



July 27, 2001

Dallas District Office
4040 N. Central Expressway
Suite 300
Dallas, Texas 75204

Ref: 2001-DAL-WL-31

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David L. Sparks, R.Ph., President/CEO
Professional Compounding Centers of America, Inc.
9901 S. Wilcrest
Houston, Texas 77099

Dear Mr. Sparks:

FDA Investigators Kari M. Laynor and Jose Martinez conducted inspections of your facility located in Houston, Texas, on January 19-21 and 25, and on June 19-21, 2000. The inspections disclosed that your firm receives antibiotics and other bulk drug substances (active pharmaceutical ingredients – APIs), inactive ingredients, and excipients from manufacturers and distributors. These drug products are subsequently repackaged and relabeled for further distribution for compounding of human and veterinary drugs.

A form FDA-483, Inspectional Observations, was issued and discussed with you at the completion of the January, 2000 inspection. Deviations from current good manufacturing practices (CGMPs), which were observed during this inspection, cause APIs and components, for human and veterinary use, that are repacked and distributed by your firm to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).¹

The inspection revealed significant violations of CGMPs:

- Failure to ensure that non-penicillin beta-lactam drugs (cephalosporins), repacked in common equipment and facilities with penicillin drugs, have not been exposed to cross-contamination with penicillin.

¹ Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

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- Failure to ensure that penicillin products have not been exposed to cross-contamination with cephalosporins.

This situation creates public health concerns associated with the considerable potential for cross-sensitivity and the possible life-threatening consequences of unintended exposure. The Agency considers the separation of penicillin production from cephalosporin drug production, and the separation of penicillin and cephalosporin drug production from non-beta-lactam drug production to be an important current good manufacturing practice.

We have reviewed your February 22, 2000, response to the inspection indicating corrections have been initiated in the CGMP areas of employee training, batch production records, and acceptance and documentation of laboratory test results. However, your response does not satisfactorily address some significant violations. Violations, which require a response, include (1) additional CGMP violations, (2) violations related to misbranding, and (3) violations related to animal drug products. We have listed some, but not all, of the specific violations in the following paragraphs.

CGMP Deviations — Adulteration

1. Failure to conduct repacking of penicillin API powders and repacking of cephalosporin API powders in separate facilities.

For example, your firm repacks penicillin G potassium salt USP, ampicillin USP, amoxicillin USP, and cephalexin USP powders in the penicillin repacking room #1132 on the same repacking equipment. Additionally, sampling for testing and acceptance of all incoming penicillins and cephalosporins for repacking purposes takes place in room #1132 on the same equipment.

2. Failure to have separate air-handling systems for repacking penicillin API powders and cephalosporin API powders.

In the penicillin repacking room #1132, activities such as employee gowning, incoming product sampling, and repacking of penicillin and cephalosporin APIs take place in or on common equipment with a laminar air flow (LAF) hood. The room is serviced by a single air-handling system and air is exhausted from the repacking equipment during operation and is recirculated back into the repacking room.

3. Failure to validate repacking processes, processing controls, and containment controls, and failure to qualify equipment used in drug repacking operations, including the LAF hoods, and filter systems used for repacking penicillins and cephalosporins.

Your firm's Antibiotic Detection Project (a one-time sampling procedure) conducted in December 1999 alone does not serve to validate the processes of the penicillin

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repackaging operations and the containment controls used by your facility. In addition, your written response to this issue is unsatisfactory for purposes of validating this system and processes. A once or twice a year sampling for the presence of beta-lactams is not adequate to demonstrate that your containment controls, and the penicillin repackaging room air handling system, will adequately prevent cross contamination of beta-lactam drugs with non-beta-lactam drugs. After initial daily testing to validate the adequacy of your containment controls, CGMP requires an ongoing monitoring program to demonstrate that your containment controls continue to prevent cross contamination. Our investigators provided information during the inspection on process validation that should assist in your efforts to attain CGMP compliance.

4. Failure to provide assurance through drug testing that non-penicillin API powders have not been exposed to cross-contamination with penicillin.

Your firm has not conducted appropriate testing of non-penicillin and non-cephalosporin APIs repacked in the penicillin Room #1132. Because both penicillin and cephalosporin APIs are repacked on common equipment using a common air-handling system in this room, a reasonable possibility exists that both of these beta-lactam product types have been exposed to cross-contamination by the other. In addition, without an adequate containment-monitoring program, you cannot provide assurance that the possibility of cross contamination of all non-beta-lactam products with penicillin or cephalosporin does not exist. Therefore, you also have failed to provide assurance through drug testing that non-beta-lactam drugs have not been exposed to cross contamination with beta-lactam drugs.

5. Failure of your written cleaning procedures to provide assurance that contamination does not occur during repacking operations that may alter the safety, identity, strength, quality, or purity of the drug product.

In your response to the FDA-483, you included Attachment 1, which is an expanded version of the SOP B.4 for Pre-Pack Area Maintenance and Cleaning Procedures. This SOP does not satisfactorily address the cleaning procedures to be followed as a means of ensuring that penicillins and cephalosporins do not become cross-contaminated from employees, equipment, or processing steps resulting from the use during processing of common facilities, equipment, and utensils.

6. Failure to establish a stability-testing program designed to assure the stability characteristics of repackaged drug substances.

Your firm labels your repackaged drug substances with the bulk drug manufacturer's expiration dates, without establishing equivalency of your container/closure system with the manufacturer's container/closure system. In lieu of stability testing of the drug substance in the repackaged container, your firm should have data demonstrating that the drug is repackaged into an equivalent container/closure system that is at least as

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protective or more protective than the manufacturer's system. This would include data demonstrating equivalence regarding water vapor permeation (protection against oxidation and moisture) and compatibility with the drug substance (ingredient migration from the container to the drug and vice versa).

7. Failure to validate the computerized software system used in the control and monitoring of API and component lot production histories.

The [REDACTED] system is used by PCCA to identify incoming quality control accepted APIs and components for use in repacking. This system also assures other drug product control functions, such as generating bar-coded finished product labeling, and matching labeling and product identification to product warehouse storage locations for assurance of accepted finished product distribution control measures. Your firm has failed to validate the performance of the [REDACTED] system to ensure its accuracy and reliability.

Violations Related to Misbranding

Misbranding - APIs Not Covered by INDs or approved NDAs

Our investigators determined that your firm has been repacking and distributing bulk drug substances that were withdrawn or removed from the market for reasons of safety or effectiveness to pharmacies engaged predominantly in the compounding of human drug products. These substances also are not covered by Investigational New Drug exemptions (INDs) or approved New Drug Applications (NDAs). The drugs your firm has shipped include:

- phenacetin bulk powder
- dipyrone bulk powder
- dihydrostreptomycin sulfate bulk powder
- adenosine-5-monophosphate (adenosine phosphate) bulk crystals
- bulk chloroform liquid

FDAMA² added section 503A to the Act relating to pharmacy compounding. Section 503A exempts compounded drugs from sections 501(a)(2)(B), 502(f)(1) and 505 of the Act as long as other specified conditions are met. One of the conditions is that the licensed pharmacist or licensed physician not compound with a bulk drug product that appears on a list published by the Secretary in the Federal Register of drug products that have been withdrawn or removed from the market because they are unsafe or not effective. Pursuant to section 503A(d)(1) of the Act, FDA published the list of "Withdrawn or Removed Drug Products" in the Federal Register as a final rule on March 8, 1999. The rule became effective on April 7, 1999 and stated that such drug products may not be legally used for compounding human drug products.

² FDAMA, the Food and Drug Administration Modernization Act, signed into law on November 21, 1997,

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Recently, the United States Court of Appeals for the Ninth Circuit declared section 503A of the Act to be invalid in its entirety³. The United States Department of Justice is considering whether to seek further judicial review of this ruling. Because the question of further review is pending, it is FDA's current position that 503A is invalid only in the Ninth Circuit. Regardless, the Agency remains seriously concerned about the public health risks associated with the distribution of bulk drug substances for use in compounding that were withdrawn or removed from the market for reasons of safety or effectiveness.

These drugs are misbranded within the meaning of section 502(f)(1) of the Act. They do not qualify for exemption under Title 21 Code of Federal Regulations (CFR) 201.120 because they are offered for use in the compounding of drug products that are new drugs under section 201(p). There are no approved applications filed pursuant to sections 505(b) or 505(j) for phenacetin, dipyron, dihydrostreptomycin sulfate, adenosine-5-monophosphate, or chloroform.

During the June 19-21, 2000, inspection, the following drugs, which also were withdrawn or removed from the market for reasons of safety or effectiveness, were noted to bear the statement "Caution: For Manufacturing, Processing or Repacking": phenacetin, adenosine-5-monophosphate, and chloroform.

Section 201.122 of Title 21 Code of Federal Regulations (21 CFR 201.122), provides for an exemption to section 502(f)(1) of the Act for a drug in a bulk package intended for processing, repacking, or use in the manufacture of another drug if its label bears that statement. However, section 201.122 specifies that the exemption shall not apply to "a substance intended for a use in manufacturing, processing, or repacking which causes the finished article to be a new drug....", unless the terms of section 201.122(a), (b), or (c) can be met.

Because there are neither active IND exemptions, nor approved NDAs on file for these drugs, any manufacturing using these substances would result in the manufacture of unapproved new drugs in violation of section 505 of the Act. As a result, these substances are not exempted from section 502(f)(1) of the Act under 21 CFR 201.122.

Misbranding – Failure to List

The following bulk drug substances repacked and distributed by PCCA are further misbranded within the meaning of section 502(o) of the Act in that the drugs have not been listed as required by section 510(j) and 21 CFR 207.20.

- phenacetin
- dipyron
- dihydrostreptomycin sulfate

³ *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001).

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- chloroform
- adenosine-5-monophosphate
- butamben
- cobalt
- diethylstilbestrol
- nitrofurazone
- potassium chloride
- povidone
- reserpine
- sulfathiazole
- tetracycline

The requirement for drug listing was brought to the attention of PCCA management in FDA Regulatory Letters dated December 5, 1985, and October 2, 1989.

In addition, we contacted FDA staff responsible for maintaining CDER's drug listing and registration database regarding your contention that your firm was unable to list your products because the FDA was unable to supply you with the proper coding for bulk chemicals used for compounding. We were told that your firm's prior attempts at listing failed because you did not include sufficient and correct information regarding the bulk drug substances and their packaging on the form FDA 2657. Contrary to your firm's written response to the January 2000, inspectional findings, drug listing was not affected by the lack of information supplied about the drug products compounded using these bulk drug substances. We advise you to contact Kathy Smith, Division of Data Management Systems (301-594-1086) to clarify any misunderstandings you may have regarding the drug listing process. Ms. Smith has indicated that she will provide you with the necessary information so that you may list your products.

Violations Related to Animal Drug Products

FDA's Center for Veterinary Medicine (CVM) finds that your firm is also in violation of sections 501(a)(5), 502(f)(1), and 502(o) of the Act in that:

Your firm has relabeled several APIs that appeared on CDER's Withdrawn Drug List dated March 8, 1999, and codified under 21 CFR 216.24 specifically for veterinary use, including dipyrone and dihydrostreptomycin. Such relabeling causes those APIs to meet the definition of a new animal drug under section 201(v) of the Act, and to be in violation of section 501(a)(5) of the Act in that they are not approved. Most animal drugs compounded by a pharmacist are in violation of section 501(a)(5) of the Act because they are new animal drugs, which are not approved, when they bear directions for use in animals. Unlike human drugs, animal drugs are not covered by section 503A, Pharmacy Compounding, of the Food and Drug Administration Modernization Act. Therefore, animal drugs compounded from active pharmaceutical ingredients are subject to the same approval requirements as manufactured animal drugs. The

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exception to this is found in the Animal Medicinal Drug Use and Clarification Act (AMDUCA) codified at 21 CFR part 530.13, which legalized the compounding of animal drugs from already approved products.

Additionally, your firm repacks APIs and excipients that do not bear indications for veterinary use but are intended for use in the compounding of drugs for animal use. APIs (i.e. bulk drug) that are sold to pharmacists, pharmacies, veterinarians or any other parties and that are used in the compounding of unapproved new animal drugs are misbranded under section 502(f)(1) of the Act in that they lack adequate directions for use in accordance with 21 CFR 201.122 and are not exempt from the requirement for maintaining adequate directions for use. Your firm has no system in place to provide distribution control over repackaged APIs intended for animal use to assure that they are in compliance with 21 CFR 201.122 and to ensure that they are used only to produce animal drugs which are covered by approvals. Finally, your firm has no written agreements in place with shippers and recipients in accordance with 21 CFR 201.150 ensuring that APIs will not be adulterated or misbranded by the end users. It appears that your firm has no knowledge of the eventual end use of the APIs that you repackage and ship in interstate commerce.

In addition, your firm has failed to list products with CVM. Failure to complete such listing causes your firm's products intended for veterinary use to be misbranded under section 502(o) of the Act.

In summary, although extensive, the above violations are not intended to be an all-inclusive list of deficiencies at your facility. Additionally, the above listed products are not intended to represent all possible violative products of your firm. It is your responsibility to ensure that *all* your drug products are in compliance with federal laws and regulations. Failure to promptly correct all violations and prevent future violations may result in regulatory action, such as seizure and/or injunction.

Please notify this office within 15 working days of receipt of this letter of the specific steps you have taken to correct these violations, including an explanation of each step being taken to prevent the recurrence of the violations.

You should address your reply to this letter to the Food and Drug Administration, Attention: Jim Lahar, Compliance Officer.

Sincerely,



Michael A. Chappell
Dallas District Director

MAC:jrl