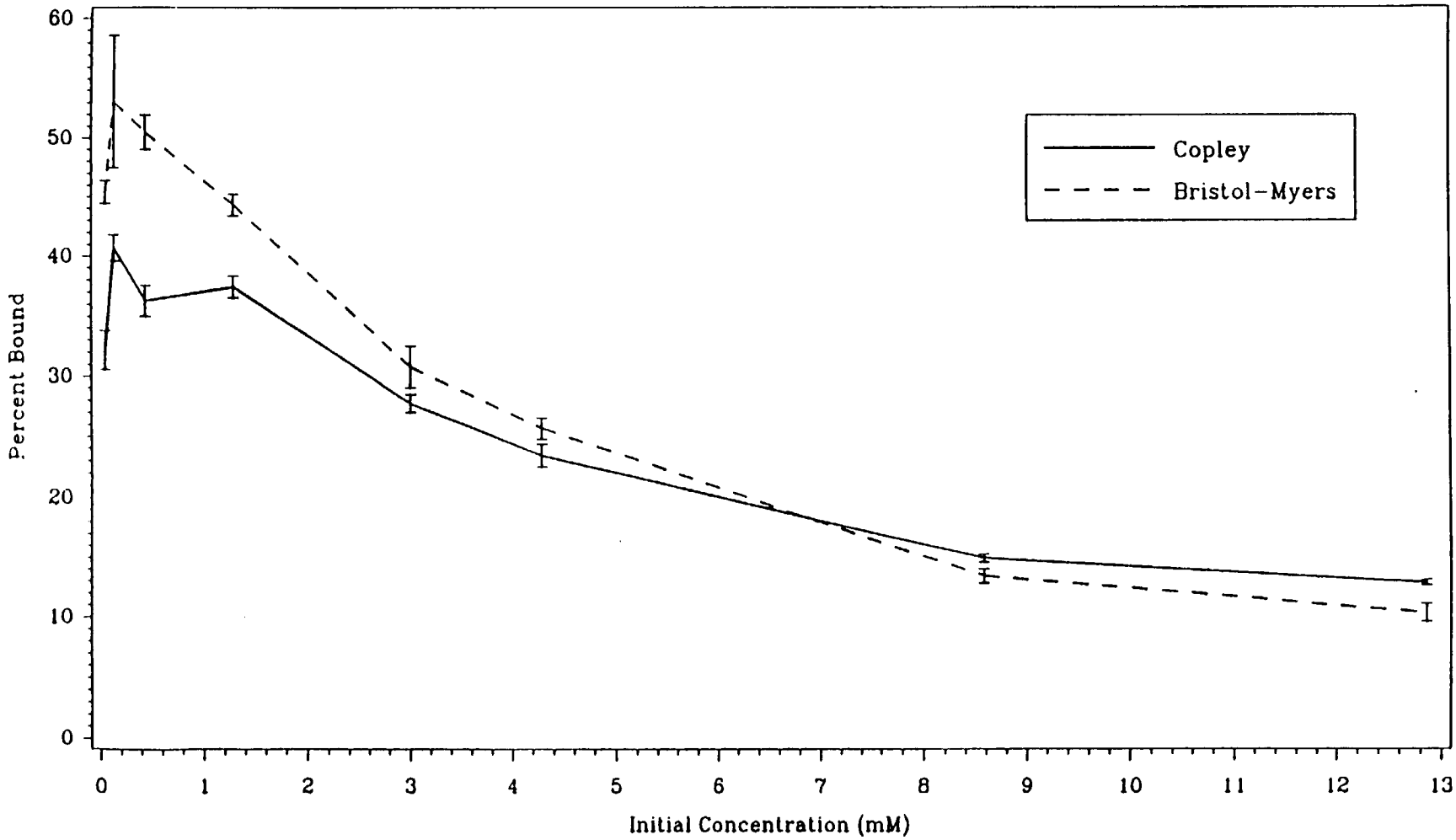
Figure 3-C: TDCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 10

In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

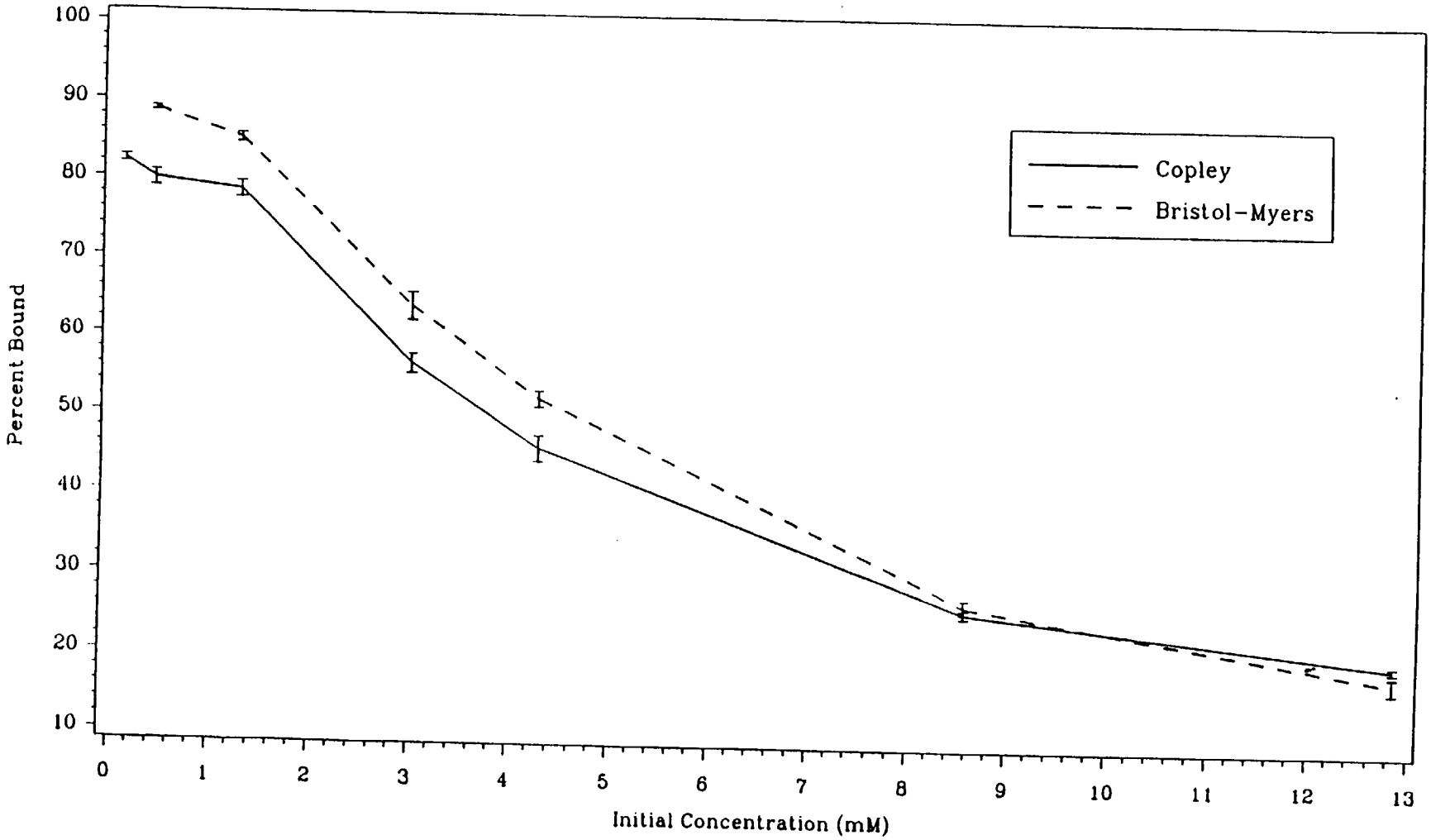
Figure 4-A: GCA Percent Bound
Mean ± Standard Error (n = 6)



Attachment - 11

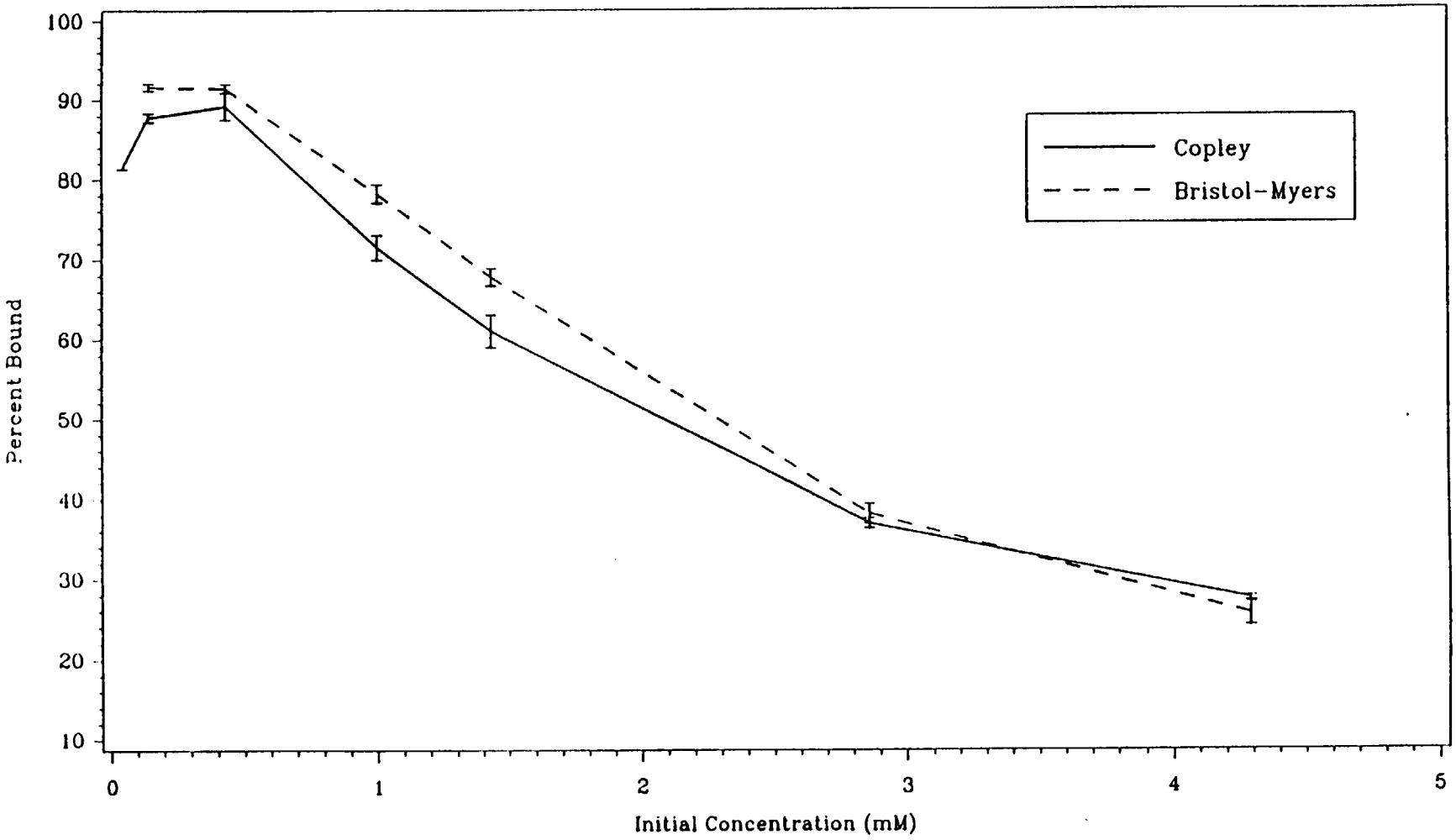
In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

Figure 4-B: GCDA Percent Bound
Mean ± Standard Error (n = 6)



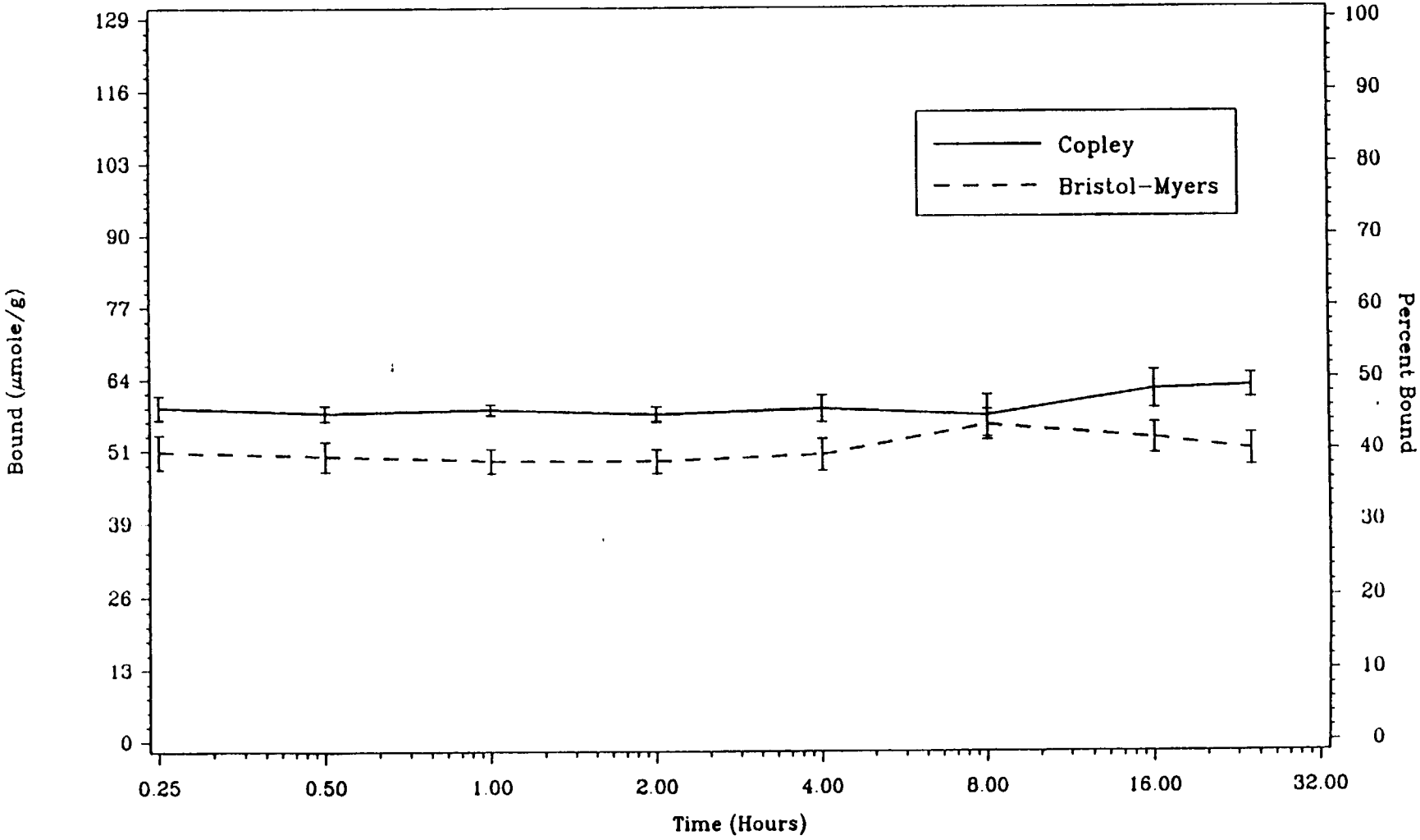
In Vitro Bioequivalence Study of Cholestyramine Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

Figure 4-C: TDCA Percent Bound
Mean ± Standard Error (n = 6)

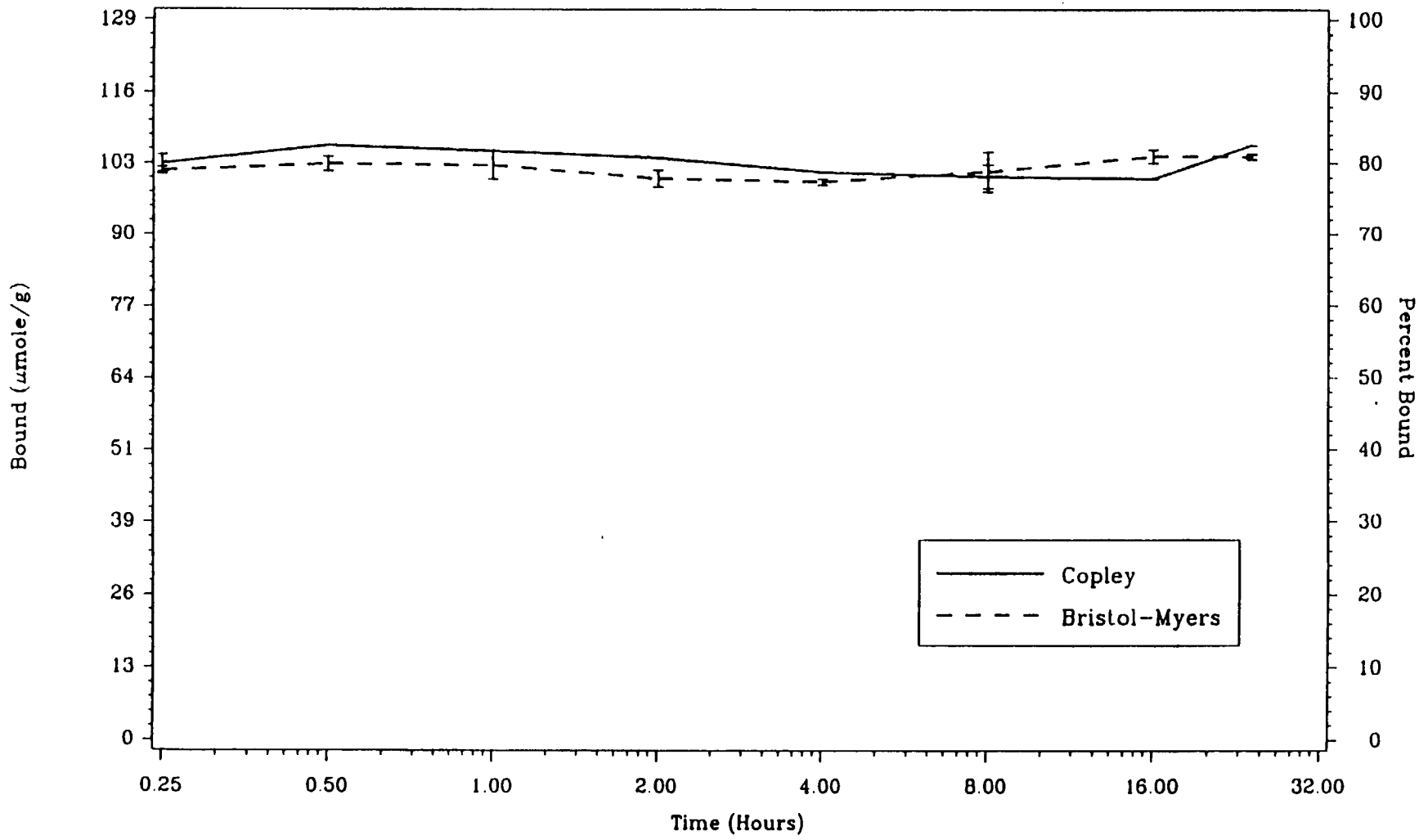


Attachment

In Vitro Bioequivalence Study of Cholestyramine Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 0.3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 5–A: GCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error (n = 6)

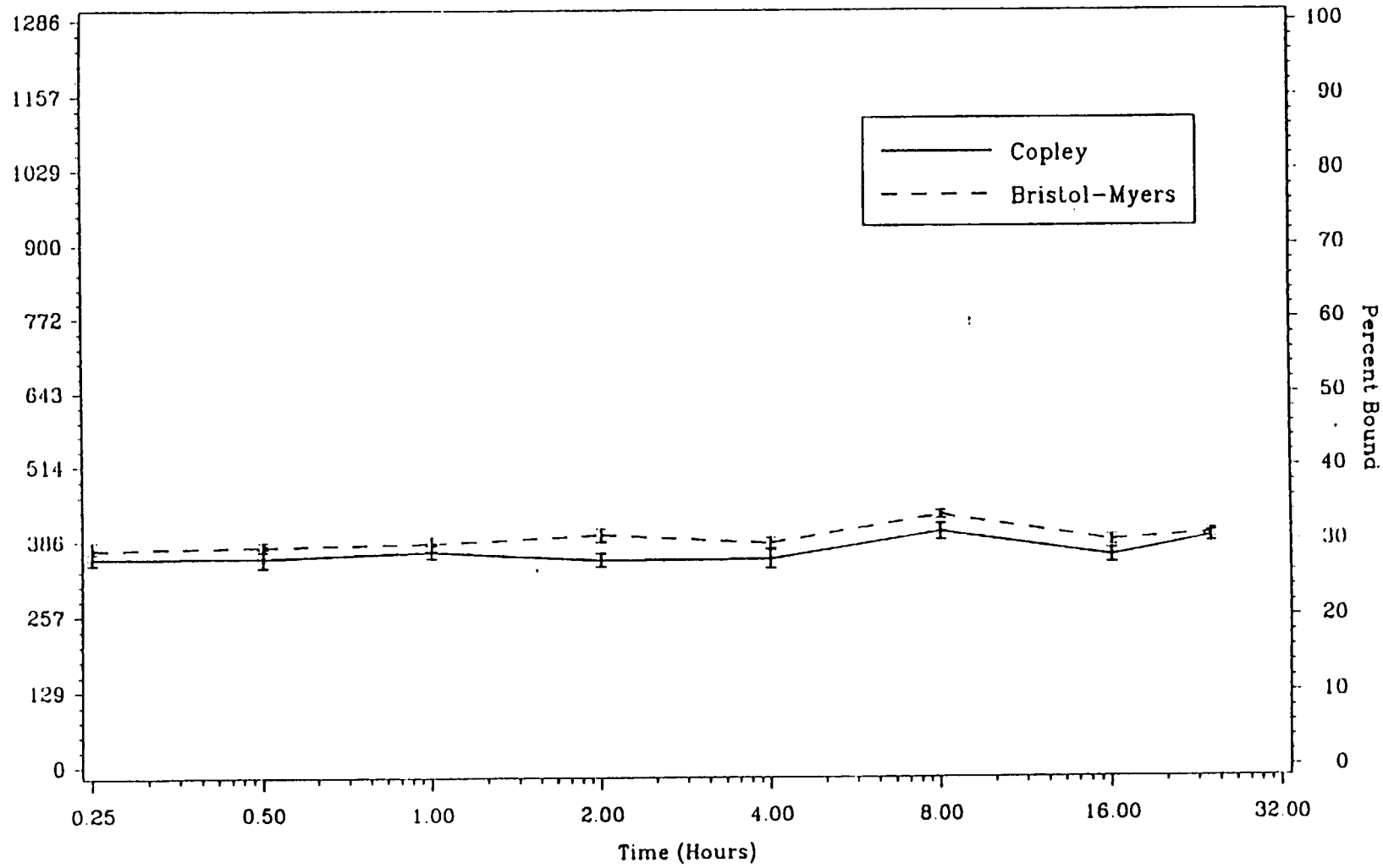


In Vitro Bioequivalence Study of Cholestyramine Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 0.3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 5-B: GCDA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error



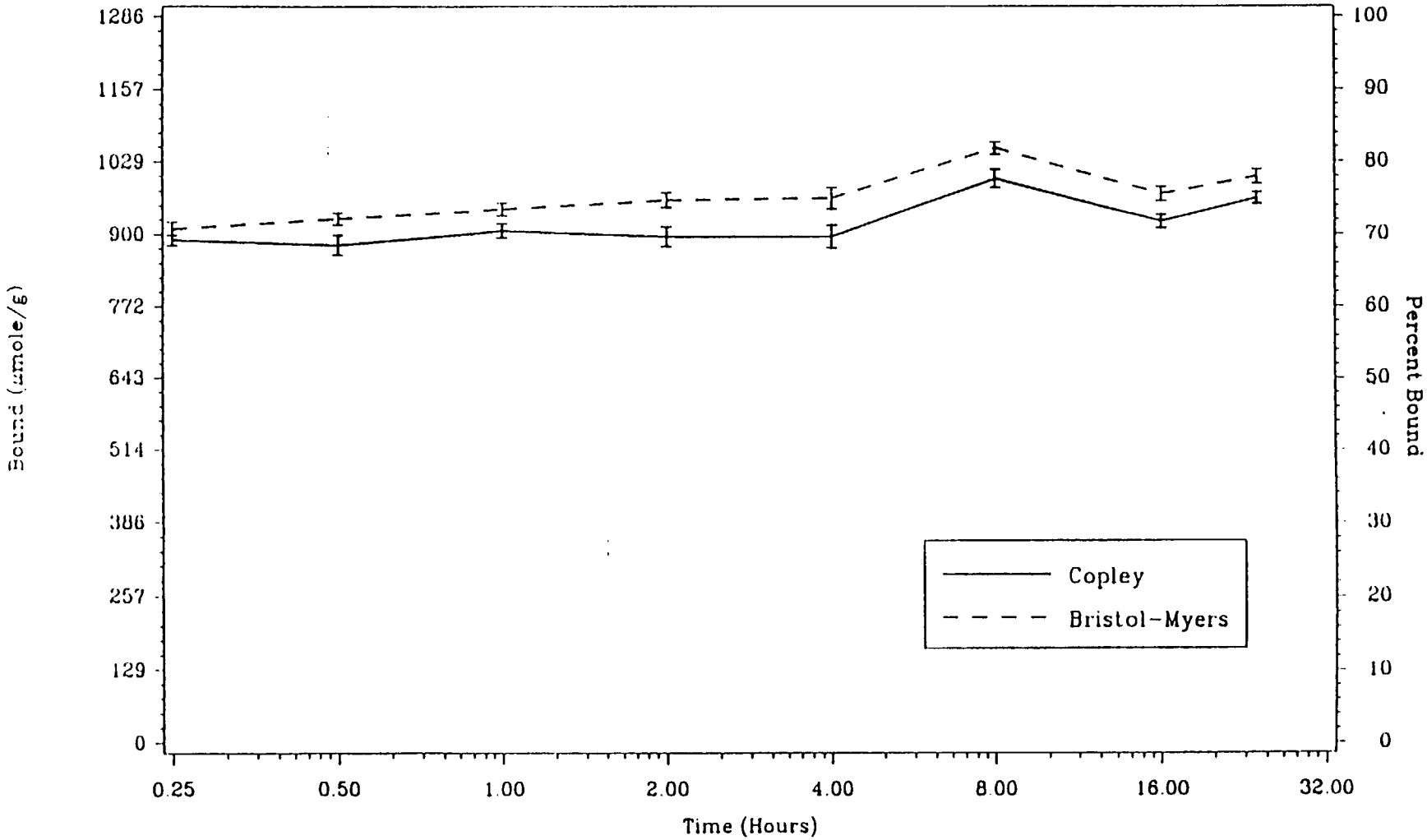
Attachment-15

In Vitro Bioequivalence Study of Cholestyramine Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6-A: GCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 16

In Vitro Bioequivalence Study of Cholestyramine Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6-B: GCDA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error



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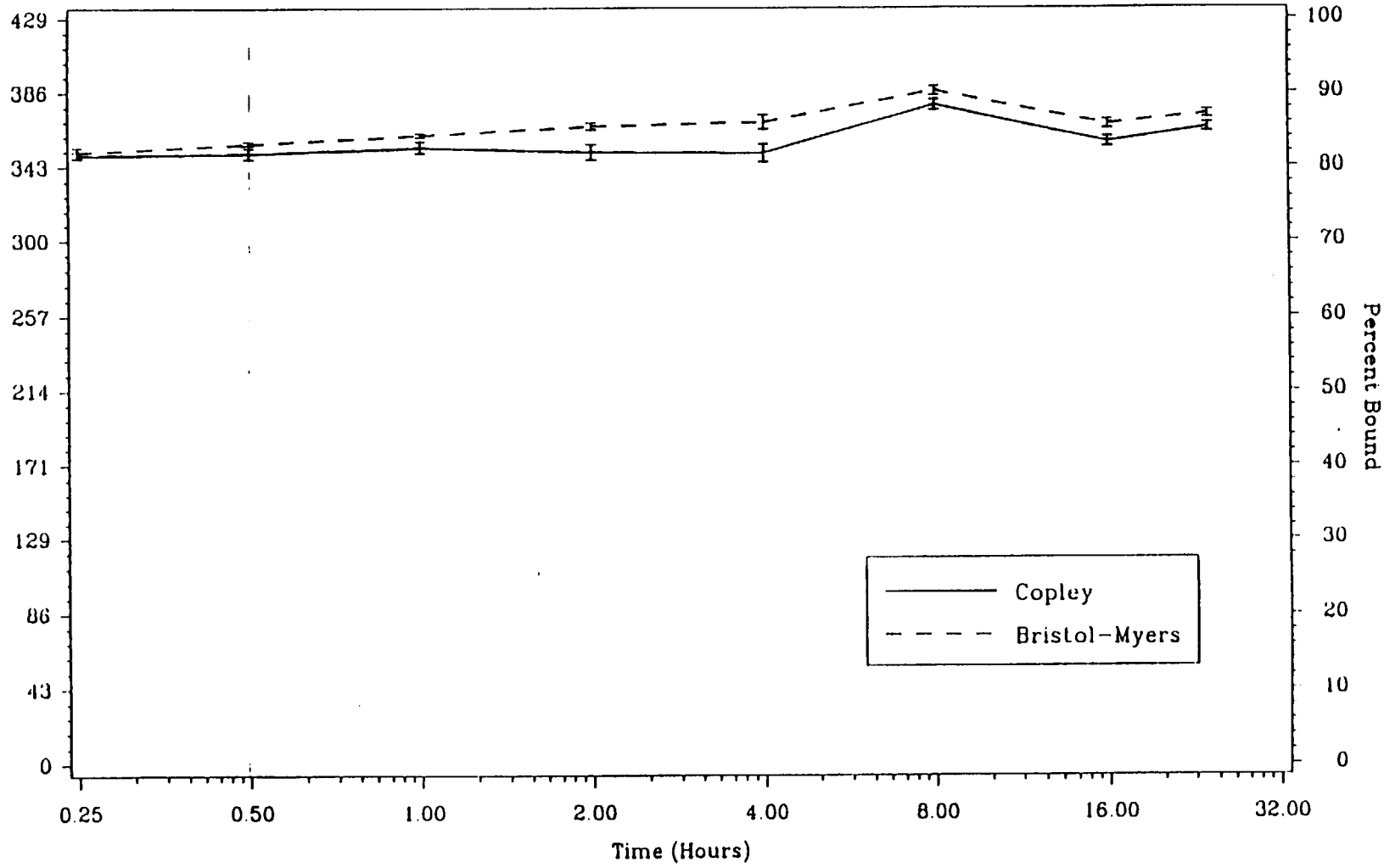
Attachment 17

In Vitro Bioequivalence Study of Cholestyramine Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6-C: TDCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error



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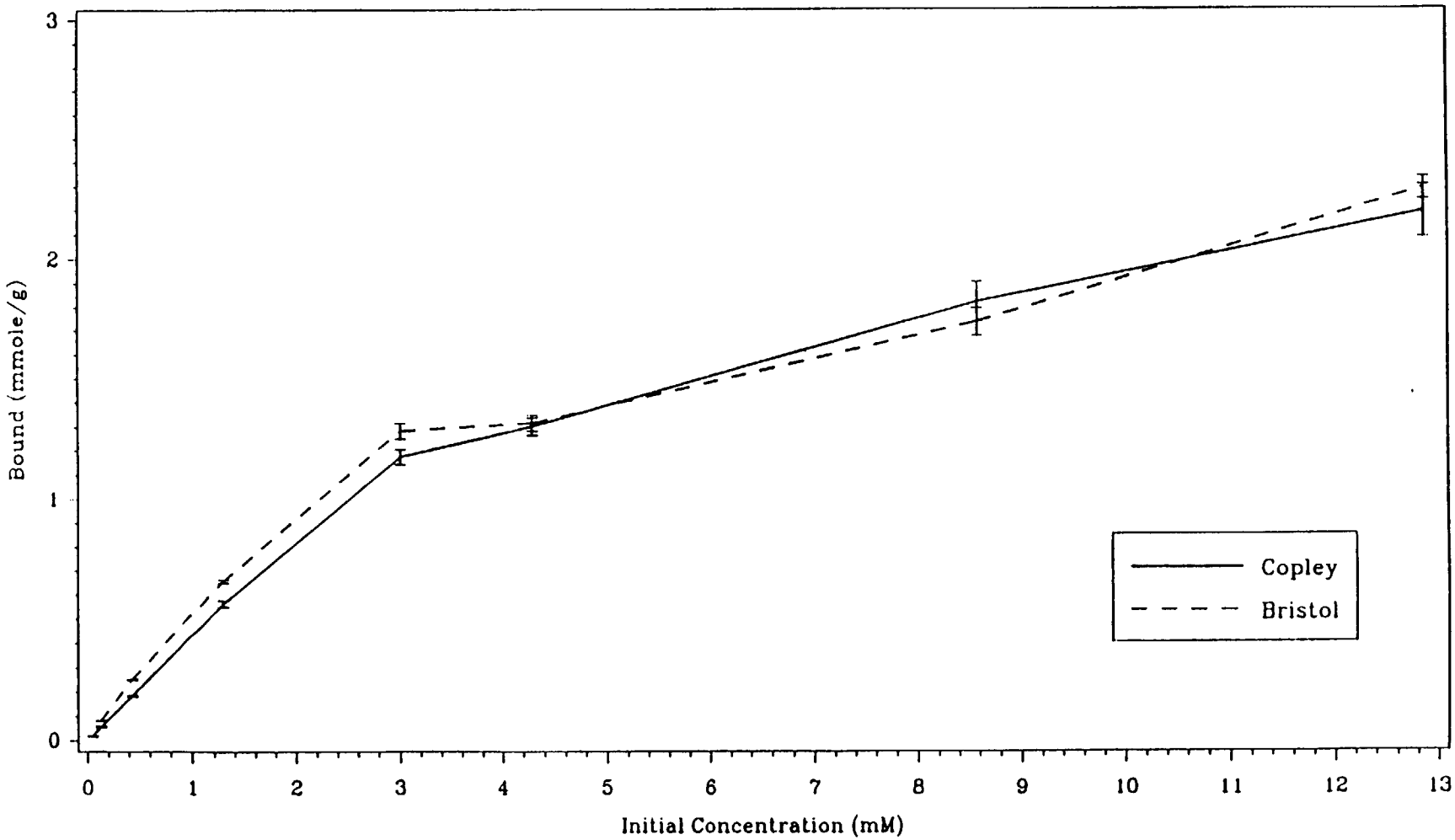
Attachment - 18

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

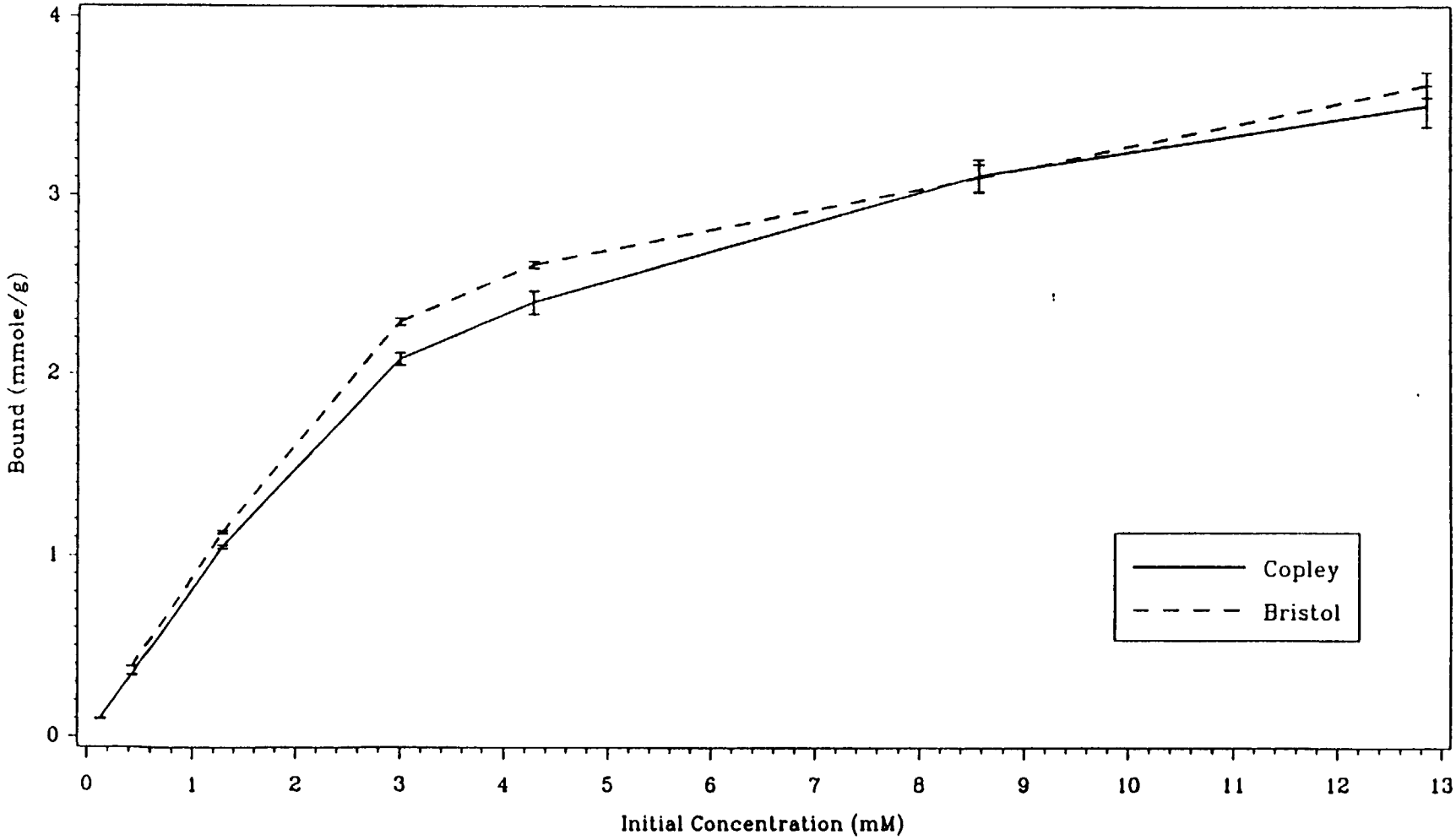
Figure 1-A: GCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment-19

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

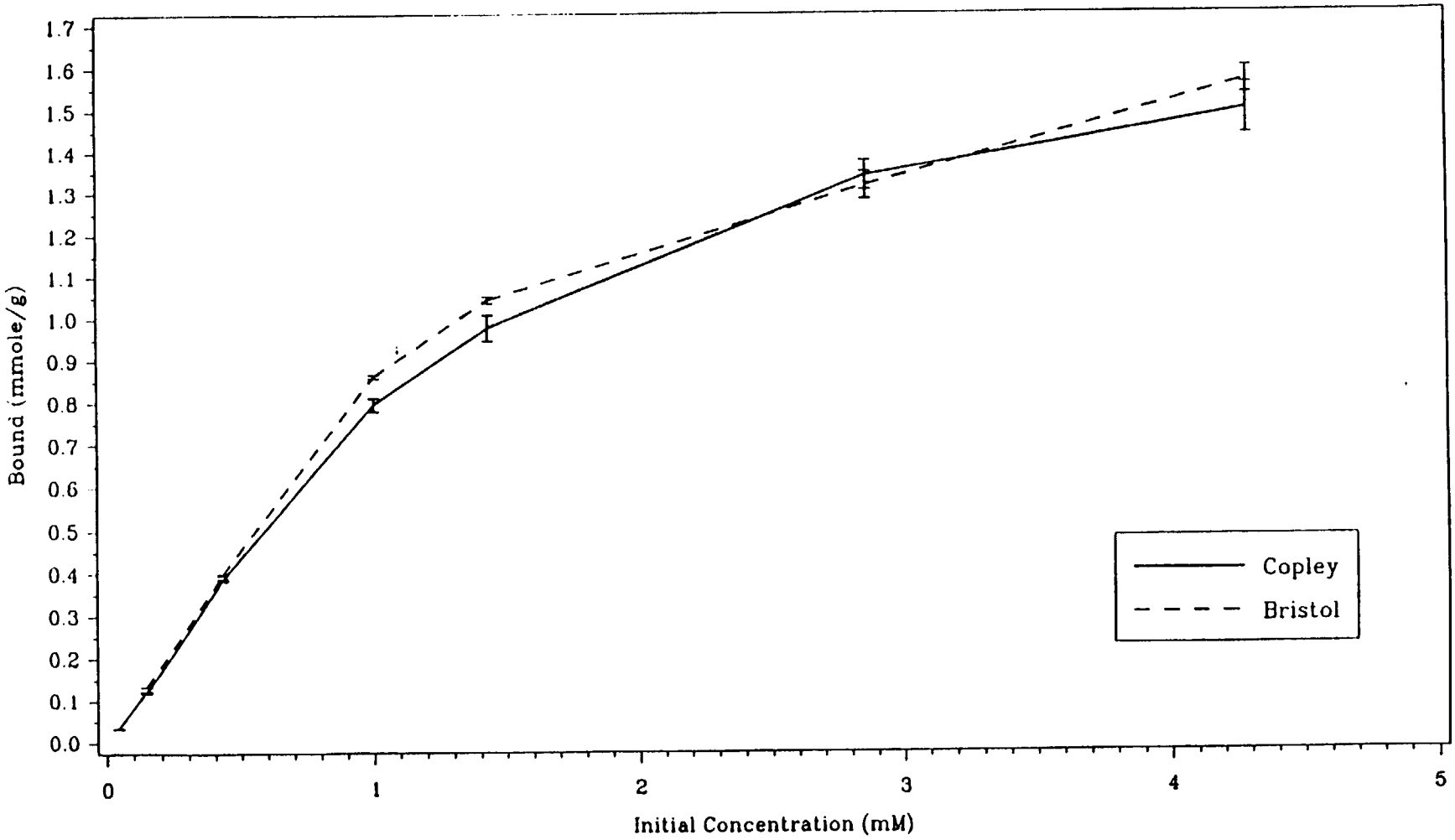
Figure 1-B: GCDA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 20

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

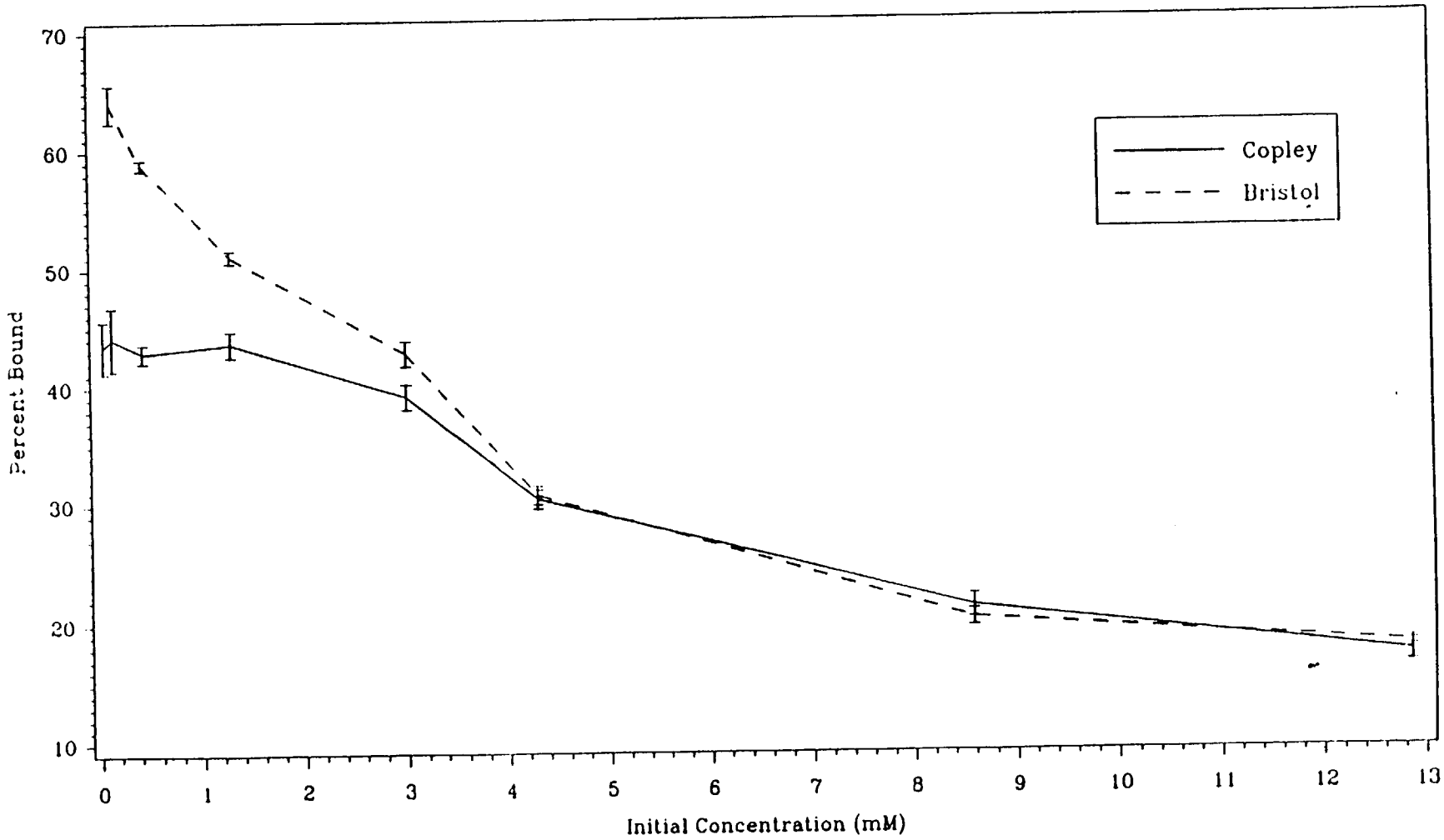
Figure 1-C: TDCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 21

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

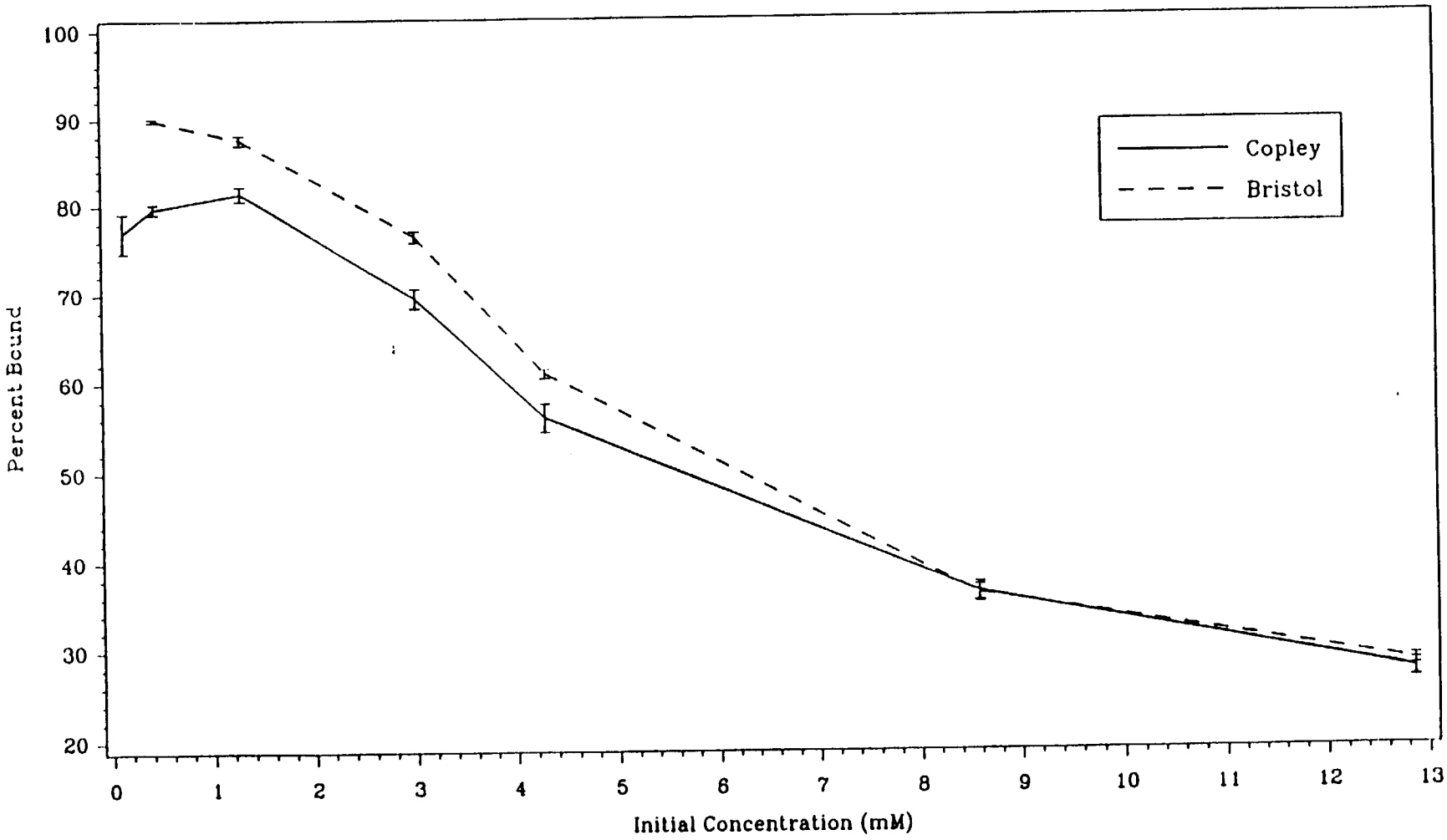
Figure 2-A: GCA Percent Bound
Mean ± Standard Error (n = 6)



Attachment - 22

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

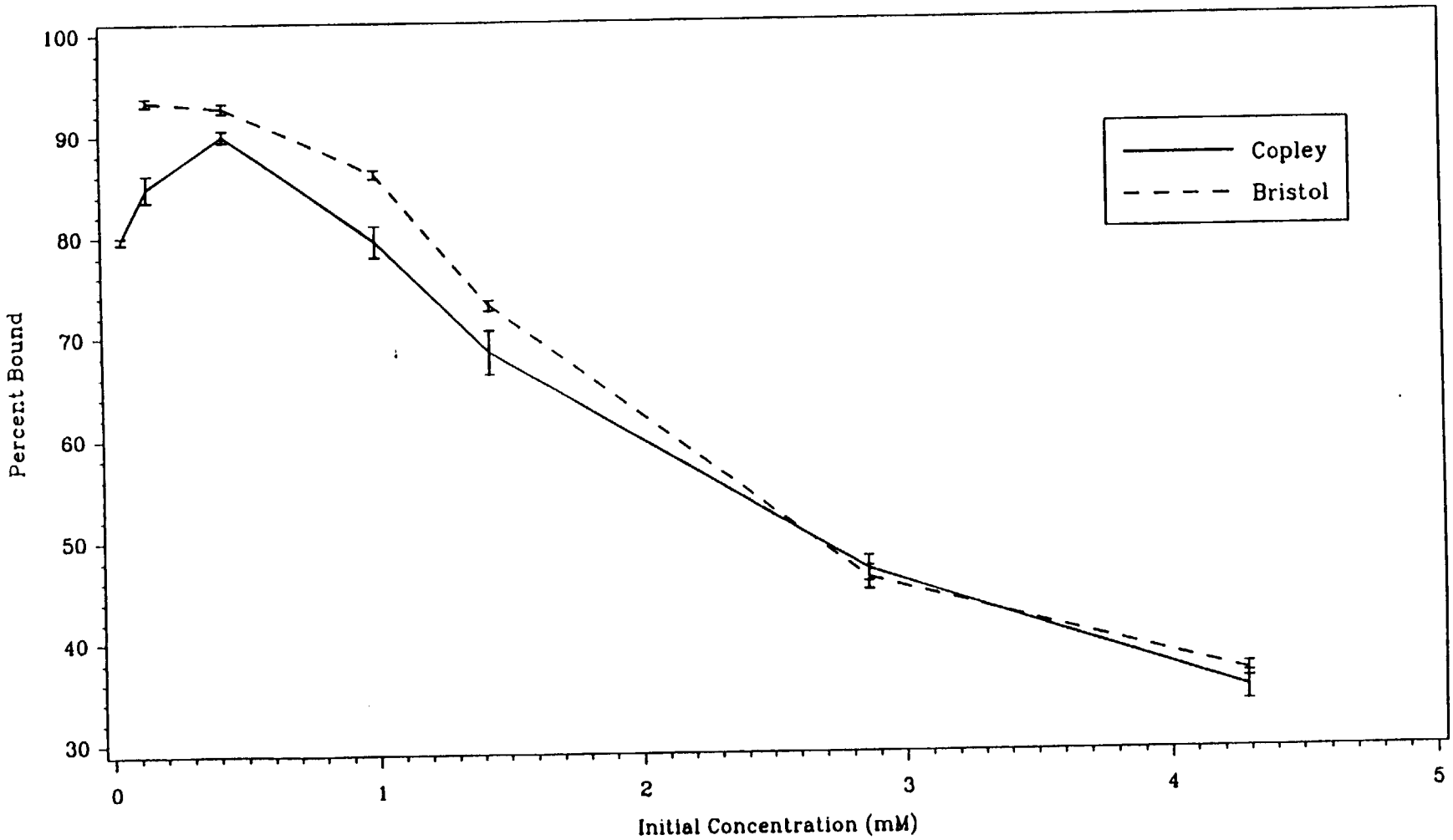
Figure 2-B: GCDA Percent Bound
Mean ± Standard Error (n = 6)



Attachment-23

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C Without Acid Pre-treatment

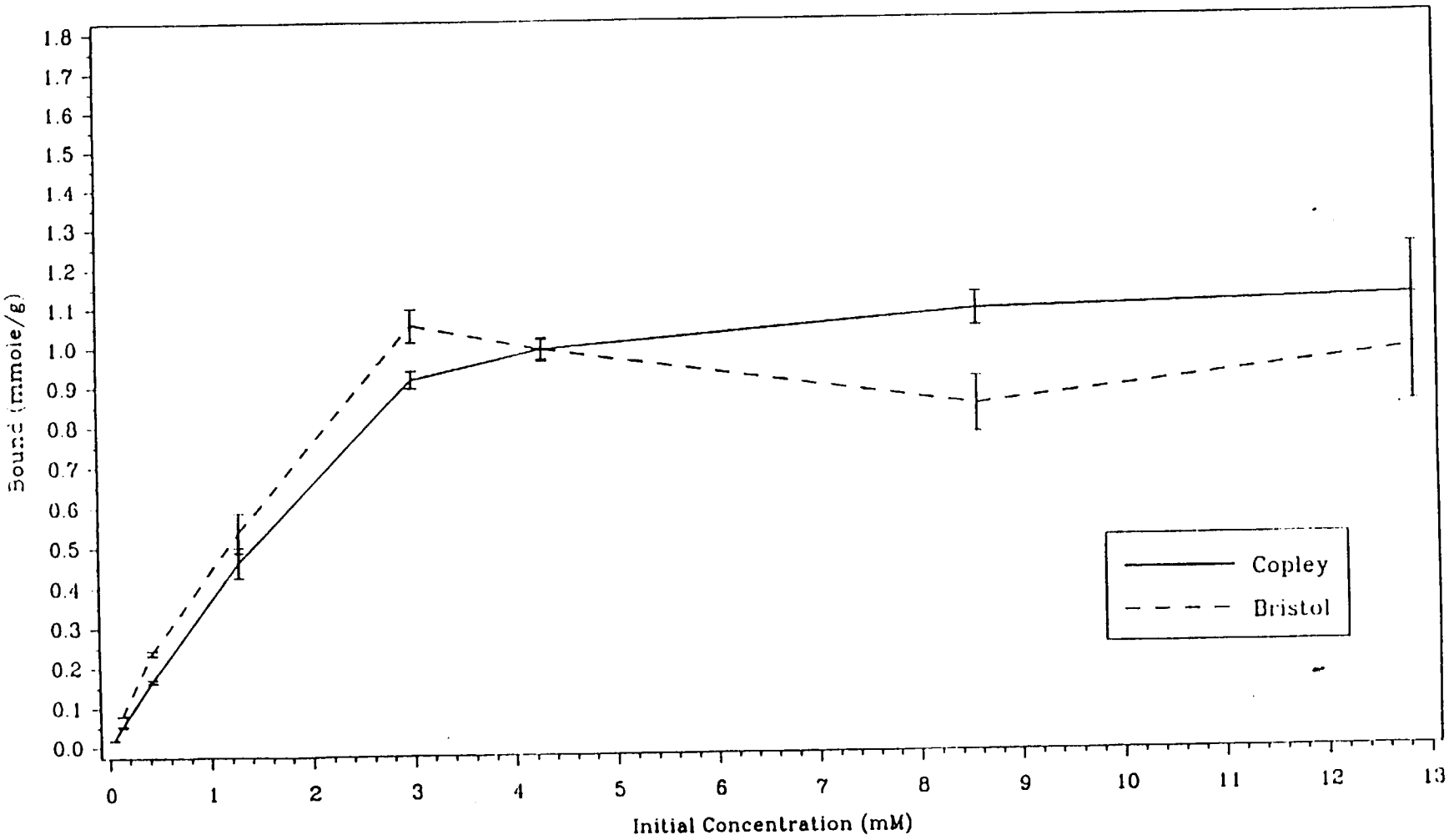
Figure 2-C: TDCA Percent Bound
Mean ± Standard Error (n = 6)



Attachment - 4

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

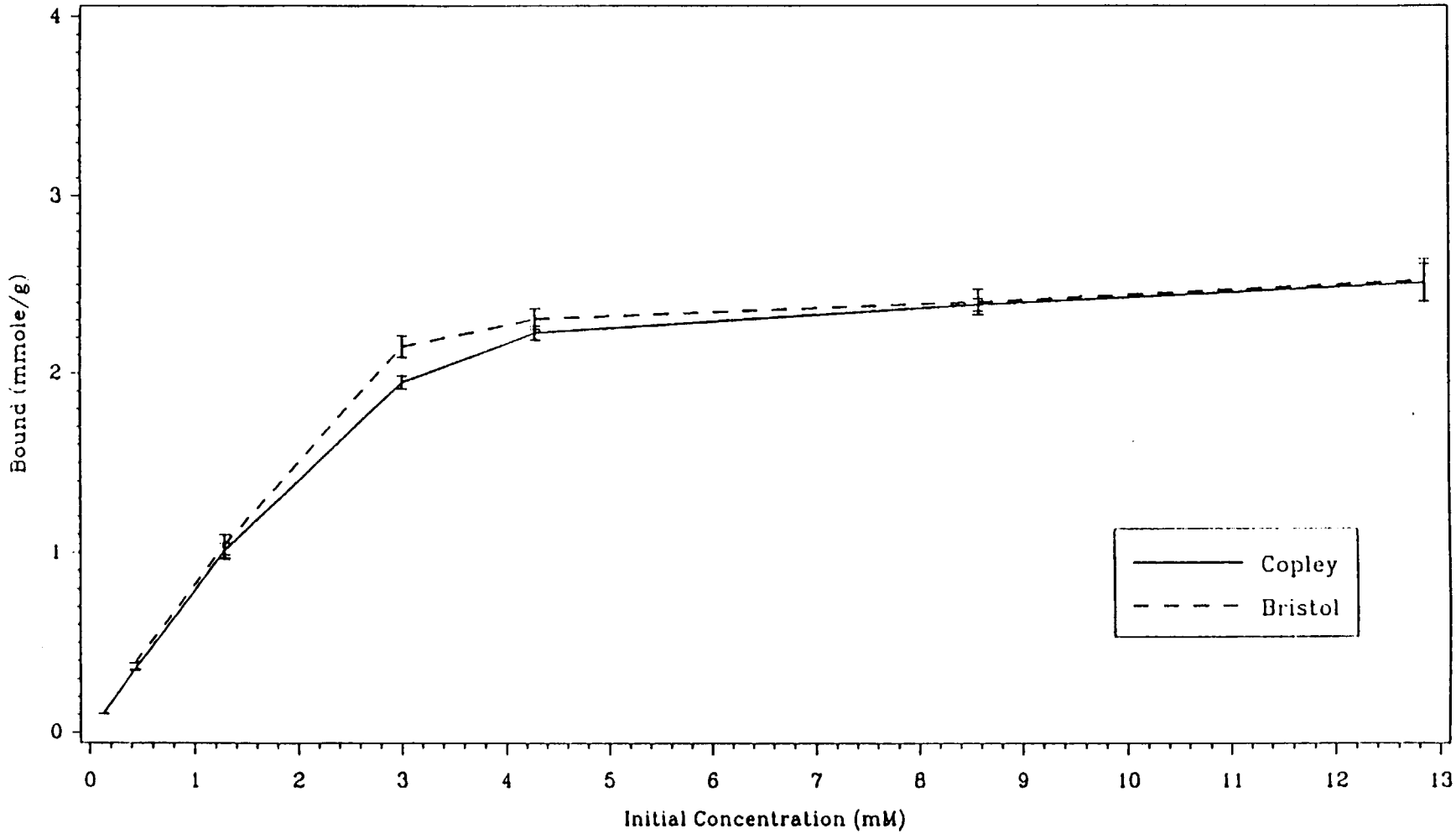
Figure 3-A: GCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment - 25

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

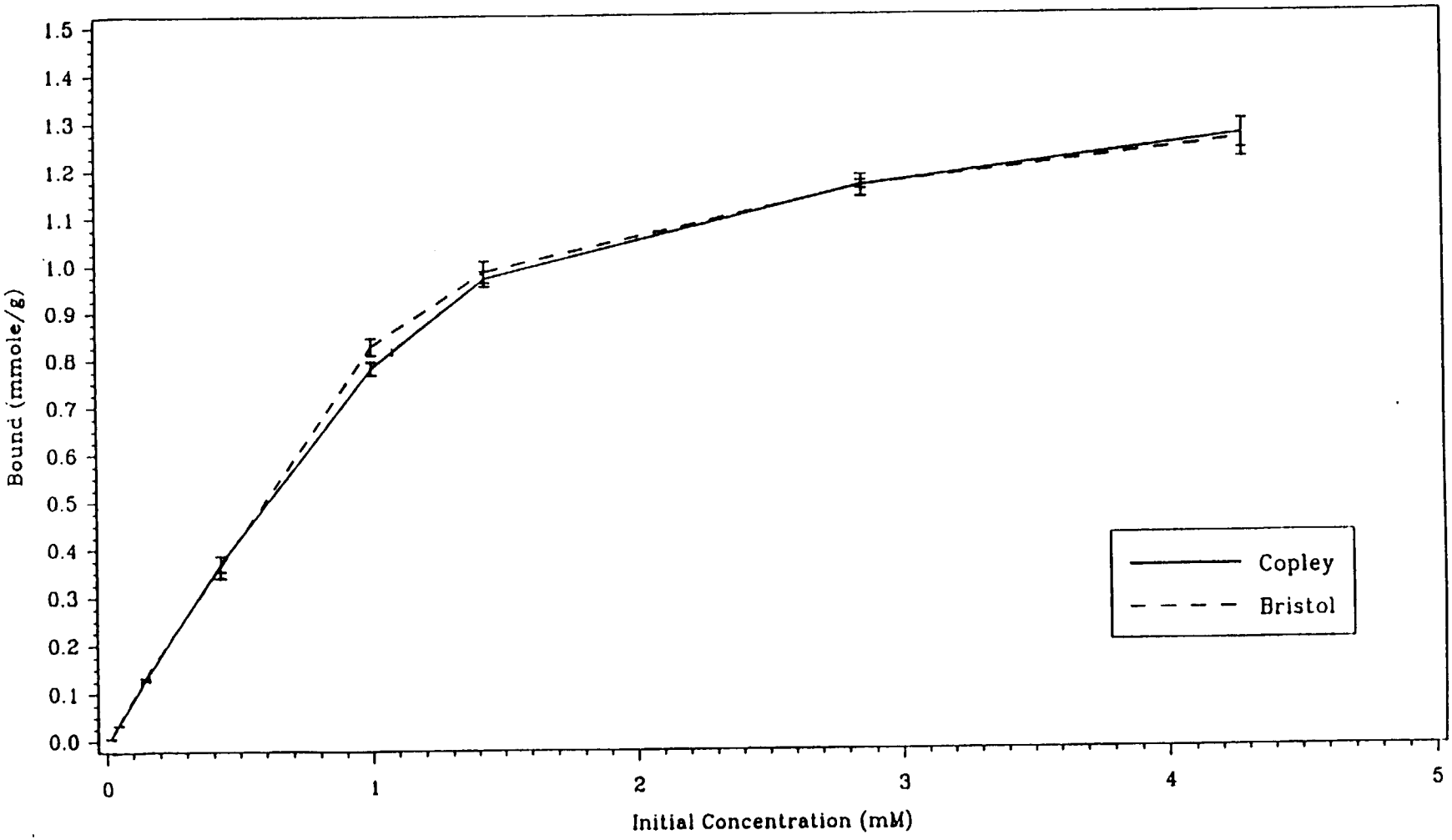
Figure 3-B: GCDA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment-26

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

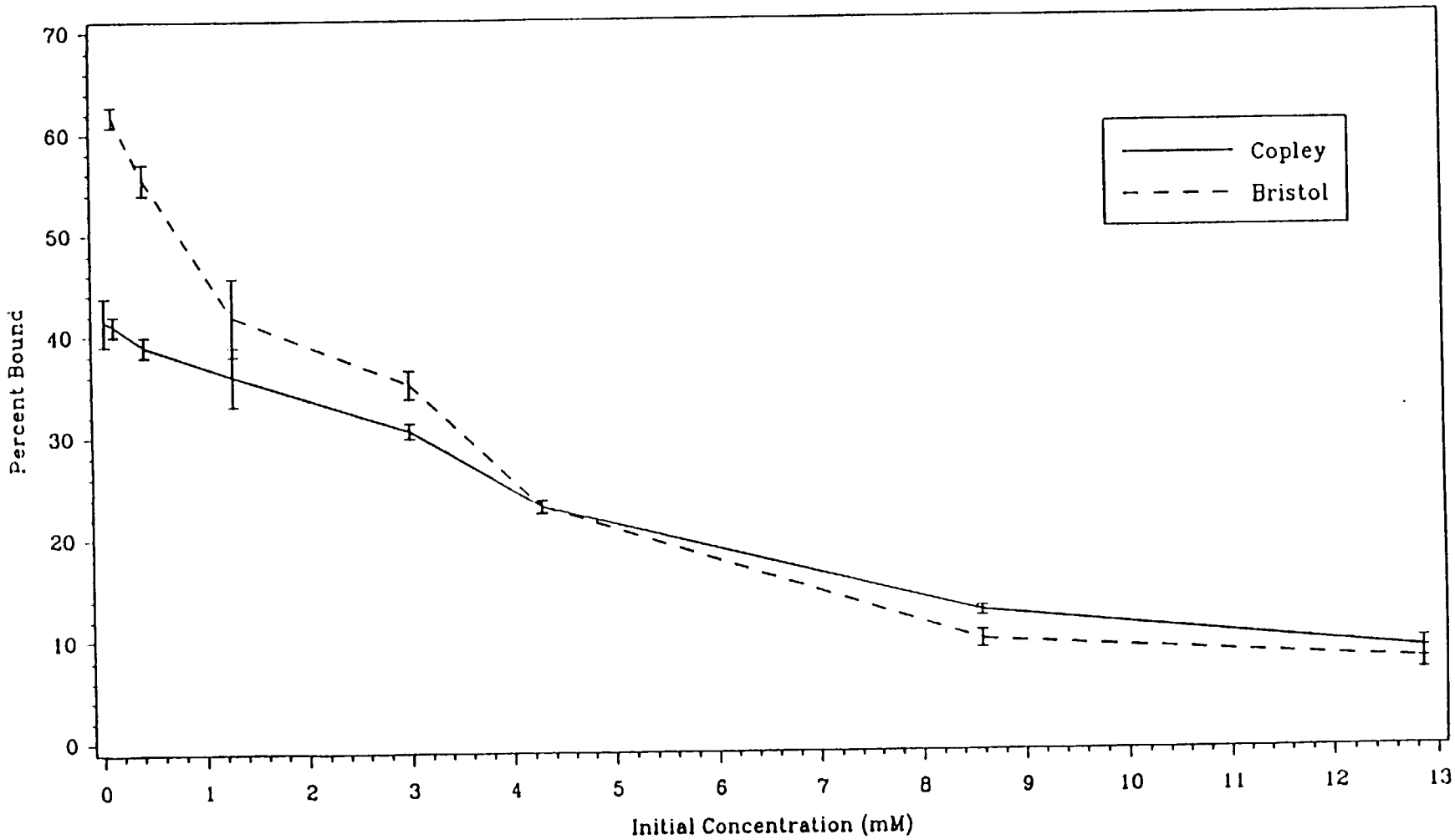
Figure 3-C: TDCA Amount Bound (mmole/gram of Resin)
Mean ± Standard Error (n = 6)



Attachment-27

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
in Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

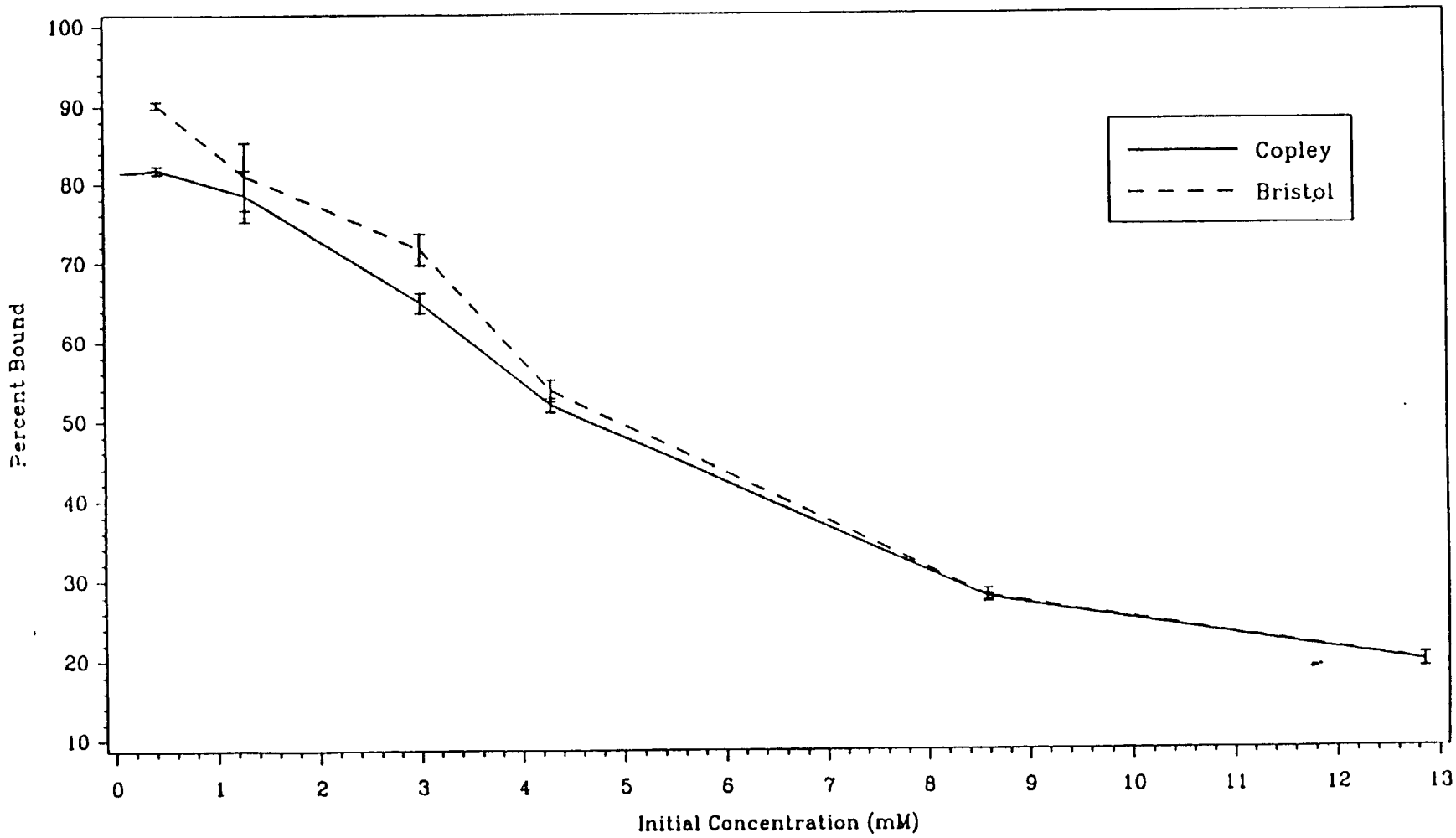
Figure 4-A: GCA Percent Bound
Mean ± Standard Error (n = 6)



Attachment-28

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

Figure 4-B: GCDA Percent Bound
Mean ± Standard Error (n = 6)



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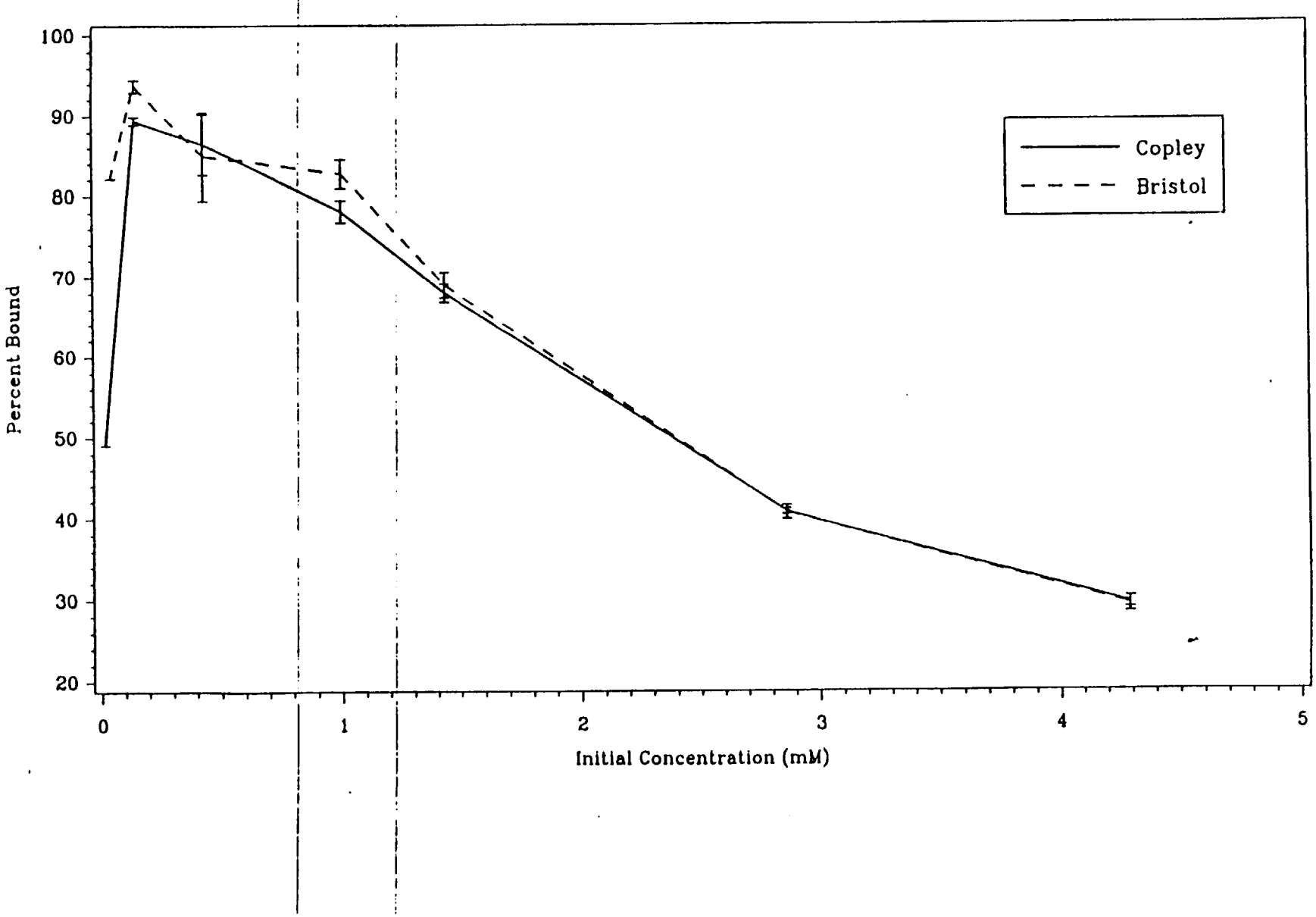
Attachment - 29

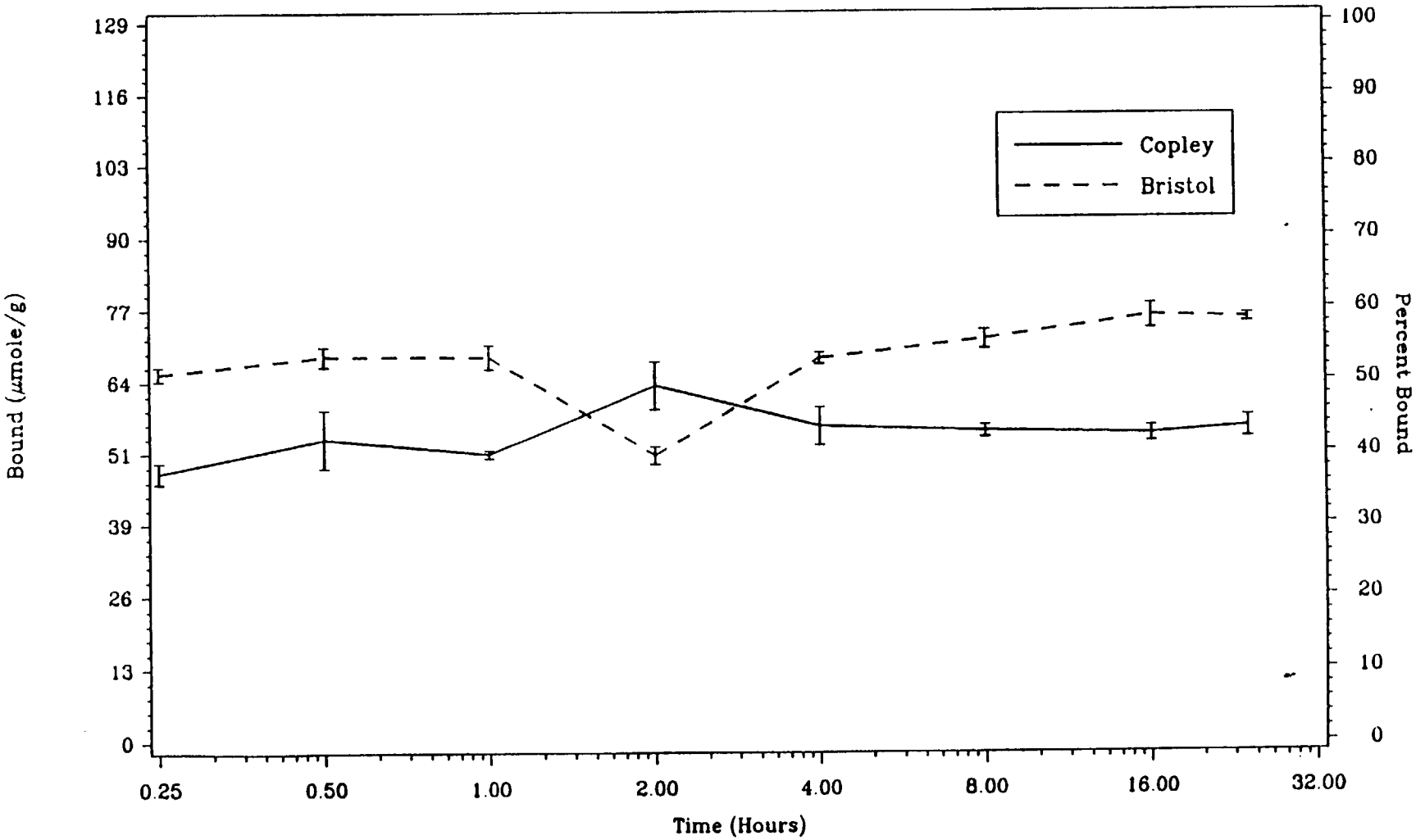
In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Equilibrium Binding of Cholestyramine With Bile Acid Salts (GCA, GCDA and TDCA in Molar Proportion 3:3:1)
In Simulated Intestinal Fluid (SIF) at 37°C With Acid Pre-treatment

Figure 4-C: TDCA Percent Bound
Mean ± Standard Error (n = 6)



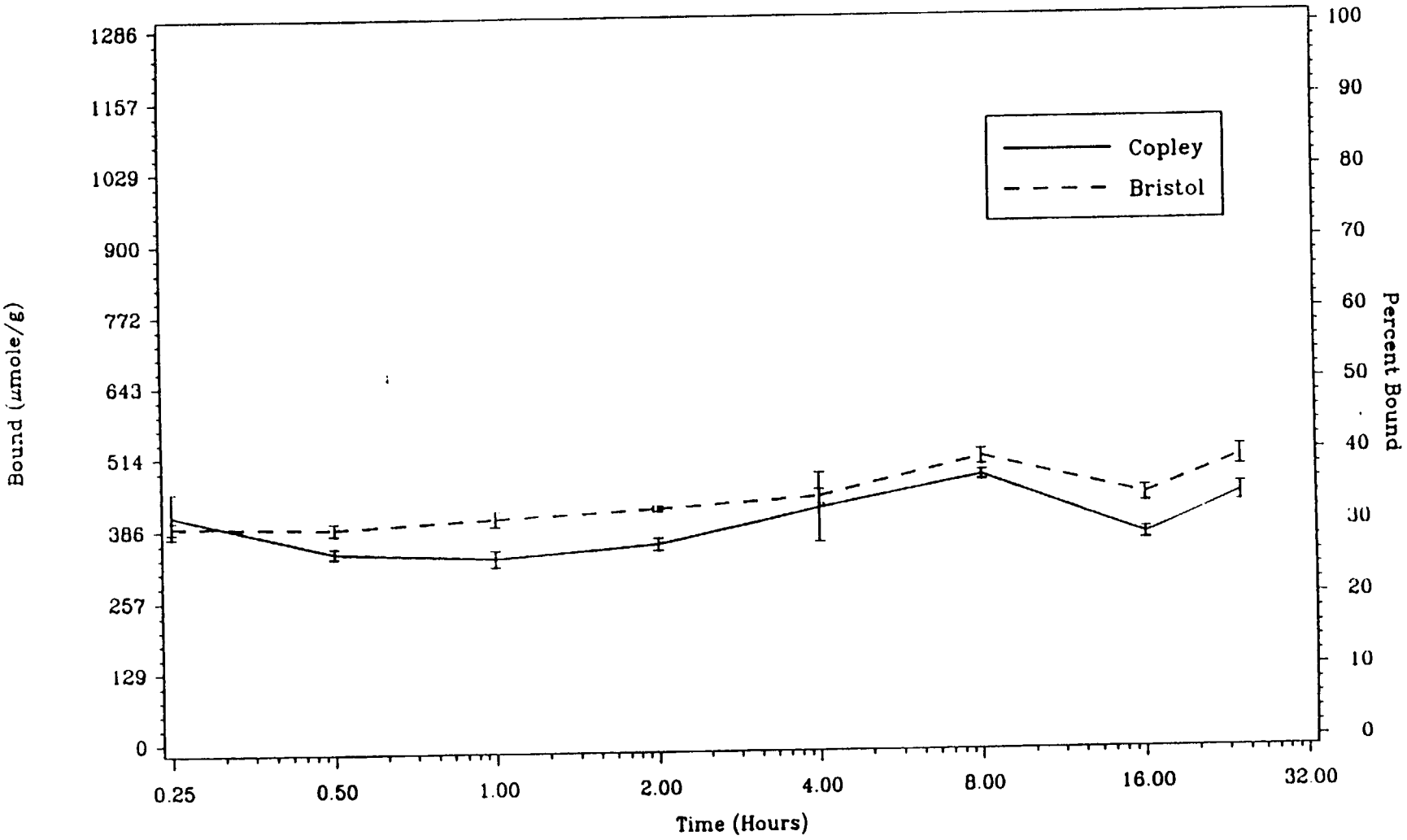
Attachment 30

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 0.3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 5–A: GCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error (n = 6)



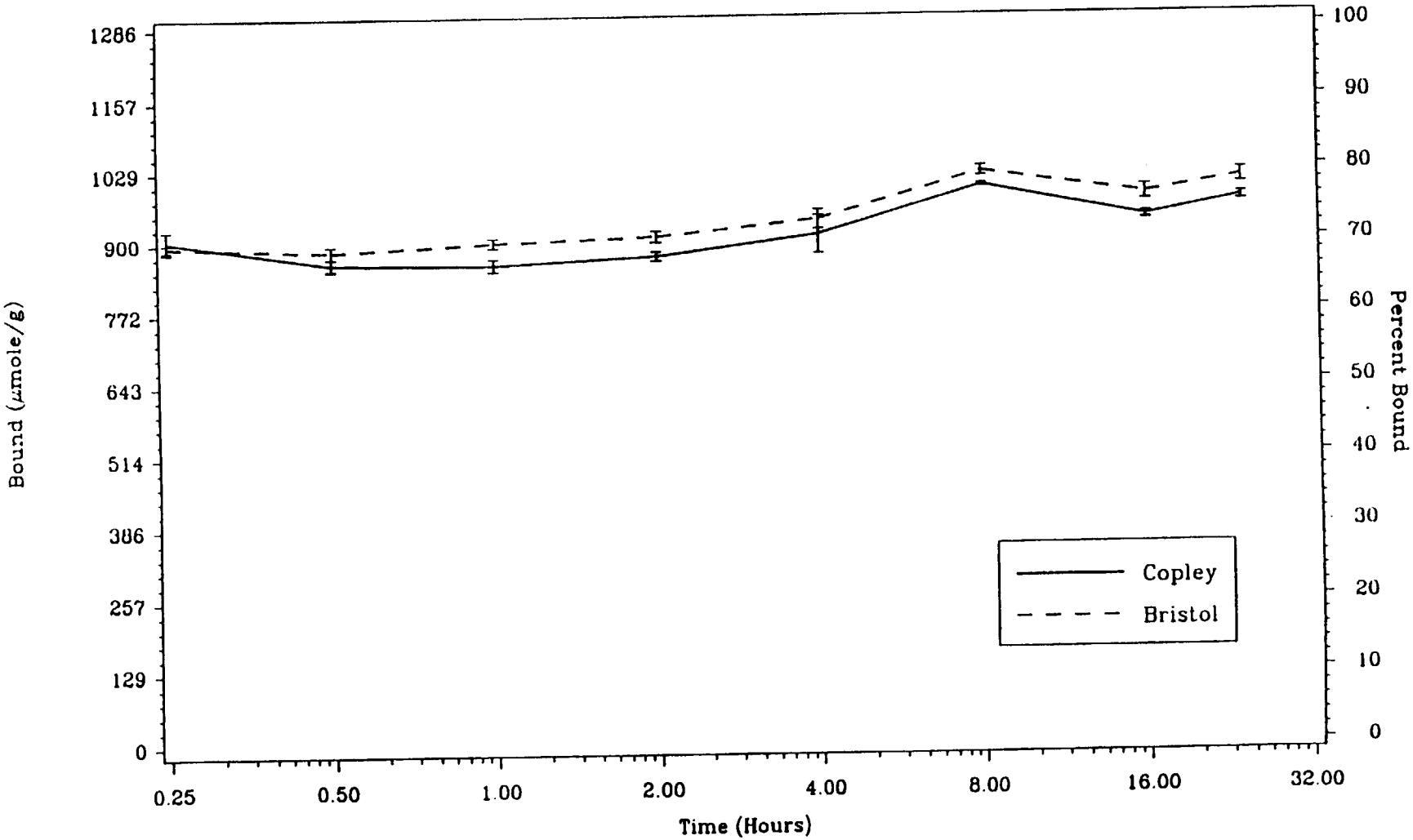
Attachment 31

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6–A: GCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error (n = 6)



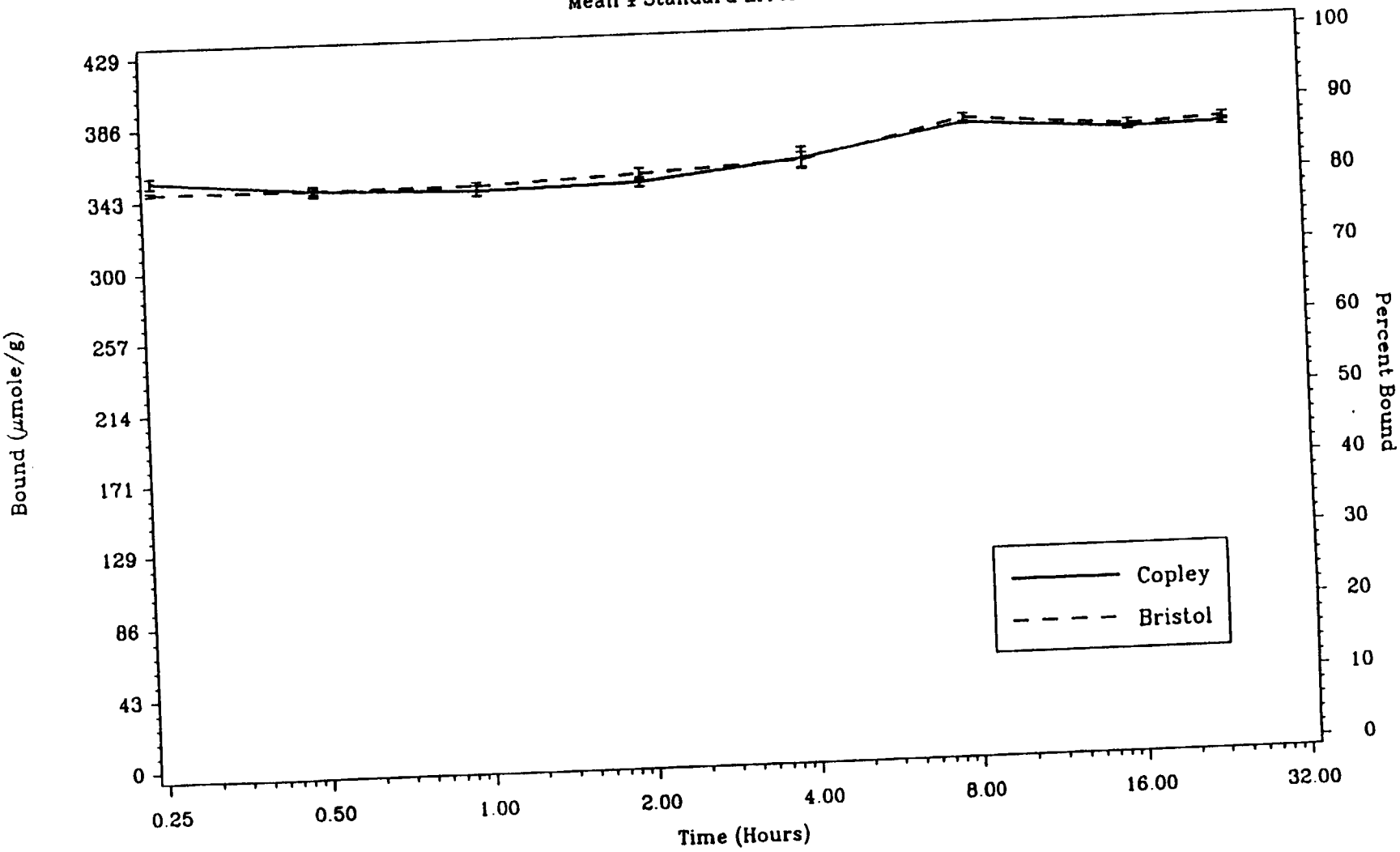
Attachment - 32

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6-B: GCDA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error



Attachment - 33

In Vitro Bioequivalence Study of Cholestyramine (Light) Resin
Kinetics of Binding of Cholestyramine With Bile Acid Salts in 3 mM Aqueous Bile Acid Salts Solution
(GCA, GCDA and TDCA in Molar Proportion 3:3:1) Incubated With Added Sodium Chloride (0.1 M) at 37°C
Figure 6-C: TDCA Amount Bound (μmole/gram of Resin)
Mean ± Standard Error



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **74-555** Date of Submission: **December 11, 1997**

Applicant's Name: **Copley Pharmaceutical, Inc.**

Established Name: **Cholestyramine for Oral Suspension, USP (Light)**

Labeling Deficiencies:

1. CONTAINER (5 g packet and 210 g can)

   Satisfactory in final print.

2. CARTON (60 x 5 g)

   We note the print appears blurred and difficult to read. Please note that for computer generated labels to be acceptable as final print, they must be of actual size, color and clarity. Please revise accordingly.

3. INSERT:

   a. Replace the Federal Law prohibits..." statement with "Rx Only".

   b. CLINICAL PHARMACOLOGY

      i. Paragraph two, first sentence - Revise to read "adsorbs" rather than

      ii. Clinical Studies, paragraph one - Delete from "Carcinogenesis, Mutagenesis, Impairment of Fertility" in the last sentence.

   c. INDICATIONS AND USAGE

      i. The abbreviation for deciliter is "dL" rather than Revise throughout this section.

      ii. Number one - Delete the last sentence of the last paragraph. [In addition, in the...]

d. PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility, paragraph two - Insert "5" as a superscript following "LRC-CPPT" in the last sentence.

e. OVERDOSAGE

Overdosage with cholestyramine...

f. DOSAGE AND ADMINISTRATION, Concomitant Therapy - Revise to read "Preliminary" rather than in the first sentence.

Please revise your insert labeling, as instructed above, and submit final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74555

CORRESPONDENCE

ANDA 74-554, Cholestyramine Powder, 4 g Resin
ANDA 74-555, Cholestyramine Light Powder, 4 g Resin

JUL 5 1996

Copley Pharmaceutical Inc.
Attention: Bernie Grubstein
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Mr. Grubstein:

Reference is made to the Abbreviated New Drug Applications for Cholestyramine Powder, 4 g Resin, and Cholestyramine Light Powder, 4 g Resin

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. ANDA 74-555, Cholestyramine Light Powder, 4 g Resin:

   The ratio of the mean of the total bile acid salt binding affinity constant (K1) data obtained by Langmuir's linear or best-fit nonlinear equation, are outside the acceptable ±20% confidence interval of the reference. The equilibrium binding study at 0.1-30 mM total bile salt concentrations, without acid pre-wash will need to be repeated. The calculations should include the individual bile salt binding, total bile salts binding, basic statistics, affinity constants (linear and nonlinear K1), capacity constants (linear and nonlinear K2), test/reference ratios, and 90% CI for the K2 parameter. The product must pass the 90% CI criteria of 80-120 for the K2 parameter, and maintain a 0.8-1.2 ratio for K1 parameter.

2. ANDA 74-554, Cholestyramine Powder, 4 g Resin:

   1. The Division of Bioequivalence has completed its review and has no further questions at this time.

   2. The binding capacity assay described in USP 23 should be incorporated into your manufacturing controls and stability program.

   3. Please note that the bioequivalency comments for ANDA 74-554, Cholestyramine Powder, 4 g Resin, expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry,

manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-555

Copley Pharmaceutical Inc.
Attention: W.E. Brochu, Ph.D.
Canton Commerce Center
25 John Road
Canton, MA 02021

AUG 1 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated October 3, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cholestyramine for Oral Suspension, USP (Light).

Reference is also made to your amendments dated November 24, 1994, October 2 and 26, 1995, and April 8, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. You failed to submit the comparative information using standard Questran of Bristol Myers Squibb as the reference product. We refer to your correspondance dated October 2, 1995. e HS

2. We note that you propose to use the "modified" USP Loss on Drying (LOD) method. You must use the USP LOD method "as is" and comply with it as your modified procedure does not give comparable results. You may use the Karl Fischer test as an additional test and make batch corrections based on these test results. We acknowledge your intention to pursue a change of the LOD test with USP.

3. You failed to submit a cGMP statement from your alternate microbiological testing facility - Microbiological Research Associates, Acton, MA.

4. Please delete your proposed overage of % of Cholestyramine Resin to compensate for manufacturing loss. You may adjust the actual amount of Cholestyramine Resin weighed based on moisture and exchange capacity analyses only. Please submit revised manufacturing batch records.

5. Please revise your release specifications for the finished drug product to include pH and dispersibility. Please also include the pH test in the stability program.

6. Please revise your release and stability specifications to include Chloride Content of % calculated against the assay for the finished drug product. Please validate the method in the drug substance monograph for this purpose.

7. Please lower your limits for Trimethylamine (TMA) and Dialyzable Quaternary Amine for release and stability as follows:

Dialyzable Quaternary Amine as Benzyltrimethyl-ammonium Chloride:	NMT	%
Trimethylamine (TMA):	NMT	%
Total Impurities:	NMT	%

8. Please submit a copy of revised release specifications incorporating the revisions requested in this letter. Similarly, submit a revised stability protocol including the revisions requested in this letter.

B. Labeling Deficiencies:

Deficiencies pertaining to ANDA 74-555 (Light):

1. CONTAINER

a. ✓ 5 g packet

i. Add the following:

Usual Dosage: See package insert.

ii. We encourage you to differentiate your two products by the use of boxing, contrasting colors or some other means.

b. ✓ 210 g can

i. First Panel

Revise the expression of strength to read as follows:

4 grams...per scoopful*

[Note: Add asterisk (*)]

ii. Second Panel

Revise to read:

*Each level scoopful...

[Note: Add asterisk (*)]

iii. See comment a(ii) under CONTAINER.

2. CARTON (60 x 5 g packets)

a. Front and Back Panels

i. Revise the expression of strength to read as follows:

4 grams...per packet*

ii. Add the following:

*Each packet contains 4 grams of anhydrous cholestyramine in 9 grams of Cholestyramine for Oral Suspension (Light).

b. Top Panel

Add a statement that the container is not child-resistant.

c. See comment a(ii) under CONTAINER.

3. INSERT

a. DESCRIPTION

i. Paragraph 1, sentence 2 - Revise to read:

Cholestyramine resin is quite hydrophilic, but insoluble...

ii. Include the molecular weight, molecular formula and the chemical name.

b. CLINICAL PHARMACOLOGY

Insert the following text to appear as a subsection after the last paragraph:

Clinical Studies
In a large, placebo-controlled, multi-clinic study, LRC-CPPT[1], hypercholesterolemic subjects

treated with cholestyramine resin had mean reductions in total and low-density lipoprotein cholesterol (LDL-C) which exceeded those for diet and placebo treatment by 7.2% and 10.4%, respectively. Over the seven-year study period the cholestyramine resin group experienced a 19% reduction (relative to the incidence in the placebo group) in the combined rate of coronary heart disease death plus non-fatal myocardial infarction (cumulative incidences of 7% cholestyramine resin and 8.6% placebo). The subjects included in the study were men aged 35 to 39 with serum cholesterol levels above 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to females and other segments of the hypercholesterolemic population.

Two controlled clinical trials have examined the effects of cholestyramine monotherapy upon coronary atherosclerotic lesions using coronary arteriography. In the NHLBI Type II Coronary Intervention Trial[2], 116 patients (80% male) with coronary artery disease (CAD) documented by arteriography were randomized to cholestyramine resin or placebo for five years of treatment. Final study arteriography revealed progression of coronary artery disease in 49% of placebo patients compared to 32% of the cholestyramine resin group ($p<0.05$), a 35% reduction of disease progression with cholestyramine resin treatment.

In the St. Thomas Atherosclerosis Regression Study (STARS)[3], 90 hypercholesterolemic men with CAD were randomized to three blinded treatments: usual care, lipid-lowering diet, and lipid-lowering diet plus cholestyramine resin. After 36 months, follow-up coronary arteriography revealed progression of disease in 46% of usual care patients, 15% of patients on lipid-lowering diet and 12% of those receiving diet plus cholestyramine resin($p<0.02$). The mean absolute width of coronary segments decreased in the usual care group, increased slightly (0.003 mm) in the diet group and increased by 0.103 mm in the diet plus cholestyramine group ($p<0.05$). Thus in these randomized controlled clinical trials using coronary arteriography, cholestyramine resin monotherapy has been demonstrated to slow progression[2,3] and promote regression[3] of atherosclerotic lesions in the coronary arteries of patients with or at risk for coronary artery disease.

The effect of intensive lipid-lowering therapy on coronary atherosclerosis has been assessed by arteriography in hyperlipidemic patients. In these randomized, controlled clinical trials, patients were treated for two to four years by either conventional measures (diet, placebo, or in some cases low dose resin), or intensive combination therapy using diet plus colestipol (an anion exchange resin with a mechanism of action and an effect on serum lipids similar to that of Cholestyramine for Oral Suspension (Light)) plus either nicotinic acid or lovastatin. When compared to conventional measures, intensive lipid-lowering combination therapy significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions in patients with or at risk for coronary artery disease.

c. INDICATIONS AND USAGE

Number 1 - Delete the second and third paragraphs and replace with the following text:

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Treatment should begin and continue with dietary therapy specific for the type of hyperlipoproteinemia determined prior to initiation of drug therapy. Excess body weight may be an important factor and caloric restriction for weight normalization should be addressed prior to drug therapy in the overweight.

Prior to initiating therapy with cholestyramine resin, secondary causes of hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism), should be excluded, and a lipid profile performed to assess Total cholesterol, HDL-C, and triglycerides (TG). For individuals with TG less than 400 mg/dl (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{Total cholesterol} - [(\text{TG}/5) + \text{HDL-C}]$$

For TG levels > 400 mg/dl, this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or

normal despite elevated Total-C. In such cases cholestyramine resin may not be indicated.

Serum cholesterol and triglyceride levels should be determined periodically based on NCEP guidelines to confirm initial and adequate long-term response. A favorable trend in cholesterol reduction should occur during the first month of cholestyramine resin therapy. The therapy should be continued to sustain cholesterol reduction. If adequate cholesterol reduction is not attained, increasing the dosage of cholestyramine resin or adding other lipid-lowering agents in combination with cholestyramine resin should be considered.

Since the goal of treatment is to lower LDL-C, the NCEP[4] recommends that LDL-C levels be used to initiate and assess treatment response. If LDL-C levels are not available then Total-C alone may be used to monitor long-term therapy. A lipoprotein analysis (including LDL-C determination) should be carried out once a year. The NCEP treatment guidelines are summarized below.

		LDL-Cholesterol mg/dl (mmol/L)	
Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

*Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).
**Other risk factors for coronary heart disease (CHD) include: age (males≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dl (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dl (≥1.6 mmol/L).

Cholestyramine resin monotherapy has been

demonstrated to retard the rate of progression[2,3] and increase the rate of regression[3] of coronary atherosclerosis. In addition, in the LRC-CPPT trial, cholestyramine resin therapy reduced the combined rate of coronary heart disease death and non-fatal MI.

d. PRECAUTIONS

i. General

A) Delete paragraph one.

B) Revise paragraph three to read:

...be higher. Caution should also be exercised in patients with renal insufficiency or volume depletion, and in patients receiving concomitant spironolactone.

C) Revise paragraph four to read:

...constipation. The dosage should be increased gradually in patients to minimize the risk of developing fecal impaction. In patients with pre-existing constipation, the starting dose should be 1 packet or 1 scoop once daily for 5 to 7 days, increasing to twice daily with monitoring of constipation and of serum lipoproteins, at least twice, 4 to 6 weeks apart. Increased fluid intake and fiber intake should be encouraged to alleviate constipation and a stool softener may occasionally be indicated. If the initial dose is well tolerated, the dose may be increased as needed by one dose/day (at monthly intervals) with periodic monitoring of serum lipoproteins. If constipation worsens or the desired therapeutic response is not achieved at one to six doses/day, combination therapy or alternate therapy should be considered. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with cholestyramine resin may aggravate hemorrhoids.

ii. Information for Patients

Add the following text as the last sentence:

Sipping or holding the resin suspension in the mouth for prolonged periods may lead to changes in the surface of the teeth resulting in discoloration, erosion of enamel or decay; good oral hygiene should be maintained.

iii. Drug Interactions

A) Revise paragraph one to read:

...warfarin, thiazide diuretics (acidic),...preparations, estrogens and progestins, and digitalis...sequestrant. Cholestyramine resin may interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance...

B) Revise paragraph two to read:

...absorption of fat-soluble vitamins such as A, D, E and K. When...(or parenteral) forms of fat-soluble vitamins should be considered.

C) Revise paragraph three to read:

SINCE...CONCURRENTLY, IT IS RECOMMENDED THAT PATIENTS SHOULD...

iv. Carcinogenesis, Mutagenesis, Impairment of Fertility

A) Delete "and" from the subsection heading.

B) Revise the last sentence of paragraph two to read:

...above, a six-year post-trial follow-up analysis of the LRC-CPPT patient population has been completed (a total of 13.4 years of in-trial plus post-trial follow-up) and revealed no significant difference in the incidence of cause-specific mortality or cancer morbidity between cholestyramine and placebo treated patients.

v. Pregnancy

A) Revise the subsection heading to read:

Pregnancy: Teratogenic Effects, Pregnancy Category C

B) Hyphenate "fat-soluble".

e. ADVERSE REACTIONS

A) Paragraph 2 - Delete "dyspepsia".

B) Paragraph 4 - Revise to read:

...took a cholestyramine for oral suspension product. One...

C) Miscellaneous - Revise to read:

...dental bleeding, dental caries, erosion of tooth enamel, tooth discoloration.

f. OVERDOSAGE

Revise to read:

...been reported in a patient taking 150% of the maximum recommended daily dosage for a period of several weeks. No ill effects were reported. Should an overdosage occur, the chief...

g. DOSAGE AND ADMINISTRATION

Concomitant Therapy - Revise to read:

...lovastatin, simvastatin, and fluvastatin.

h. CLINICAL STUDIES - Delete this section.

i. REFERENCES - Revise this section to read:

1. The Lipid Research...

2. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI type II coronary intervention study. Circulation 1984;69: 313-24.

3. Watts, GF, Lewis B, Brunt JNH, Lewis ES, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas Atherosclerosis Regression Study (STARS). Lancet 1992;339:563-69.

4. National Cholesterol Education Program. Second Report of the Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994 Mar;89(3):1333-445.

j. Relocate the temperature storage recommendations to the HOW SUPPLIED section.

Please revise your container labels and carton and insert labeling, as instructed above, and submit final printed container labels, carton and insert labeling. To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

C. Bioequivalence Deficiencies:

Please refer to the letter dated July 5, 1996.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/11/98

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-555

Copley Pharmaceutical, Inc.
Attention: Robert Kelly
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated October 3, 1994 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Cholestyramine for Oral Suspension, USP (Light).

Reference is made to our not approvable fax of April 8, 1997.

The following comments pertain to labeling deficiencies only.

In addition to the comments regarding your insert labeling in our fax of April 8, 1997, revise your insert labeling to be in accord with recent changes in the labeling of the listed drug (Questran®; Bristol-Myers Squibb; Approved August 22, 1997; Revised December 9, 1996), as follows:

1. CLINICAL PHARMACOLOGY, Clinical Studies

   a. Insert the following text to appear as the last sentence of paragraph one:

      (See also PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

   b. Revise the last sentence of paragraph two to read as follows:

      ...resin group ($p<0.05$).

      [Note: Delete]

   c. Revise the last sentence of paragraph three to read as follows:

      ...patients with coronary artery disease.

2. PRECAUTIONS

a. Drug Interactions, Last paragraph - Delete from the last sentence.

b. Carcinogenesis, Mutagenesis, Impairment of Fertility - Revise the last sentence to read as follows:

...six-year post-trial follow-up of the...

[Note: Delete

c. Pregnancy - Revise this subsection to read as follows:

There are no adequate and well controlled studies in pregnant women. The use of cholestyramine in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighted against the possible hazards to the mother and child. Cholestyramine is not absorbed systemically, however, it is known to interfere with absorption of fat-soluble vitamins; accordingly, regular prenatal supplementation may not be adequate (see PRECAUTIONS: Drug Interactions).

d. Pediatric Use - Revise this subsection to read as follows:

Although an optimal dosage schedule has not been established, standard texts[6-7] list a usual pediatric dose of 240 mg/kg/day of anhydrous cholestyramine resin in two to three divided doses, normally not to exceed 8 g/day with dose titration based on response and tolerance.

In calculating...Cholestyramine for Oral Suspension, USP (Light).

The effects of...unknown. Also see "ADVERSE REACTIONS".

3. ADVERSE REACTIONS

Delete the last two sentences of paragraph two and insert the following text:

Rare reports of intestinal obstruction, including two deaths, have been reported in pediatric patients.

4. REFERENCES

Insert the following text as the last two references:

6. Behrman RE et al (eds): *Nelson, Textbook of Pediatrics*, ed 15. Philadelphia, PA, WB Saunders Company, 1996.

7. Takemoto CK et al (eds): *Pediatric Dosage Handbook*, ed 3. Cleveland/Akron, OH, Lexi-Comp, Inc., 1996/1997.

Please revise your package insert labeling, and submit in final print with your amendment to our fax dated April 8, 1997. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with the differences annotated and explained.

This letter addressed unique issues involving only labeling. Again, we refer you to our fax dated April 8, 1997, for the requirements to reopen the file on this application.

Sincerely yours,

/S/ for 9-26-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-555
Division File
HFD-610/JPhillips
njg/9/26/97/X:\NEW\FIRMSAM\COPLEY\LTRS&REV\74555.LOL
LETTER OUT

Endorsements:
HFD-613/CHolquist C. Holquist 9-25-97
HFD-613/JGrace

ANDA 74-555

Copley Pharmaceuticals Inc.
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton MA 02021

FEB 20 1997

Dear Sir:

Reference is made to the Abbreviated New Drug Application submitted on August 23, 1996, for Cholestyramine Light Powder, 4g resin.

The Office of Generic Drugs (OGD) has reviewed the bioequivalence data submitted and the following comment is provided for your consideration:

> The *in vitro* studies conducted by Copley Pharmaceutical, Inc. on its cholestyramine light, 4 g resin/5 g dose, Lot # 300Z01, comparing it with Bristol-Myers Squibb's Questran Light^{R} , 4 g resin/dose unit, Lot #K3J21B, has been found unacceptable, due to the following:
>
> The claim that reproducible K1 values cannot be obtained is not accurate. You have cited Singh et al. 1993 study presented at AAPS Meeting, Orlando, FL, to support the claim. However, the data presented there were preliminary results. Since then, OGD has obtained data from ANDAs which show that the reproducible K1 values (within ±20%) can be obtained.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDAs 74-554 Cholestyramine for Oral Suspension, USP
74-555 Cholestyramine for Oral Suspension, USP (Light)

Copley Pharmaceutical Inc.
Attention: Bernie Grubstein
Canton Commerce Center
25 John Road
Canton, MA 02021

MAY 16 1995

Dear Sir:

This is in reference to your abbreviated new drug applications dated September 27 (ANDA 74-554), and October 3, 1994 (ANDA 74-555), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cholestyramine for Oral Suspension, USP.

The applications are deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1. DMF is deficient. The DMF holder has been notified. Please confirm their response to our letter. Outstanding deficiencies must be resolved by the DMF holder prior to approval of these applications.

2. We have the following comments regarding the composition of the drug products:

   a. Please clarify the actual D&C Yellow #10 to be used in processing ANDA 74-554. The information provided in the composition statement, batch record and material specifications are not consistent.

   b. We do not consider a fixed % overage of the Cholestyramine Resin as appropriate for the manufacturing of these drug products. We suggest that you devise a formula to calculate the actual amount required in manufacturing these drug products based on the Loss On Drying (LOD) and assay of a particular lot of the drug substance plus an estimated reasonable manufacturing loss. Please revise the composition accordingly.

3. We have the following comments regarding the raw materials control:

   a. Please revise your specifications for Citric Acid Anhydrous USP and Colloidal Silicon Dioxide NF in accordance with USP 23/NF 18 to include Organic Volatile Impurities (OVI).

   b. Please revise the specifications for Acacia NF in accordance with the USP 23/NF 18 to include its botanic characteristic and Organic Volatile Impurities (OVI).

   c. Please revise your SOPs regarding the retesting for all raw materials. We require that retesting be performed annually unless you can provide in-house stability data up-front to support a longer retesting period of more than one year.

   d. Please submit quantitative composition and safety information per GRAS and/or FEMA for Spray Dried Orange Flavor and Spray Dried Kiwi Flavor . We request you to add an identification test to these raw material specifications. Please also provide references to the appropriate Food Additive Regulations. Alternatively, you may provide a letter of authorization to allow us to review the manufacturer's Drug Master File.

4. Please submit revised master batch records for the intended production size batches to include the calculation for the actual amount of Cholestyramine Resin based on the actual moisture content and the assay of the drug substance plus an estimated reasonable manufacturing loss.

5. We have the following comments regarding the container/closure systems for the drug products:

   a. We note that the canisters used to package the drug products are composed of 100% recycled materials from various sources and types. Please provide test data on heavy metals for these canisters.

   b. Please provide calibration data to ensure that the scoop to be used to measure these drug products delivers the correct dose.

6. We have the following comments regarding the stability of the drug products:

   a. Please revise your stability specifications to include testing for the potential degradation products. Please propose limits for individual and total impurities/degradants. Please also provide a validated test method and report test data generated at the next scheduled test station. Furthermore, a reasonable effort should be made to chemically identify the major degradation products.

   b. Please submit adequate stability data to support the claim made in the package insert of these drug products that these drug products remain stable for 3 days after reconstitution.

B. Labeling Deficiencies:

Deficiencies pertaining to ANDA 74-554 (Regular):

CONTAINER:

1. 9 g (single dose)

   a. Delete the word after the established name.

   b. Please include storage recommendations with a temperature range.

   c. We note your NDC number has only eight digits. We refer you to 21 CFR 207.35 which states that a NDC number shall consist of ten digits. Please revise.

   d. Please add the following statement before "Keep this and...".

      This package is not child-resistant.

   e. We prefer that the strength (or net quantity per packet) appear beneath the established name.

   f. Replace "Cholestyramine Powder" with "Cholestyramine for Oral Suspension".

2. 378 g (can)

   a. See comments under CONTAINER, as appropriate.

b. First panel - "4 grams cholestyramine resin per scoopful" should appear in bold print and relocated beneath the established name.

c. Middle panel

Revise item 5 to read as follows:

"...textured mixture is now...".

d. Last panel, Line 3 - Usual Dosage: See package insert.

e. Revise the "Each scoopful contains" statement to read:

Each scoopful (9 grams) of cholestyramine for Oral Suspension...

CARTON: 60 X 9 g packets

1. Front and Back

a. See comments under CONTAINER, as appropriate.

b. Revise the following sentence and relocate this information to appear immediately beneath the established name:

"4 grams cholestyramine resin USP, per packet."

2. Side of carton for both the beverage and food preparations:

a Revise the statement to read "PREPARATION OF CHOLESTYRAMINE FOR ORAL SUSPENSION".

b. The illustration under item 1 is labeled as Questran. Please ensure that this illustration reflects your product.

c. Delete the word . (3 locations)

d. Revise item 3 (for beverages) to read "Add 2 to 4 more ounces of...".

3. Top

a. We do not consider the following essential information and recommend its deletion:

b. We prefer that you use "cholestyramine" rather than

INSERT:

1. GENERAL COMMENT

Please make the following changes wherever it appears in the insert except where indicated below:

a. should read "cholestyramine resin".

b. should read "Cholestyramine for Oral Suspension".

2. TITLE

Delete after the established name.

3. DESCRIPTION

a. Revise the second sentence as follows:

"...resin is not absorbed...".

b. Please identify citric acid as: citric acid (anhydrous).

4. INDICATIONS AND USAGE

Items 1 and 2, sentence 1 - Cholestyramine for oral suspension is indicated...

5. PRECAUTIONS

a. General, Third paragraph.

There is a possibility ... (add "a")

b. Laboratory Tests - Hyphenate "pre-entry". (last sentence)

c. Drug Interactions, Paragraph 1 - Revise to read:

... and digitalis. Interference with the absorption of oral phosphate supplements has

been observed with another positively-charged bile acid sequestrant. The discontinuance of...

d. Carcinogenesis, Mutagenesis, and Impairment of Fertility

i. Paragraph 1 - Hyphenate "resin-treated".

ii. Paragraph 2 - ...and the multiple...

e. Pediatric Use

i. As experience in pediatric patients is limited...

ii. ...in 100 mg of Cholestyramine for Oral Suspension.

6. ADVERSE REACTIONS

a. Paragraph 2 - Less Frequent Adverse Reactions

Sentence 1 - Abdominal discomfort and/or pain, flatulence, nausea, vomiting, diarrhea, dyspepsia, eructation, anorexia, and steatorrhea, bleeding...

b. Add the following as the next subsection under "gastrointestinal":

Laboratory test changes - Liver function abnormalities.

7. DOSAGE AND ADMINISTRATION

a. First Paragraph

i. Line 1 - The recommended starting adult dose is one packet or one level scoopful (9 grams of Cholestyramine for Oral Suspension contains 4 grams of anhydrous cholestyramine resin) once or twice a day. The recommended maintenance dose for Cholestyramine for Oral Suspension is 2 to 4 packets or scoopfuls daily (8-16 grams anhydrous cholestyramine resin) divided into two doses. It is recommended that increases in dose be gradual with periodic assessment of lipid/lipoprotein levels at intervals of not less than 4 weeks. The maximum recommended daily dose is six packets or scoopfuls of Cholestyramine for Oral

Suspension (24 grams of anhydrous cholestyramine resin). The suggested time of administration is at mealtime but may be modified to avoid interference with absorption of other medications. Although the recommended dosing schedule is twice daily, Cholestyramine for Oral Suspension may be administered in 1-6 doses per day.

ii. Second paragraph, Revise as follows:

Cholestyramine for Oral Suspension should not be taken in its dry form. Always mix the dry powder with water...

b. Concomitant Therapy - Revise this subsection to read as follows:

Primary evidence suggests that the lipid-lowering effects of cholestyramine on total and LDL-cholesterol are enhanced when combined with a HMG-CoA reductase inhibitor, e.g., pravastatin, lovastatin, and simvastatin. Additive effects on LDL-cholesterol are also seen with combined nicotinic acid/cholestyramine therapy. See the Drug Interactions subsection of the PRECAUTIONS section for recommendations on administering concomitant therapy.

c. Preparation

i. The section heading "Preparation" is considered a subsection under DOSAGE AND ADMINISTRATION. Decrease the prominence of this subsection heading to be consistent with your other subsection headings.

ii. Revise line 1 - The color of Cholestyramine for Oral Suspension may vary somewhat...

iii. Revise paragraph 2 - Cholestyramine for Oral Suspension may also be...

8. HOW SUPPLIED

a. Cholestyramine for Oral Suspension, USP is available...

b. Indicate that the can is provided with a scoop.

c. Include the storage recommendations.

d. Please indicate that the scoop is not interchangeable with scoops from other products.

Please revise your labels and labeling, then prepare and submit draft labels and labeling.

Deficiencies pertaining to ANDA 74-555 (Light):

CONTAINER:

1. 5 g (Single Dose)

   a. Include the following to appear beneath the Nutra Sweet claim:

      This product also contains sucrose.

   b. Revise the established name to read as follows:

      CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT)

   c. We note your NDC numbers only has eight digits. We refer you to 21 CFR 207.35 which states that a NDC number shall consist of ten digits. Please revise.

   d. Include the following just above the "Keep this and...children." statement:

      The package is not child resistant.

   e. Include the strength (net quantity) to appear beneath the established name as seen on the carton labeling.

   f. ...4 grams of cholestyramine resin in 5 grams of Cholestyramine for Oral Suspension.

   g. Replace with "Cholestyramine for Oral Suspension".

2. 210 g

   a. See comments under CONTAINER, as appropriate.

b. Revise the Dosage statement to read as follows:

USUAL DOSAGE: See package insert.

c. We encourage you to indicate that the scoop is not interchangeable with scoops from other products.

CARTON: 60 X 5 g packets

1. Front and Back

a. See comments under CONTAINER, as appropriate.

b. Relocate "4 grams of cholestyramine resin, USP, per packet" to appear immediately beneath the established name.

c. Add the following statement:

Usual Dosage: See package insert.

2. Side of carton for both the beverage and food preparations:

a. Revise the statement to read "PREPARATION OF CHOLESTYRAMINE FOR ORAL SUSPENSION (LIGHT)".

b. The illustration under item 1 is labeled as Questran Light. Please ensure that this illustration reflects your product.

3. Top

We prefer that you use "cholestyramine" rather than

INSERT:

1. GENERAL COMMENT

a. When there is not enough room on the line for a word please use hyphens to break up the word rather than placing the word on the next line and leaving a large space.

b. Please make the following changes wherever it appears in the insert except where indicated below:

i. should read "Cholestyramine for Oral Suspension (light)".

ii. should read "cholestyramine resin".

2. TITLE

The established name should read as follows:

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT)

3. DESCRIPTION

a. Paragraph 1, first sentence - Revise as follows:

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (LIGHT), the chloride...

b. Revise the second sentence as follows:

"...resin is not absorbed..."

c. Please identify citric acid as: citric acid (anhydrous).

4. INDICATIONS AND USAGE

a. Second paragraph, fifth line

...reduction... (singular)

b. Third paragraph, line 4

...restriction for weight...

5. PRECAUTIONS

a. Information for Patients - ...Cholestyramine for Oral Suspension (Light)...

b. Pediatric Use, Second sentence.

i. As experience in pediatric patients is limited...

ii. ...100 mg of Cholestyramine for Oral Suspension (Light).

7. ADVERSE REACTIONS

Miscellaneous - Delete "dental caries".

8. DOSAGE AND ADMINISTRATION

a. Paragraph 2 - Cholestyramine for Oral Suspension (light) should not be taken in its dry form. Always mix the dry powder with water...

b. Concomitant Therapy, line 2- ...effects of cholestyramine...

c. Preparation

i. The section heading "Preparation" is considered a subsection under DOSAGE AND ADMINISTRATION. Decrease the prominence of this subsection heading to be consistent with other subsection headings.

ii. Revise line 1 - The color of cholestyramine for Oral suspension (light) may very somewhat...

iii. Revise paragraph 2, Line 1 - Cholestyramine for Oral Suspension (Light) may also be...

9. HOW SUPPLIED

a. Revise to read:

CHOLESTYRAMINE FOR ORAL SUSPENSION, USP (Light) is available in...

b. Include the storage temperature range.

c. Indicate that the can is provided with a scoop.

d. Please indicate that the scoop in not interchangeable with scoops from other products

Please revise your labels and labeling, then prepare and submit draft labels and labeling.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. The CGMP compliance of all the facilities listed in your applications shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of these applications.

2. Please submitted the current available room temperature stability data for the executed batches, if available.

The files on these applications are now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw these applications. Your amendments should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The responses to this letter will be considered as MAJOR amendments and should be so designated in your cover letters. You will be notified in a separate letter of any deficiencies in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 5/16/95

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-554, 74-555
ANDA 74-554, 74-555 /DUP
Division File x 2
Field Copy
HFD-600/Reading File

Not Approvable - MAJOR Amendment

ANDA 74-555

Copley Pharmaceutical, Inc.
Attention: Bernie Grubstein
25 John Road
Canton Commerce Center
Canton, MA 02021

NOV 16 1994

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cholestyramine for Oral Suspension, USP (Light)

DATE OF APPLICATION: October 3, 1994

DATE OF RECEIPT: October 28, 1994

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

David Konigstein
Consumer Safety Officer
(301) 594-0370

Sincerely yours,

/S/ 11/15/94

Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Copley Pharmaceutical Inc.
25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111
Fax:
Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

Labeling review done 2/9/95

3 OCTOBER 1994

RECEIVED

OCT 28 1994

GENERIC DRUGS

Roger L. Williams, M.D.
Director
Office of Generic Drugs
CDER, FDA
METRO PARK NORTH II
7500 Standish Place
Room 150
Rockville, MD 20855-2773

RE: CHOLESTYRAMINE LIGHT POWDER FOR ORAL SUSPENSION (EQ 4GM RESIN/PACKET & SCOOPFUL

Dear Dr. Williams:

Copley Pharmaceutical IHc., respectfully submits for your division's review our Abbreviated New Drug (ANDA) Application for Cholestyramine Light POwder for Oral Suspension (eq. 4gm/packet & scoopful). This application is in accordance with theguidelines set forth in Section 505(j) of the Food, Drug & Cosmetic Act.

Bioequivalence studies, in accordance with the guidelines issued were conducted at Pharmakinetics Laboratories in Baltimore, Maryland and the results demonstrating equivalence to the brand formulation, Questran Light, manufactured by Bristol Laboratories is provided with our submission.

A separate copy of this application is being forwarded to the Boston District Office in compliance with the Federal Register notice of September 1993.

Thank you for your consideration of this application.

Sincerely yours,

Bernie Grubstein

ENCLOSURES: Manufacturing, Bioequivalency, Archive Sections & Separate Binder for Section XVI, validation (2 copies).

BIOAVAILABILITY

NDA ORIG AMENDMENT

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

November 1, 1996

Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NOV 0 7 1996

MAJOR AMENDMENT with request for reclassification to MINOR AMENDMENT
Cholestyramine Powder For Oral Suspension, USP (Light)
4 gm / 5 gm
ANDA 74-555

Dear Sir:

Reference is made to our above Abbreviated New Drug Application and to your deficiency letter of August 1, 1996 (ATTACHMENT 1) which was designated as a MAJOR amendment response. We are requesting reclassification of this response to a MINOR amendment based on the following:

- **We believe that the MAJOR classification for this amendment was based on Comment 1 of the Agency's August 1, 1996 deficiency letter. We believe this to be the case since the last deficiency letter for our Cholestyramine Powder (Regular) ANDA 74-554, was identical to this letter (aside from comment 1) and was classified as a MINOR amendment.**
- **In reference to our response to comment 1 where we were instructed by Dr. Jason Gross, OGD Division of Bioequivalence, that comparative information using the standard QUESTRAN as the reference product would not be required (Ref # OGD95336), we feel reclassification to a MINOR Amendment is duly warranted.**

In regard to your deficiency comments we are providing the following responses:

A. Chemistry Deficiencies:

COMMENT 1:
You failed to submit the comparative information using standard Questran of Bristol Myers Squibb as the reference product. We refer to your correspondence dated October 2, 1995.

RESPONSE:
Copley was advised by Dr. Jason Gross based on a telephone conservation (ref #

OGD95336) that we would not be required to re-submit the comparative information using standard QUESTAN as the reference product.

COMMENT 2:
We note that you propose to use the "modified" USP Loss on Drying (LOD) method. You must use the USP LOD method "as is" and comply with it as your modified procedure does not give comparable results. You may use the Karl Fischer test as an additional test and make batch corrections based on these test results. We acknowledge your intention to pursue a change of the LOD test with USP.

RESPONSE:
We believe the current USP LOD procedure significantly underestimates the true quantity of water in the Cholestyramine Resin raw material. We have communicated with USP regarding the LOD test procedure (O'Brien to Dr. Cecil 5/3/96, USP response Cecil to O'Brien 7/18/96 provided in ATTACHMENT 2). We believe USP is currently considering this issue.

Until USP determines the outcome of our proposed LOD test procedure changes, we will comply with the USP LOD method "as is". We have added the Karl Fischer test, as an additional test, and will adjust the batch based on this test result as recommended. A copy of our revised specifications and test methods for Cholestyramine Resin USP is provided in ATTACHMENT 2.

COMMENT 3:
You failed to submit a cGMP statement from your alternate microbiological testing facility -

RESPONSE:
ATTACHMENT 3 contains the requested compliance statement from

COMMENT 4:
Please delete your proposed overage of % of Cholestyramine Resin to compensate for manufacturing loss. You may adjust the actual amount of Cholestyramine Resin weighed based on moisture and exchange capacity analyses only. Please submit revised manufacturing batch records.

RESPONSE:
As requested, Copley will not incorporate the proposed % overage of Cholestyramine Resin into its manufacturing batch records. ATTACHMENT 4 contains a copy of our revised batch record (NOTE: The packaging portion of the batch record has not been included since it has not been impacted by this revision and remains unchanged). We acknowledge that we may adjust the actual amount of Cholestyramine Resin based on moisture and exchange capacity analyses only.

COMMENT 5:
Please revise your release specifications for the finished drug product to include pH and dispersibility. Please also include the pH test in the stability program.

RESPONSE:
We have revised our finished product specifications and test method to include pH (release and stability) and Dispersibility (release). Revised finished product specifications and test methods have been included for review in ATTACHMENT 5 of this amendment.

Specification limits are identical to those limits approved in our ANDA for Cholestyramine Powder (Regular), ANDA 74-554.

pH: 2.5 - 4.5

Specification parameters and test procedures for the Dispersibility can be found in the finished product specifications and test method, respectively, found in ATTACHMENT 5. We again wish to point out that these specifications and methods are identical to those found in our approved ANDA for Cholestyramine Powder (Regular), ANDA 74-554.

COMMENT 6:
Please revise your release and stability specifications to include Chloride Content of % calculated against the assay for the finished drug product. Please validate the method in the drug substance monograph for this purpose.

RESPONSE:
As requested, we have revised our finished product release and stability specifications to include Chloride Content of % *(NOTE: same limits as specified in our approved ANDA 74-554 for Cholestyramine (Regular)*). Copies of the revised finished product specifications and test method are presented in ATTACHMENT 5. Validation of the Chloride procedure is provided in ATTACHMENT 6.

COMMENT 7:
Please lower your limits for Trimethylamine (TMA) and Dialyzable Quaternary Amine for release and stability as follows:

Dialyzable Quaternary Amine as Benzyltrimethyl-ammonium chloride:	**NMT**	**%**
Trimethylamine (TMA):	**NMT**	**%**
Total Impurities:	**NMT**	**%**

RESPONSE:
As requested, Copley has modified its finished product release and stability specifications as specified. ATTACHMENT 5 contains copies of the revised finished product specifications.

COMMENT 8:
Please submit a copy of revised release specifications incorporating the revisions requested in this letter. Similarly, submit a revised stability protocol including the revisions requested in this letter.

RESPONSE:
See response to COMMENT 7.

B. Labeling Deficiencies
Various labeling changes / additions.

Response:
The requested labeling revisions/additions have been incorporated in the labeling and 12 final printed copies (6 copies with FDA Archival copy and 6 copies with Chemistry copy) have been incorporated for final approval. Pursuant to 21CFR 314.94(a) (8) (iv), we have included a side-by-side comparison of our recently revised labeling vs. our previous version. Copies of the final printed labels and the side-by-side comparison are located in ATTACHMENT 7. NOTE: We have included color laser proofs of our can and pouch labels due to obvious space constraints.

Additional note: The Agency has requested that we include the molecular weight/chemical name for the active ingredient compound in our labeling. As discussed with OGD's Labeling Division, there is no formal molecular weight or chemical name established for Cholestyramine resin.

C. Bioequivalence Deficiencies:
Please refer to the letter dated July 5, 1996.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

> **The cGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.**

RESPONSE:
The response to the bioequivalence comments have been submitted under separate cover dated August 23, 1996 . A copy of the cover letter is provided in ATTACHMENT 8.

We acknowledge your comment regarding the cGMP compliance of the facilities, and wish to point out that the manufacturing and packaging site for this ANDA application, Copley Pharmaceutical, Inc., was inspected by FDA's Stoneham, MA Field Office in July 1995 (Copy of Field Office Letter dated October 12, 1995 recommending approval is provided in ATTACHMENT 9).

We believe we have adequately addressed the Agency's concerns regarding this submission and look forward to an expeditious approval.

Regards,

Robert Kelly
Manager, Product Registrations
(617) 575-7363 (phone)
(617) 575-7362 (fax)

attachments

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

8/23/96

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

RE: Cholestyramine Light Powder
ANDA 74-555
Response to Bioequivalence Questions

Dear Mr. Sporn:

Reference is made to ANDA #74-555 for Cholestyramine Light Powder, 4g resin and to the Agency's letter of 7/5/96. This submission provides responses to the issues raised for this ANDA only. The Agency's letter of 7/5/96 included comments for this and our ANDA for the standard Cholestyramine product (74-554). Responses to issues related to ANDA 74-554 are being filed separately.

This submission provides a re-analysis of our bioequivalence data as suggested by the Agency. Based on the Agency's published work on the binding characteristics of cholestyramine and the specific technique it has recommended, it would seem that a 0.8-1.2 ratio for the K1 parameter is not consistent with the variability associated with the method. Our submission provides a more thorough discussion of this point. We believe that our data fully demonstrate our product to be bioequivalent to the reference product within the limits of the method being used. We request that the Agency reconsider its conclusions concerning these data and the bioequivalence of our product.

We look forward to a timely review and approval of our application. Please advise if there are any additional questions or concerns. I may be reached by telephone at 617-575-7520 or by FAX at 6170575-7362.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

4/8/96

N/AC
NDA ORIG AMENDMENT

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

RECEIVED
APR 09 1996
GENERIC DRUGS

RE: Cholestyramine Powder - ANDA# 74-554
Cholestyramine Light - ANDA#74-555
Deficiency Response

Dear Mr. Sporn:

Reference is made to the Agency's letter of 5/16/95 for our Chloestyramine and Cholestyramine Light ANDA's. Enclosed are our responses to the Agency's requests and questions related to chemistry and labeling. Since this is a voluminous submission, we have included tabs for each major question or section of our response to facilitate its review.

Because the Agency's letter included comments that were related to one or the other, and sometimes both of these product forms, we have developed our responses to directly correspond with the Agency's deficiency letter. Since these responses relate to 2 separate ANDA's we are submitting a copy of these responses to each ANDA with the appropriate FD356h. We trust that this will facilitate the Agency's tracking and filing of our submissions.

We hereby certify that a true copy of this submission has been provided to FDA's New England Office.

Please contact my at 617-575-7560 if there are any questions or issues related to this submission.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

1.1

Copley Pharmaceutical Inc.
25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111
Fax:
Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

October 26, 1995

AMENDMENT
N/A A

Charles Ganley, M.D.
Acting Director,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Re: ANDA # 74-555
Cholestyramine For Oral Suspension (Light)
Additional External Microbiology Testing Laboratory

Dear Dr. Ganley:

Copley wishes to provide for the addition of as an alternate microbiology testing facility to all of its approved and pending product applications. Based on guidance provided by the Agency's Mr. Nuhvich, we are simultaneously submitting supplements to each application (amendments in the case of pending applications) with a cross reference to all affected applications.

We consider these supplements/amendments to be "minor" in nature.

A copy of each of these supplements is also simultaneously being provided to the Boston District Field Office (copy of cover letter attached).

Sincerely,

Wm E. Brochu

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

NAI
"Will respond to RLD change etc."
10/16/95

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

10/2/95

ORIG NEW SUBMIS

Charles Ganley, M.D.
Acting Director,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Re: ANDA 74-555

Dear Dr. Ganley

This confirms our understanding of information provided by the Agency's Mr. Russell concerning recent decisions made by the Agency concerning the reference product for cholestyramine - light products.

The Agency has determined that the reference product for both "standard" and "light" cholestyramine products is standard Questran produced by Bristol Myers Squibb. As such all comparative information contained in our ANDA 74-555, including the in-vitro bioequivalence data must be re-submitted using the standard BMS Questran product as the reference.

As requested by Mr. Russell, I am confirming Copley's intention to resubmit the comparative information contained in our cholestyramine light ANDA using standard Questran as the comparator product.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

RECEIVED
OCT 06 1995
GENERIC DRUGS

13 OCT 95

Orig

File Draft 12/14

Copley Pharmaceutical Inc.
25 John Road
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(617) 821-6111
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N.J. (201) 894-1553

21 November 1994

ROGER L. WILLIAMS, M.D.
DIRECTOR
OFFICE OF GENERIC DRUGS
CDER, FDA
METRO PARK NORTH II
7500 STANDISH PLACE
ROOM 150
ROCKVILLE, MARYLAND 20855-2773

RE: CHOLESTYRAMINE LIGHT ORAL POWDER, 4gmresin/5gm
ANDA: 74-555

Dear Dr. Williams:

The enclosed page providing a blueprint drawing of the measuring scoop to be provided in each container of Cholestyramine Light Oral Powder USP, 4gm resin/5gm, was inadvertently omitted from our recent submission.

It has been paginated as page 1147.1 for Section XIV, Packaging Components in our original submission.

We are very sorry for this oversight.

Sincerely yours,

Bernie Grubstein

6 Dec 94 Pending

Dick to Bio

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 28, 1998

Ms. Nancy Chamberlin
Project Manager, Division of Bioequivalence
Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NDA/ANDA AMENDMENT
N/AB

Cholestyramine for Oral Suspension, USP (Light)
ANDA No. 74-555

Dear Ms. Chamberlin:

Per your telephone request of July 20, 1998, enclosed please find raw study data on diskette for **Study No. 084-08-11226** entitled, "Equilibrium Binding of Cholestyramine with Bile Acid Salts (in Simulated Intestinal Fluid (SIF) at 37^{0}C without Acid Pre-Treatment". The study was submitted to the Agency as part of the November 19, 1997 Major Amendment for Cholestyramine for Oral Suspension, USP (Light), ANDA No. 74-555.

Should you have any questions regarding this information, please do not hesitate to contact me at (781) 575-7353.

Sincerely,

COPLEY PHARMACEUTICAL, INC.

Gary M. Lewis

Gary M. Lewis
Manager, Regulatory Affairs

Enclosures:

RECEIVED
JUL 29 1998
GENERIC DRUGS

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

July 6, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

N/AM

MINOR AMENDMENT
Cholestyramine for Oral Suspension, USP (Light)
ANDA # 74-555

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application No. 74-555 for Cholestyramine for Oral Suspension, USP (Light) which was submitted on October 3, 1994.

Further reference is made to our amendments dated November 19, 1997, December 11, 1997, and February 26, 1998, and to the Agency's deficiency letter of May 4, 1998.

The purpose of this submission is to respond to the Agency's deficiency letter of May 4, 1998. For the convenience of the reviewer, we have reiterated FDA comments followed by our response. In addition, we acknowledge your comments 1-3 under Item B. We are also providing twelve copies of final printed labeling, as well as an annotated side-by-side comparison with the insert labeling of the previous version which reflect FDA's requested changes.

Should you have any questions regarding this minor amendment, please contact the undersigned at (781) 575-7695 or Mr. Gary Lewis at (781) 575-7353.

Sincerely,

COPLEY PHARMACEUTICAL, INC.

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures:
Archive Copy (blue folder): 1 copy
Chemistry, Manufacturing, Controls Copy (red folder): 1 copy

RECEIVED
JUL 08 1998
GENERIC DRUGS

Nadine 7-9-98

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

N/AB

July 1, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
Cholestyramine for Oral Suspension, USP (Light)
ANDA # 74-555

VIA FACSIMILE

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application No. 74-555 for Cholestyramine for Oral Suspension, USP (Light), and to our February 26, 1998 submission responding to FDA's Bioequivalence Deficiency Letter of February 19, 1998.

Further reference is made to June 19, 1998, June 23, 1998 and June 24, 1998 telephone conversations between Ms. Nancy Chamberlin at FDA's Division of Bioequivalence and our representatives, Ms. Regina Yeh and Mr. I. Nudelman regarding the review of the February 26, 1998 Bioequivalence Amendment. During those discussions, Ms. Chamberlin indicated that the February 26, 1998 Bioequivalence Amendment was deficient since the data provided in the amendment was not enough to cover the actual biostudy period. To ensure that the product was still stable during the actual biostudy, Ms. Chamberlin requested that Copley provide current stability data for Assay of Cholestyramine Resin for Biobatch No. 300Z01.

The purpose of this submission is to provide Assay of Cholestyramine Resin results for Biobatch No. 300Z01. The Assay was performed on June 24, 1998. The mean result of assay (99.9%) was well within the specification limits of 85%-115% which demonstrates that the product is stable after 52 months of storage and, as a result, the biobatch was good at the time the biostudy was completed in October 1997 for Cholestyramine for Oral Suspension, USP (Light).

Should you have any questions regarding this amendment, please contact the undersigned at (781) 575-7363.

Sincerely,
COPLEY PHARMACEUTICAL, INC.

Gary M. Lewis
Manager, Product Registrations
Regulatory Affairs

RECEIVED
1998
GENERIC DRUGS

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

February 26, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Bioequivalency Amendment
Deficiency Responses to Bioequivalency Letter dated February 19, 1998
Cholestyramine for Oral Suspension, USP (Light)
ANDA# 74-555

Dear Mr. Sporn:

Reference is made to our ANDA #74-555 for Cholestyramine for Oral Suspension, USP (Light) submitted October 3, 1994, and to the Agency's bioequivalency letter dated February 19, 1998 (Copy attached).

Enclosed is the Copley's response to the bioequivalency deficiency question. We have demonstrated the acceptability of the study drug used in the biostudy by providing the Agency the stability data monitored over a period of 36 months. We trust that the Agency will find the response adequate to grant its approval to our application. Thank you for your cooperation.

If you have any additional questions please contact the undersigned at (781) 575-7695. Thank You!

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures: Archive Copy (Blue folder): 1 copy
Pharmacokinetic Copy (Orange folder): 1 copy

COPLEY PHARMACEUTICAL, INC.

Bioequivalency Amendment
Deficiency Responses to Bioequivalency Letter dated February 19, 1998
Cholestyramine for Oral Suspension, USP (Light)
ANDA# 74-555

FIELD COPY CERTIFICATION

This is to certify that the field copy submitted in accord with 21 CFR 314.96(b) of the Code of Federal Regulations is a true copy of the technical section of our bioequivalency amendment for Cholestyramine Light Powder for Oral Suspension, 4 g / 5 g, ANDA # 74-555.

Regina S. Yeh, MS, RAC
Senior Regulatory Affairs Associate
Copley Pharmaceutical, Inc.

2/26/98
Date

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

December 11, 1997

Richard Penta
New England District
Food and Drug Administration
1 Montvale Ave
Stoneham MA 02180-3500

Amendment (Chemistry and Labeling)
Deficiency Responses to Letters of April 8, 1997 and September 29, 1997
Cholestyramine for Oral Suspension, USP (Light)
ANDA# 74-555

Dear Mr. Penta:

Pursuant to 21CFR314.96(b), Copley is forwarding a true copy of amendment filed with the above referenced application. Copley certifies that the material contained in this "field copy" are true copies of the technical section of our amendment for ANDA # 74-555 that was submitted to FDA headquarters.

If there are any questions or concerns regarding these data, please feel free to call or fax at the following numbers: 781-575-7828 (direct dial) or 781-575-7362 (fax).

Sincerely,

Regina S. Yeh
Senior Regulatory Affairs Associate

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

December 11, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

FPL
NDA ORIG AMENDMENT
AC

Amendment (Chemistry and Labeling)
Deficiency Responses to Letters of April 8, 1997 and September 29, 1997
Cholestyramine for Oral Suspension, USP (Light)
ANDA# 74-555

Dear Mr. Sporn:

Reference is made to our ANDA #74-555 for Cholestyramine for Oral Suspension, USP (Light) submitted October 3, 1994, and to the Agency's deficiency letters dated April 8, 1997 (Bioequivalence, Microbiology Test Laboratory, and Labeling) and September 29,1997 (labeling) (Attached).

Please be informed that Copley Pharmaceutical, Inc. has provided the Agency the bioequivalence information in response to the bioequivalence deficiencies addressed in the April 8, 1997 letter under a separate cover (submitted November 20, 1997). Enclosed in this amendment are responses to the remaining chemistry and labeling deficiencies in the April 8, 1997 letter and the labeling deficiencies in the September 29, 1997 letter.

In regard to your deficiency comments we are providing the following responses:

Chemistry Deficiency:
(Response # 1 to April 8, 1997 letter)

A revised cGMP compliance statement from
is provided in this submission.

Labeling Deficiencies:
(labeling responses to April 8, 197 and September 29, 1997 letters)

The requested labeling revisions have been incorporated in our labeling and 12 copies of final printed labeling (6 copies with Archival copy and 6 copies with CMC copy) are provided to the Agency for approval. We have also provided the side-by-side comparison of our recently revised labeling vs. our previous version.

With the inclusion of the chemistry and labeling deficiency responses under this amendment, we believe all deficiencies have been adequately addressed. We trust the Agency will find these responses adequate to grant its approval to our application. Thank you for your cooperation.

If you have any additional questions please contact I. Nudelman at (781) 575-7695 or Regina Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828.

Thank You!

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures: Archive Copy (Blue folder): 1 copy
Chemistry, manufacturing and control copy (Red folder): 1 copy

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

November 19, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Major Amendment (Bioequivalence)
Deficiency Responses for Letters of February 20, 1997 and April 8, 1997
Cholestyramine for Oral Suspension, USP (Light)
ANDA# 74-555

Dear Mr. Sporn:

Reference is made to our ANDA #74-555 for Cholestyramine for Oral Suspension, USP (Light) submitted October 3, 1994, and to the Agency's deficiency letters dated February 20, 1997 (Bioequivalence) and April 8, 1997 (Bioequivalence, Microbiology Test Laboratory, and Labeling) (Attached).

In order to facilitate the Agency's review of this submission, we are presenting herewith the Bioequivalence information. We will provide the CMC and Labeling portion of the replies to the above referenced deficiency letters under a separate cover. Please be informed that we will also provide the final printed package insert labeling and the side-by-side comparison requested in the September 27, 1997 deficiency letter. We anticipate to submit the CMC and labeling deficiency responses by the week of December 1, 1997. With the anticipated inclusion of the CMC and labeling deficiency responses under a separate submission, we believe all deficiencies will be adequately addressed then.

Bioequivalence Deficiencies:
(FDA letters of February 20, 1997 and comment # 2 of April 8, 1997)

The Agency's requirements for the In-Vitro Bioequivalence Study of Cholestyramine for oral suspension, USP (Light) were reviewed during a telephone discussion of March 7, 1997 between S.G. Nerurkar, Ph.D. of the Division of Bioequivalence and William Brochu, Ph.D. of Copley Pharmaceutical Inc. Dr. Nerurkar advised Copley to repeat the experiment and present the calculations described in the July 5, 1996 Bio deficiency letter (see Response to February 20, 1997 letter). The requested study encompasses the equilibrium binding study at 0.1mM to 30 mM total bile salt concentrations, without acid pre-wash, with specific calculation requirements

The requested in-vitro study was successfully completed and as can be noted in the enclosed In-Vitro Bioequivalence Study Report (provided in 2 volumes), the Copley Pharmaceutical's Cholestyramine for oral suspension, USP (Light) has been demonstrated to be bioequivalent to the Bristol Laboratories®' Questran® Light. The conclusion is based on the comparable results of capacity and affinity of binding to a mixture of three bile salts, observed in in-vitro equilibrium binding studies.

We believe that the enclosed in-vitro bioequivalence study report adequately addresses the bioequivalence deficiencies raised in the February 20, 1997 and April 8, 1997 letters. If you have any additional questions please contact I. Nudelman at (781) 575-7520 or Regina Yeh (Senior Regulatory Affairs Associate) at (781) 575-7828.

Thank You!

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures: Archive Copy (Blue folder): 1 copy (2 volumes)
Pharmacokinetic Copy (Orange folder): 2 copies (2 volumes each)