DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE

Food and Drug Administration
Denver District Office
Building 20 - Denver Federal Center
P. O. Box 25087
Denver, Colorado 80225
TELEPHONE: 303-236-3000

October 21, 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Samuel T. Poxon
President and Owner
Calvin Scott & Company, Inc.
209 Eubank Blvd. NE
Albuquerque, New Mexico 87123

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Ref. # DEN-99-02

Dear Mr. Poxon:

During an inspection of your firm Calvin Scott and Company, on July 24 through August 6, 1998, Investigator Cynthia Jim determined that your firm repackages and relabels prescription and non-prescription drugs, including Schedule III and IV drugs. The products you repackage and relabel are drug products as defined by section 201(g) of the Federal Food, Drug, and Cosmetic Act (the Act). The above stated inspection revealed that your products are adulterated within the meaning of Section 501(a)(2)(B) of the Act in that the controls used for the manufacturing, processing, packing, or holding of these products are not in conformance with current Good Manufacturing Practice regulations under Title 21, Code of Federal Regulations (21 CFR), parts 210 and 211. Deviations noted during the inspection include, but are not limited to the following:

1. Failure to establish a written testing program designed to assess the stability characteristics of repackaged drug products and to develop stability test results used in determining appropriate storage conditions and expiration dates. For example, your firm does not have a written stability testing program, but has conducted a one time composite assay and dissolution test on some of the drug products you repackage. However, you have not tested an adequate number of batches of each repackaged drug product in each container closure system in which the drug product is marketed; used statistical criteria to determine sample size and test intervals for each drug attribute; defined storage conditions for samples; and defined reliable, meaningful, and specific test methods.

2. Failure of repackaged drug products to bear expiration dates determined by appropriate stability studies to assure drug products meet appropriate standards of identity, strength, quality, and purity at time of use. For example:

   a. The one time composite assay and dissolution test on some of the drug products you repackage is not adequate to support the use of the bulk drug manufacturer's original expiration date. Therefore, the expiration dates, which are currently used on your repackaged drug products, are not acceptable.

   b. No stability studies were observed to support expiration dates on repackaged drug products beyond the expiration date of the bulk drug manufacturer's original expiration date. For example, L-Thyroxine Sodium 100 mcg, lot CON-1297, was given a repackaged expiration date of 8/99, but the expiration

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date of the bulk drug product was 8/98. Phentermine 30 mg, lot CS-0102, was given a repackaged expiration date of 2/99, but the expiration dates of the co-mingled bulk drug products included lot 6L208, expiration date of 2/99; lot 6K071, 12/98; lot 6L212, 2/99; lot 6H093, 10/98; and lot 6F068, 10/98.

3. Failure of the Master Control and Production Records to include a description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling. For example, no specifications were observed for containers and closures used for repackaging drug products. Master labels were not observed for repackaged drug products.

4. Failure to verify the accuracy of all preparations before commencing the repackaging process to prevent mix-ups as required by SOP [redacted] or to verify the proper product and count prior to distribution as required by SOP [redacted]. For example:

   a. Supramine 37.5 mg, Lot CS-8524, was released and distributed labeled as Phendimetrazine 35 mg.

   b. Phendimetrazine 35 mg, Lot CS-7652, was released and distributed labeled as Phentermine.

   c. 14 count Phentermine 18.75 mg, Lot CON 1597, was labeled as 7 count Phentermine.

5. Failure of Batch Production and Control Records to include complete information relating to the production and control of each batch in that a lot number is not assigned to each repackaging operation when a bulk shipment is repackaged in more than one operation from the original manufacturer's bulk container. For example:

   a. The following drug products were repackaged in more than one operation, but each operation was assigned the same lot number as that assigned to the original manufacturer's bulk container, then distributed to more than one consignee:

      i. Phendimetrazine 35 mg tablets, Lot CS-0277 repackaged on various dates between 1/16/98 and 6/4/98.

      ii. Phentermine HCl 30 mg capsules, Lot CS-0102 repackaged on various dates between about 12/23/97 and 2/25/98.

      iii. Phentermine HCl 30 mg capsules, Lot CS-0021 repackaged on various dates between about 1/6/98 and 3/9/98, and also had two repackaging operations on 1/7/98 and 1/14/98 where product labeling was identical making them indistinguishable.

      iv. Diethylpropion 25 mg tablets, Lot CS-0287 repackaged on various dates between 1/28/98 and 4/17/98.

   b. The following bulk shipments were commingled and assigned the same Calvin Scott lot number prior to repackaging operations:

      i. Phentermine 30 mg capsules with lot numbers 6L208, 6K071, 6L212, 6H093, and 6F068 were co-mingled and assigned Calvin Scott number CS-0102 .

      ii. Phentermine 37.5 mg tablets with lot numbers 9-0396 and 8-2096 were co-mingled and assigned Calvin Scott number CS-0023.

      iii. Phentermine 8 mg tablets with lot numbers 1-2297 and 5-1997 were co-mingled and assigned Calvin Scott number CS-0157.

      iv. Diethylpropion 25 mg tablets with lot numbers 1-1497 and 10-0696 were co-mingled and assigned Calvin Scott number CS-0074.

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v. Pondimin 20 mg tablets with lot numbers 091327, 0961280, 091272, and 091313 were co-mingled and assigned Calvin Scott number CON-1797.

6. Failure of batch production and control records to always include complete labeling control records, including specimens or copies of all labeling. For example:

a. The repackaging records for the following drug product failed to include the date of the relabeling operation: Phentermine 30 mg capsules, Lot CS-0102, repackaged on 12/29/97, 1/7/98, 1/14/98, 1/16/98, 1/21/98, and 1/29/98.

b. The repackaging records for the following drug product failed to have a copy of the label attached: Phentermine 30 mg capsules, Lot CS-0102, repackaged on 1/12/98.

c. The repackaging records for the following drug products failed to reconcile the quantity of labels issued, used, and destroyed: (i) the Repackaging Request form for Phentermine 30 mg capsules, Lot CS-0092, repackaged on 3/9/98 indicated that [redacted] labels were requested and that [redacted] labels were completed, i.e., used; however, [redacted] labels were listed as surplus and destroyed; (ii) the Repackaging Request form for Phentermine 30 mg capsules, Lot CS-0102, repackaged on 12/30/97 indicated that [redacted] labels were requested; however, [redacted] labels were completed, i.e., used, and [redacted] labels were listed as surplus and destroyed.

7. Failure to reconcile the use of each lot of drug product in inventory records and to investigate and document any unexplained discrepancies. For example:

a. The Detail Transaction Report for Phentermine 30 mg, Lot CS-0081, indicated that [redacted] capsules were received on 3/24/97 and placed in inventory. On 7/17/97 a physical count showed a shortage of [redacted] capsules and the inventory was adjusted. On 1/5/98 a physical count showed a shortage of [redacted] capsules and the inventory was adjusted. On 1/30/98 the lot was shown as depleted; however, a shortage of [redacted] capsules was shown. The inventory was adjusted to zero. This was not investigated.

b. The Detail Transaction Report for Phenzene 35 mg, Lot CS-0112, indicated that [redacted] tablets were received on 4/15/97 and placed in inventory. On 6/18/97 a physical count showed a shortage of [redacted] tablets and the inventory was adjusted to zero. This was not investigated.

8. Failure to retain a reserve sample that was representative of each lot in each shipment of drug product. For example:

a. The following are examples of 1997 reserve samples that were missing:

i. Thyroid : Lot CS-0067

ii. Ditex: Lot CS-0289

iii. Donnatal: Lot CS-0056

iv Phentermine: Lots CS-0079, CS-0171, CS-0081, CS-0134, CS-0146, CS-0051, CS-0015

v. Supramine: Lots CS-0135, CS-0090

vi. Phendimetrazine: Lots CS-0218, CS-0068

b. No reserve samples were observed for drug product repackaged under consignment.

c. The following bulk drug lots were commingled and assigned one Calvin Scott lot number; however, only one reserve sample was retained:

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i. Phentermine: Lot CS-0023 from manufacturer's bulk lots 090396 and 082096

ii. Phentermine: Lot CS-0157 from manufacturer's bulk lots 012297 and 061997

iii. Phentermine: Lot CS-0008 from manufacturer's bulk lots 120396 and 120496

iv. Diethylpropion: Lot CS-0074 from manufacturer's bulk lots 100696 and 11497

9. Failure of records for returned drug products to include the reason for the return, date of disposition, and ultimate disposition. Records of returned drug products were not always found or were not accurate. For example:

a. The RTS (return to stock) form was used to record the return of drug products; however, this form did not include the reason for the return, date of disposition, and ultimate disposition. Documentation of this information was not observed.

b. The following returns were not documented:

i. Any drug product which was returned and not placed back into stock

ii. [xxx] Phentermine Lot CS-0162 on 2/5/98

iii. [xxx] Phentermine Lot CS-0008 on 3/5/98

iv. [xxx] Phendimetrazine Lot CS-0112 on 3/5/98

v. [xxx] Phentermine Lot CS-0051 on 3/5/98

vi. [xxx] Thyroid ½ gram Lot CS-0273 on 3/5/97

vii. [xxx] Thiazide Lot CS-0018 on 3/5/98

viii. [xxx] Phentermine Lot CS-0011

c. The following returns were recorded differently on the RTS (return to stock) form versus the Inventory Receipt Log as follows:

i. [xxx] Thyroid 1 gram Lot CS-9917 returned on 5/15/97 versus [xx] DHEA

ii. [xxx] Diethylpropion 75 mg Lot CS-9637 returned on 6/19/96 versus [xxxx] Diethylpropion 25 mg

iii. [xxx] Phendimetrazine Lot CS-9774 returned on 8/22/96 versus [xxx] Phendimetrazine 35 mg Lot CS-9974

We are in receipt of your letter responding to the Form FDA 483, List of Observations, which issued at the conclusion of our inspection. Your promised corrective actions will be evaluated during our next inspection.

One of our primary areas of concern is the lack of adequate stability studies to support expiration dates used on each repackaged drug product in each container type. Under certain conditions, the original bulk drug manufacturer's expiration date may be used without conducting stability studies; however, all conditions must be met. These conditions can be found in the Draft Guideline on Repackaging of Solid Oral Dosage Form Drug Products. Our investigator indicated that you already had a copy.

You must conduct adequate stability studies of all repackaged drug products because our review shows that even if these conditions referenced in the draft guideline are adjusted to meet your firm's operations, you do not meet these conditions. Examples of conditions which must be met are:

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A. The original bulk container of drug product was not opened previously and the entire contents repackaged in one operation; and

B. The original bulk drug manufacturer's container was other than glass and the repackaging container was demonstrated to be equivalent to or exceed the original bulk manufacturer's container in terms of water vapor permeation and compatibility with the drug product, or where the original bulk drug manufacturer's container is polyethylene, the repackaging container meets current USP standards for high density polyethylene containers; and

C. The repackaging container either meets or exceeds the original bulk manufacturer's container specifications for light transmission or meets current USP standards for light transmission; and

D. The repackaging container meets or exceeds the special protective features of the original bulk manufacturer's container, e.g., for material leaching and low moisture; and

E. The repackaging container-closure system meets current USP standards for a "tight container" or a well-closed container."

The following are examples of repackaged drug products which were not repackaged in one operation from the original manufacturer's bulk container that had not been opened previously. No stability studies were observed for these drug products:

1. Phendimetrazine 35 mg tablets, Lot CS-0277 repackaged on various dates between 1/16/98 and 6/4/98

2. Phentermine HCl 30 mg capsules, Lot CS-0102 repackaged on various dates between about 12/23/97 and 2/25/98

3. Diethylpropion 25 mg tablets, Lot CS-0287 repackaged on various dates between 1/28/98 and 4/17/98

Specifications for each characteristic for each type of original bulk drug manufacturer's container were not observed; therefore, a comparison could not be made against specifications of the containers used for repackaging. Your firm did not have specifications for each characteristic, e.g., actual test results for water vapor permeation, light transmission, material leaching, and low moisture for each container type used in repackaging operations. You had a letter from your supplier of amber containers which indicated that the amber containers comply with 21 CFR 177.1520 and 21 CFR 175.300; however, actual test results were not included in the letter, nor did the supplier letter indicate whether the closure system met USP standards for a "tight container" or a "well-closed container" as required in the USP for the specific drugs you repackage. You indicated that your polyethylene bags met 21 CFR 177.1350 and 21 CFR 177.1520; however, these regulations are for food products and are not acceptable justification for using the containers for pharmaceuticals.

The following are examples of repackaged drug products which were repackaged into either heat sealed plastic bags (HS), zip lock plastic bags (RB), child resistant amber vials (CRC), and bulk white plastic bottle for which no stability studies were observed. Documentation that these container/closure systems met or exceeded "B" through "E" above for the original manufacturer's bulk container was not observed:

1. Phendimetrazine 35 mg tablets in HS, Lots CS-0073, CS-0267, CS-0277, CS-0300, CS-0311, CS-0334, CS-0384; in RB, Lots CS-9652, CS-9920, CS-9775; and in CRC, Lots CS-0119, CS-0262, CS-280, CS-029

2. Phendimetrazine 105 mg capsules in HS, Lot CS-0265

3. Phentermine HCl 8 mg tablets in HS, Lots CS-0175; in CRC, Lot CS-0164; and in bulk white bottles, Lot CS-0164

4. Phentermine HCl 15 mg capsules in HS, Lot CS-0098; and in bulk white bottles, Lot CS-0133

5. Phentermine HCl 30 mg capsules in HS, Lots CS-0021, CS-0097, CS-0101, CS-0102, CS-0357; in CRC, Lots CS-0081, CS-0102, CS-0103; and in bulk white bottles, Lot CS-0102

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6. Supramine 37.5 mg tablets in HS, Lot CS-0141; and in CRC, Lot CS-0143

7. Supramine 37.5 mg capsules in HS, Lot CS-0285

8. Supramine 37.5 mg capsules in RB, Lot CS-9922

9. Diethylpropion HCl 25 mg tablets in HS, Lots CS-0287, CS-0383, CS-9875; and in CRC, Lots CS-0072, CS-0074, CS-0287

10. Phenobarbital ½ gram tablets in HS, Lot CS-0295

11. Meprobamate 400 mg tablets in CRC, Lot CS-0274

12. Meridia 15 mg capsules in bulk white bottles, Lot CS-0338

13. Pondimin 20 mg tablets in HS, Lot CS-0184

Because your firm does not appear able to meet all of the above conditions "A" through "E", you must conduct adequate stability studies to support expiration dates used on all repackaged drug products. During the inspection, our investigator provided you with copies of the Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics and the CDER Guideline for Industry for Stability Testing of New Drug Substances and Products. These guidelines provide the type of stability program and data that would be acceptable. Your current practice of testing some of your drug products one time is not acceptable.

You should also review all labels used on repackaged drug products to assure they contain all necessary information, such as a prescription legend and appropriate warning statements.

During our inspection, you mentioned the possibility of hiring the services of a consultant to deal with GMP issues, and specifically stability issues. Should you decide to follow this course of action we recommend you consider the following factors when hiring a Quality Consultant:

1. How long the consultant has worked with the drug GMP regulations, and specifically with firms which repackage and relabel drug products.

2. Is the consultant's knowledge current?

3. How does the consultant know what CDER's "current" policies and interpretations are for drug GMP's, and specifically for repackaged and relabeled drug products?

4. Does the consultant participate in training courses?

5. Is the consultant frequently asked to give presentations at FDA/Industry sponsored seminars? What have been the reactions to these presentations?

6. One of the primary attributes of a good consultant is to be a "good communicator". The consultant must be able to communicate problems and provide solutions in a clear, concise manner and in such a way that your company knows how to perform corrections the "right" way, the first time.

7. Has the consultant been deposed and/or testified as an expert witness, either for the FDA or for industry?

8. Obtain a listing of the consultant's clients over the last several years. Check these references.

9. What types of certifications does the consultant have, i.e., is the certification recognized by professional societies, etc?

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The violations identified at the beginning of this letter are not intended to be an all inclusive list of deficiencies at your facility. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action, including seizure or injunction, without further notice. Federal agencies are advised of the issuance of all warning letters for drug products so that they may take this information into account when considering the award of contracts.

Please advise this office, in writing, within fifteen (15) working days after receipt of this letter, of the specific actions you have taken to correct the violations. Your response may refer to your August 19, 1998 letter where applicable, but should include: (1) each step that has or will be taken to completely correct the current violations and prevent the recurrence of similar violations; (2) the time when correction will be completed; (3) any reason why the corrective action is not completed within the response time; and (4) any documentation necessary to indicate correction has been achieved.

Your response should be directed to Mr. Russell W. Gripp, Compliance Officer, at the above address.

Sincerely,

Gary C. Dean
District Director