IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
DALLAS DIVISION

IN THE MATTER OF ESTABLISHMENT INSPECTION OF:	)	
ApotheCure, Inc. 4001 McEwen Rd., Ste. 100 Dallas, Texas 75244	)	APPLICATION FOR INSPECTION WARRANT UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

To the United States Magistrate, United States District Court for the Northern District of Texas:

Charles D. Brown, a duly authorized investigator of the Dallas District Office, United States Food and Drug Administration ("FDA"), United States Department of Health and Human Services, since October 23, 1984, hereby applies for an administrative inspection warrant pursuant to 21 U.S.C. § 374 for the following establishment:

ApotheCure, Inc.
4001 McEwen Rd., Ste. 100
Dallas, Texas 75244

In support of this application, I, Charles D. Brown, represent as follows:

1. An inspection performed pursuant to 21 U.S.C. § 374 does not require an inspection warrant. United States v. Argent Chemical Laboratories, Inc., 93 F.3d 572, 577-78 (9th Cir. 1996). If a party does not consent to an inspection, however, courts have held that "FDA [is] obliged to obtain an administrative warrant in order to effect the inspection . . . ." United States v. Jamieson-McKames Pharmaceuticals, Inc., 651 F.2d 532, 540 (8th Cir. 1981), cert. denied, 455 U.S. 1016 (1982).

2. ApotheCure, Inc. ("ApotheCure") is a pharmacy licensed in the state of Texas and is engaged in the processing, packing, and/or holding of various human drugs intended for use in the cure, mitigation, treatment, or prevention of disease and/or intended to affect the structure or any function of the human body. These products are "drugs" as defined in the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 321(g), and therefore are subject to FDA jurisdiction. These products include, but are not limited to, colchicine injection for intravenous use in the treatment of

back and neck pain ("colchicine for injection"), polidocanol for injection, estriol, and dimercaptorpropanesulfonic acid for injection ("DMPS"). Some of ApotheCure's products, such as colchicine for injection, are not compounded on a patient-specific basis, but instead are labeled "For Office Use Only" and distributed to physicians nationwide. ApotheCure receives various drugs from sources outside of Texas, after introduction into interstate commerce. ApotheCure also processes drug components into finished dosage form drugs, e.g., colchicine for injection, and introduces, or causes them to be introduced, into interstate commerce, in violation of 21 U.S.C. §§ 331(a), (d), and (k).

3. Due to reports from the Portland, Oregon medical examiner of the deaths of three patients following the administration by a Portland clinic of ApotheCure's compounded colchicine for injection 1mg/2ml, the Texas State Board of Pharmacy ("TSBP"), which is responsible for enforcement of the Texas pharmacy rules and regulations, on April 26, 2007, requested, and ApotheCure agreed, to cease production of colchicine for injection pending the results of further investigation by the TSBP. At the request of the Portland medical examiner, an outside laboratory analyzed the two lots of colchicine for injection compounded by ApotheCure, which were gathered from the Oregon clinic and suspected to have caused the deaths ("suspect lots"), and found one lot to be super-potent and the other lot to be sub-potent. FDA analysis later confirmed these results.

4. On April 26, 2007, after the TSBP's request, Danny D. Horner and I, duly authorized FDA Investigators from FDA's Dallas District Office, initiated an inspection at ApotheCure, based on the reports from the Portland, Oregon medical examiner and initial analysis results of ApotheCure's compounded colchicine for injection, as described above. We showed our credentials and issued a Notice of Inspection (Form FDA 482) to Gary Osborn, R.Ph., C.C.N., ApotheCure's owner and Chief Executive Officer. FDA's limited inspection of ApotheCure from April 26 to May 3, 2007, regarding the colchicine for injection revealed poor compounding practices at ApotheCure. For example, we observed that the firm did not have proper procedures to ensure that ingredients its employees used in

compounding the drugs were accurately measured and mixed, and Mr. Osborn confirmed to FDA investigators that ApotheCure has no method of determining the actual amount of active drug ingredients incorporated into any particular compounded product, including the suspect lots. In addition, ApotheCure did not have adequate quality controls and procedures in place for sterile drug compounding to ensure that the drugs are suitable for their intended use. For example, the sterile water that ApotheCure uses in compounding its injectable drug products states on its labeling, "Contraindications: Not for injection."

5. Our limited inspection also revealed that ApotheCure was compounding the drug polidocanol for injection. We further determined that the firm's Professional Product Catalog ("ApotheCure's Catalog") listed DMPS and estriol capsules as being available for purchase. Polidocanol for injection, DMPS, and estriol are not components of any FDA-approved drugs.

6. Based on these observations, on May 3, 2007, we attempted to inspect ApotheCure's compounding of polidocanol for injection, DMPS, and estriol capsules and to evaluate the facility and the controls used for compounding sterile and nonsterile drug products. We sought to review and evaluate information regarding both the suppliers of the polidocanol and DMPS bulk active ingredients and the production records for the compounded injectable drugs. Mr. Osborn refused to produce these records for inspection. We then requested a complete list of drugs compounded by the firm. Mr. Osborn told the investigators, "That's outside the colchicine, you are out of your boundaries, and I do not have to give you anything." We again requested the list, and Mr. Osborn replied, "Absolutely not," and "if there is an incident with my products, you are welcome, otherwise stay out." Mr. Osborn continued, "As a matter of fact, I will not let you in the facility again." We referred Mr. Osborn to the Form FDA 482 (see Attachment A), and explained that it addresses FDA's authority to inspect pharmacies. Mr. Osborn abruptly exited the room without further comment, and ApotheCure's financial officer escorted us out of the facility.

7. As explained in detail in paragraphs 18 - 20, below, on multiple prior occasions, ApotheCure's compounded drug products have been linked to serious adverse health effects in patients or complaints from hospitals. Further, Mr. Osborn previously refused to permit FDA access to the firm and/or its records to follow-up on the adverse events associated its compounded drugs.

ApotheCure Is Subject To The FDA's Full Inspectional Authority

8. Pursuant to the first sentence of 21 U.S.C. § 374(a)(1), duly designated FDA employees are authorized to enter and inspect any factory, warehouse, or establishment in which drugs are manufactured, processed, packed, or held for introduction into interstate commerce or after such introduction, and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. This provision grants FDA authority to inspect pharmacies. See Wedgewood Village Pharmacy v. United States, 421 F.3d 263, 268-71 (3d Cir. 2005). Pursuant to the third sentence of 21 U.S.C. § 374(a)(1), in an establishment, like ApotheCure, in which prescription drugs and nonprescription drugs intended for human use are manufactured, processed, packed, or held, FDA may inspect "all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs [or] nonprescription drugs intended for human use, . . . which are adulterated or misbranded within the meaning of the Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of the Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of [the] Act."

9. Under 21 U.S.C. § 374(a)(2)(A), pharmacies that meet certain requirements are exempt from the "records" inspection provisions of the *third* sentence of 21 U.S.C. § 374(a)(1), but not the

general inspection provisions of the *first* sentence of 21 U.S.C. 374(a)(1).[1] One of the requirements for the limited exemption from the "records" inspection provisions of the third sentence of 21 U.S.C. § 374(a)(1) is that the pharmacy must not, "through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale *other than in the regular course of their business of dispensing or selling drugs at retail.*" 21 U.S.C. § 374(a)(2)(A) (emphasis added). This limited exemption does not apply to ApotheCure.

10. Based on ApotheCure's history and the information we were able to obtain before ApotheCure refused to permit FDA to continue the most recent inspection, ApotheCure is operating outside the traditional pharmacy practice of dispensing and selling drugs at retail and is subject to the full inspection provisions of 21 U.S.C. § 374.

11. FDA evaluates several factors to determine whether a pharmacy is operating as a compounding pharmacy dispensing drugs at retail, thus qualifying for the exemption from full inspection, or as a drug manufacturer. FDA has set forth these factors, as well as its longstanding policy regarding pharmacy compounding, in Compliance Policy Guide ("CPG") for FDA Staff and Industry, Section 460.200, Pharmacy Compounding. See Attachment B. CPG § 460.200 explains that certain establishments with retail pharmacy licenses are engaged in manufacturing and distributing

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[1] The Court of Appeals for the Third Circuit has reviewed a denial of a compounding pharmacy's motion to quash an administrative warrant issued pursuant to 21 U.S.C. § 374. Wedgewood, 421 F.3d 263. The Third Circuit held that "the exemption granted to pharmacies under *[21 U.S.C.] § 374(a)(2)(A)* only applies, by its own terms, to the 'third sentence of paragraph (a),' i.e., the records provision. The general inspection authority contained in the first sentence is not circumscribed by that exemption. It is therefore clear that the text of *[21 U.S.C.] § 374(a)* authorizes the FDA to inspect [compounding] pharmacies. ..." Id. at 270 (emphasis in original); see also Medical Center Pharmacy, Inc., v. Gonzales, 451 F. Supp. 2d 854, 866 (W.D. Tex. 2006) (under 21 U.S.C. § 374(a)(1), FDA is authorized to conduct inspections of "all pertinent equipment, finished and unfinished materials, containers, and labeling found in pharmacies" and, in addition, may conduct inspection of pharmacy records when a pharmacy is not in compliance with criteria set forth in 21 U.S.C. § 374(a)(2)), appeal on other grounds pending, No. 06-51583 (5th Cir.).

unapproved new drugs for human use in a manner outside the bounds of traditional pharmacy practice and in violation of the Act. For example, some firms receive and use large quantities of bulk drugs to manufacture large quantities of unapproved drugs in advance of receiving valid prescriptions for individually identified patients, and some firms sell these drugs to physicians and patients with whom they only have a remote professional relationship. These activities are analogous to manufacturing and distributing drugs; therefore, pharmacies engaged in such activities must comply with the provisions of the Act that pertain to manufacturers.

12. The factors that FDA will consider when deciding whether a pharmacy is engaging in activities that extend beyond the scope of traditional pharmacy practice include, among other things: whether the pharmacy is compounding drugs in anticipation of and in amounts that exceed historical demand consistent with valid prescriptions received; whether the compounded drugs are made from bulk active ingredients that are not components of any FDA-approved drug; whether the compounded drugs are copies of or are essentially copies of FDA-approved, commercially available products; and whether the pharmacy is operating in conformance with applicable state law regulating the practice of pharmacy. As CPG § 460.200 states, the list of factors is not intended to be exhaustive, and other factors may be appropriate for consideration in a particular case.

13. During the limited inspection from April 26 to May 3, 2007, we found that ApotheCure's colchicine for injection is not compounded on a patient-specific basis, but instead is labeled "For Office Use Only" and distributed to physicians nationwide. We found that, in the past twelve months, ApotheCure distributed its colchicine for injection – all labeled "For Office Use Only" - to twenty states, and none was shipped on a patient-specific basis. In addition, the investigators noted that ApotheCure compounded and distributed one shipment consisting of 315 vials of colchicine for injection containing 10 ml each to a physician who, in the past twelve months, had ordered and received 1830 vials of colchicine for injection containing 10 ml each. The quantity of colchicine for

injection sent to that physician represents an average use of 152 10 ml vials of colchicine for injection per month. ApotheCure's drug volume and distribution pattern appears to fall outside the traditional pharmacist/patient/practitioner relationship and, pursuant to CPG § 460.200, may indicate that the firm is operating outside of the business of dispensing or selling drugs at retail and engaging in activities more akin to that of a drug manufacturer.

14. During our recent limited inspection, we also observed that the firm was not operating in a state of quality control. For example: (A) ApotheCure did not have proper procedures in place to ensure that the ingredients used in compounding drugs were accurately measured and mixed and that the compounding process was documented; (B) ApotheCure did not conduct testing on finished products to assure the potency of the colchicine for injection; (C) ApotheCure used sterile "Water For Irrigation," instead of sterile "Water For Injection," as a component for making injectable drugs, even though the label on the water for irrigation stated, "Contraindications: Not for injection;" and (D) although ApotheCure's colchicine for injection – which was labeled as "preservative free" – bore an expiration date of one year, the firm had not done stability studies to support its decision to assign a one-year expiration date to this product. Despite the serious adverse events, including life-threatening injuries and death, related to ApotheCure's colchicine for injection, ApotheCure advised us during the limited inspection that it intended to start making this product again. However, as of July 6, 2007, ApotheCure represented to FDA via e-mail that it was not producing colchicine for injection.[2]

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[2] To follow-up on the reported colchicine-related deaths, the Texas Department of State Health Services (TDSHS) recently inspected ApotheCure. On July 3, 2007, at the conclusion of the inspection, the TDSHS issued to ApotheCure a list of observations (Form E-14), which cites deviations from TDSHS-enforced laws and regulations applicable to firms registered with the state of Texas as drug and food manufacturers. The Form E-14 cited, among other things, that ApotheCure had distributed in interstate commerce colchicine for injection that failed to meet the strength of active ingredient declared on product labeling, and that ApotheCure processed over-the-counter drugs without maintaining quality assurance records for those products.

15. In addition, during the limited inspection, we observed that ApotheCure was in the process of compounding a batch of polidocanol for injection. Polidocanol is not an active ingredient in any FDA-approved drug product and, as stated above, under CPG § 460.200, compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs is inconsistent with the regular course of dispensing or selling drugs at retail. FDA has serious concerns about the public health risks associated with the compounding of polidocanol for injection. Known adverse events of polidocanol include deep venous thrombosis, necrosis, and ulceration at the treated site. Additionally, reversible cardiac arrest after polidocanol sclerotherapy has been reported.

16. Further, we obtained a copy of ApotheCure's catalog used for promotion of its compounded drugs. In reviewing the drug products available in the catalog, FDA identified additional compounded drugs for which the active ingredients are not components of FDA-approved drugs, including DMPS and estriol. As noted above, compounding finished products from such components is inconsistent with the regular course of dispensing or selling drugs at retail.

17. ApotheCure's catalog also offers compounded finished drugs that are commercially available in the marketplace, or that are essentially copies of commercially available FDA-approved drug products. These include among others, Triamcinolone Injection 40%, Progesterone Injection 50 mg/ml, and Progesterone Capsules 100 mg and 200 mg. Pursuant to CPG 460.200, such compounding may be inconsistent with the regular course of dispensing or selling drugs at retail.

18. On August 4, 2004, FDA attempted, in conjunction with the TSBP, to inspect ApotheCure in response to a report from the New Jersey Poison Control System indicating that patients were experiencing symptoms of arsenic poisoning following administration of a phosphatidylcholine injectable drug compounded by ApotheCure. On the first day of the joint inspection, FDA requested records related to the compounding of the phosphatidylcholine injectable drug, but Mr. Osborn refused to allow FDA to continue and refused to provide the information requested regarding the product

linked to the patient injuries. The TSBP took over the inspection and collected samples, but Mr. Osborn later refused to let the TSBP complete the inspection. In furtherance of the State's efforts, FDA conducted analyses of the limited samples collected by the State and determined that one lot of ApotheCure's phosphatidylcholine injection did not contain the drug's active ingredient.

19. On August 13 - 26, 1996, FDA inspected ApotheCure in response to reports of patients developing abscesses after the administration of ApotheCure's compounded Adrenal Cortex Extract. The inspection revealed that the firm lacked adequate process controls. In addition to Adrenal Cortex Extract, FDA collected and analyzed several other compounded injectable products. FDA's laboratory analysis revealed the presence of mold growth in at least one product. Based on the findings from this inspection and a previous inspection (described in the next paragraph), on October 1, 1996, FDA issued a letter to the firm reiterating that at least two of its drugs were adulterated under the Act, 21 U.S.C. §§ 351(a)(1) and (c).

20. From April 22 to May 2, 1996, FDA initiated an inspection of ApotheCure following a complaint from a hospital that the firm's compounded Procaine 1% injection lacked required labeling. The inspection revealed that the firm's compounding processes lacked quality control. In addition, the inspection revealed that the firm was compounding copies of commercially available FDA-approved drugs. FDA collected and analyzed samples of some of the firm's compounded products. FDA laboratory analysis revealed product discrepancies, including multiple drug products that were found to be sub-potent, that were outlined in a letter dated August 5, 1996, from FDA to the firm. The letter resulted in product recalls by ApotheCure because the drugs were adulterated under the Act, 21 U.S.C. §§ 351(a)(1) and (c).

21. For the reasons described above, FDA has serious concerns about the public's risk of adverse health effects from drugs compounded by ApotheCure. ApotheCure has compounded drugs that are significantly super- or sub-potent, which can cause overdoses or ineffective treatment,

respectively. ApotheCure also compounds injectable drugs that do not have sufficient assurances of sterility. As stated in CPG § 460.200, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action because, under these facts, the pharmacy would be operating outside the business of dispensing or selling drugs at retail.

22. The findings from FDA's limited inspection of April 26 to May 3, 2007; the review of ApotheCure's catalog; and findings from previous FDA and state inspections indicate that ApotheCure is engaged in activities that exceed the scope of the regular course of the practice of retail pharmacy. These activities include compounding drugs in anticipation of receiving a prescription (except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions), compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs, and compounding copies or essentially copies of FDA-approved drugs. Based on this available information, ApotheCure is subject to a full inspection of its records by the FDA pursuant to 21 U.S.C. § 374(a)(2)(A).

A Warrant Is Needed For A Complete And Effective Inspection
Pursuant To 21 U.S.C. § 374

23. Because: (A) Mr. Osborn refused further inspection on May 3, 2007; (B) ApotheCure compounds drugs in anticipation of receiving prescriptions; (C) ApotheCure compounds drug products using active pharmaceutical ingredients that are not components of FDA-approved drugs; (D) ApotheCure compounds drug products that are copies or essentially copies of FDA-approved drugs; and (E) FDA has concern about the quality and potency of ApotheCure's compounded drug products, their widespread distribution, and the public health and safety following use of ApotheCure's compounded products, FDA is seeking an administrative inspection warrant. The warrant is necessary

for FDA to have access to the production and distribution records to determine the full extent to which this firm's activities are consistent with those of a drug manufacturer rather than a retail pharmacy, and to evaluate the full extent of violations of the Act, including the new drug approval requirements, and the Act's adulteration and misbranding provisions.

24. During the inspection, FDA will attempt to:

(A) determine the extent to which ApotheCure is compounding drugs using active pharmaceutical ingredients that are not components of FDA-approved drugs;

(B) determine the frequency and volumes of drug production batches, the frequency and volumes of shipments, and the number and types of consignees, e.g., physicians, clinics, hospitals, or other state licensed pharmacies, who are receiving ApotheCure's compounded prescription drugs, in order to determine the scope of the compounding by evaluating the extent to which compounding is being done for third parties for resale;

(C) determine the extent to which drug products are being compounded in anticipation of receiving prescriptions, including quantities, and how such amounts compare to the amounts compounded after receiving valid prescriptions;

(D) determine the extent to which ApotheCure compounds drug products that are copies or that are essentially copies of FDA-approved drug products, without documentation of individual patient medical need for particular variations;

(E) determine whether ApotheCure is compounding any human drug products that have been withdrawn or removed from the market for safety reasons;

(F) determine whether ApotheCure has adequate quality controls in place for all of ApotheCure's compounded drug products, including products purported to be sterile, and any potential public health concerns associated with ApotheCure's products;

(G) determine whether ApotheCure receives valid prescriptions for individually identified patients prior to dispensing the compounded drugs;

(H) identify the original manufacturers of active pharmaceutical ingredients used by ApotheCure to compound drug products, and determine whether these ingredients have been manufactured in FDA-registered facilities and meet official compendial requirements; and

(I) determine whether ApotheCure is engaged in any activities that could adversely impact public health.

25. ApotheCure's recent refusal of an FDA inspection indicates that any other attempt at an FDA inspection is likely to be refused. Without an inspection warrant, it will not be possible for us to conduct a complete or effective inspection of ApotheCure pursuant to 21 U.S.C. § 374.

Request For A Warrant

26. Therefore, pursuant to 21 U.S.C. § 374, FDA seeks an Administrative Inspection Warrant for entry to the facilities of ApotheCure, Inc., 4001 McEwen Rd., Ste. 100, Dallas, Texas, for the following purposes: (A) to inspect ApotheCure's facilities, and all things therein, including equipment, finished and unfinished materials, containers, labeling, records (including electronic and computer records), files, papers, processes, controls, and facilities, bearing on whether prescription drugs or nonprescription drugs intended for human use which are adulterated or misbranded within the meaning of the Act, or which may not be manufactured, introduced into interstate commerce, sold, or offered for sale by reason of any provision of the Act, have been or are being manufactured, processed, packed, transported, or held in such facilities, or otherwise bearing on violation of the Act; (B) to collect samples as deemed necessary by FDA; and (C) to take photographs as deemed necessary by FDA.

Process For Inspection After Issuance Of The Warrant

27. FDA will conduct the planned inspection during regular business hours. We will begin the planned inspection as soon as practicable after issuance of the warrant and will complete the inspection with reasonable promptness, assuming full cooperation by ApotheCure. We will present written Notices of Inspection and appropriate credentials as prescribed in 21 U.S.C. § 374(a).

28. As the investigator, I may be accompanied by one or more additional duly authorized FDA investigators, agents, and/or local law enforcement officers. A United States Marshal may also accompany me.

29. A return will be made to the Court within ten (10) days after the completion of the inspection.

Sworn to and subscribed by:

Charles D. Brown, Investigator
U.S. Food and Drug Administration

The above-named affiant personally appeared before me this 3rd day of August, 2007, and upon oath stated that the facts set forth in this application are true to the best of his knowledge and belief.

United States Magistrate Judge

ATTACHMENT

A

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1 DISTRICT OFFICE ADDRESS & PHONE NO.
4040 N Central Expressway
Dallas TX 75204
214 253-5200

TO

2. NAME AND TITLE OF INDIVIDUAL
Gary Osborn, R.Ph, CCN, CEO

3 DATE
4-26-07

4. FIRM NAME
Apothecure Inc.

5 HOUR
a.m.
2:45
p.m.

6. NUMBER AND STREET
4061 McEwen Road Ste 100

7. CITY AND STATE & ZIP CODE
Dallas, TX 75244

8. PHONE # & AREA CODE
972 239-0317

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

9. SIGNATURE *(Food and Drug Administration Employee(s))*
Danny D Horner Charles D. Beaver

10. TYPE OR PRINT NAME AND TITLE *(FDA Employee(s))*
Charles D. Beaver, CSO
DANNY D HORNER Investigator

[1] Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704. (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414 when the Secretary has a reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences or death to humans or animals, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use or, restricted devices which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j)). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704. (a)(2) The provisions of the third sentence of paragraph (1) shall not apply to (A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail; (B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in the course of their professional practice; (C) persons who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices solely for use in research, teaching, or chemical analysis and not for sale; (D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

Sec. 704. (a)(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 412 applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records (A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 412, or (B) required to be maintained under section 412.

Sec. 704. (b) Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

Sec. 704. (c) If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

Sec. 704. (d) Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) An accredited person described in paragraph (3) shall maintain records documenting the training qualifications of the person

and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (l)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

[3] Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing - Biological Products and Clinical Laboratories and" • • • • •

Sec. 351(c) "Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F - • • • • • "Control of Radiation.

Sec. 360 A (a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

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(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information Any regulation establishing a requirement pursuant to clause (1) of the preceding sentence shall (A) authorize such dealers and distributors to elect, in lieu of immediately furnishing such information to the manufacturer to hold and preserve such information until advised by the manufacturer or Secretary that such information is needed by the manufacturer for purposes of section 359, and (B) provide that the dealer or distributor shall, upon making such election, give prompt notice of such election (together with information identifying the notifier and the product) to the manufacturer and shall, when advised by the manufacturer or Secretary, of the need therefore for the purposes of Section 359, immediately furnish the manufacturer with the required information. If a dealer or distributor discontinues the dealing in or distribution of electronic products, he shall turn the information over to the manufacturer. Any manufacturer receiving information pursuant to this subsection concerning first purchasers of products for purposes other than resale shall treat it as confidential and may use it only if necessary for the purpose of notifying persons pursuant to section 359(a)."

• • • • • •

Sec. 360 B.(a) It shall be unlawful-
(1) • • •
(2) • • •
(3) "for any person to fail or to refuse to establish or maintain records required by this subpart or to permit access by the Secretary or any of his duly authorized representatives to, or the copying of, such records, or to permit entry or inspection, as required or pursuant to section 360A."

• • • • • •

Part G - Quarantine and Inspection

Sec. 361(a) "The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

ATTACHMENT

B

Compliance Policy Guide

Compliance Policy Guidance for FDA Staff and Industry[1]

CHAPTER - 4
SUB CHAPTER - 460

Sec. 460.200 Pharmacy Compounding

Guidance for FDA Staff and Industry

Compliance Policy Guides Manual

Sec. 460.200
Pharmacy Compounding

Submit written comments regarding this guidance document to the Dockets Management Branch (HFA-305), 5630 Fishers Lane, rm.1061, Rockville, MD 20852.

Additional copies of this document may be obtained by sending a request to the Division of Compliance Policy (HFC-230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or from the Internet at: http://www.fda.gov/ora/compliance_ref/cpg/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Center for Drug Evaluation and Research
May 2002

Contents for Page Navigation

Compliance Policy Guide
Compliance Policy Guidance for FDA Staff and Industry[1]

CHAPTER - 4
SUB CHAPTER - 460

Sec. 460.200 Pharmacy Compounding

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

INTRODUCTION

This document provides guidance to drug compounders and the staff of the Food and Drug Administration (FDA) on how the Agency intends to address pharmacy compounding of human drugs in the immediate future as a result of the decision of the Supreme Court in Thompson v. Western States Medical Center, No. 01-344, April 29, 2002. FDA is considering the implications of that decision and determining how it intends to regulate pharmacy compounding in the long term. However, FDA recognizes the need for immediate guidance on what types of compounding might be subject to enforcement action under current law. This guidance describes FDA's current thinking on this issue.

BACKGROUND

On March 16, 1992, FDA issued a compliance policy guide (CPG), section 7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. That CPG remained in effect until 1997 when Congress enacted the Food and Drug Administration Modernization Act of 1997.

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (the Modernization Act). Section 127 of the Modernization Act added section 503A to the Federal Food, Drug, and Cosmetic Act (the Act), to clarify the status of pharmacy compounding under Federal law. Under section 503A, drug products that were compounded by a pharmacist or physician on a customized basis for an individual patient were entitled to exemptions from three key provisions of the Act: (1) the adulteration provision of section 501(a)(2)(B) (concerning the good manufacturing practice requirements); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug provision of section 505 (concerning the approval of drugs under new drug or abbreviated new drug applications). To qualify for these statutory exemptions, a compounded drug product was required to satisfy several requirements, some of which were to be the subject of FDA rulemaking or other actions.

Section 503A of the Act took effect on November 21, 1998, one year after the date of the enactment of the Modernization Act. In November,

1998, the solicitation and advertising provisions of section 503A were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. The U.S. District Court for the District of Nevada ruled in the plaintiffs' favor. FDA appealed to the U.S. Court of Appeals for the Ninth Circuit. On February 6, 2001, the Court of Appeals declared section 503A invalid in its entirety (Western States Medical Center v. Shalala, 238 F.3rd 1090 (9th Cir. 2001)). The government petitioned for a writ of certiorari to the U.S. Supreme Court for review of the circuit court opinion. The Supreme Court granted the writ and issued its decision in the case on April 29, 2002.

The Supreme Court affirmed the 9th Circuit Court of Appeals decision that found section 503A of the Act invalid in its entirety because it contained unconstitutional restrictions on commercial speech (i.e., prohibitions on soliciting prescriptions for and advertising specific compounded drugs). The Court did not rule on, and therefore left in place, the 9th Circuit's holding that the unconstitutional restrictions on commercial speech could not be severed from the rest of section 503A. Accordingly, all of section 503A is now invalid.

FDA has therefore determined that it needs to issue guidance to the compounding industry on what factors the Agency will consider in exercising its enforcement discretion regarding pharmacy compounding.

DISCUSSION

FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.

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FDA believes that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice and that violates the Act. Such establishments and their activities are the focus of this guidance. Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies. For example, some firms receive and use large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of receiving a valid prescription for them.

Moreover, some firms sell to physicians and patients with whom they have only a remote professional relationship. Pharmacies engaged in activities analogous to manufacturing and distributing drugs for human use may be held to the same provisions of the Act as manufacturers.

POLICY:

Generally, FDA will continue to defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. FDA anticipates that, in such cases, cooperative efforts between the states and the Agency will result in coordinated investigations, referrals, and follow-up actions by the states.

However, when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action. In determining whether to initiate such an action, the Agency will consider whether the pharmacy engages in any of the following acts:

1. Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.

2. Compounding drugs that were withdrawn or removed from the market for safety reasons. Appendix A provides a list of such drugs that will be updated in the future, as appropriate.

3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.

4. Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.

5. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.

6. Using commercial scale manufacturing or testing equipment for compounding drug products.

7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.

8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be

appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.

9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

The foregoing list of factors is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case.

Other FDA guidance interprets or clarifies Agency positions concerning nuclear pharmacy, hospital pharmacy, shared service operations, mail order pharmacy, and the manipulation of approved drug products.

REGULATORY ACTION GUIDANCE:

District offices are encouraged to consult with state regulatory authorities to assure coherent application of this guidance to establishments that are operating outside of the traditional practice of pharmacy.

FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution. Charges may include, but need not be limited to, violations of 21 U.S.C. §§ 351(a)(2)(B), 352(a), 352 (f)(1), 352(o), and 355(a) of the Act.

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APPENDIX A

LIST OF COMPOUNDING DRUGS THAT WERE WITHDRAWN OR REMOVED FROM THE MARKET FOR SAFETY REASONS

Adenosine phosphate: All drug products containing adenosine phosphate.
Adrenal cortex: All drug products containing adrenal cortex.
Aminopyrine: All drug products containing aminopyrine.
Astemizole: All drug products containing astemizole.
Azaribine: All drug products containing azaribine.
Benoxaprofen: All drug products containing benoxaprofen.
Bithionol: All drug products containing bithionol.
Bromfenac sodium: All drug products containing bromfenac sodium.
Butamben: All parenteral drug products containing butamben.
Camphorated oil: All drug products containing camphorated oil.
Carbetapentane citrate: All oral gel drug products containing carbetapentane citrate.
Casein, iodinated: All drug products containing iodinated casein.

Chlorhexidine gluconate: All tinctures of chlorhexidine gluconate formulated for
use as a patient preoperative skin preparation.
Chlormadinone acetate: All drug products containing chlormadinone acetate.
Chloroform: All drug products containing chloroform.
Cisapride: All drug products containing cisapride.
Cobalt: All drug products containing cobalt salts (except radioactive forms cobalt
and its salts and cobalamin and its derivatives).
Dexfenfluramine hydrochloride: All drug products containing dexfenfluramine
hydrochloride.
Diamthazole dihydrochloride: All drug products containing diamthazole dihydrochloride.
Dibromsalan: All drug products containing dibromsalan.
Diethylstilbestrol: All oral and parenteral drug products containing 25 milligrams or
more of diethylstilbestrol per unit dose.
Dihydrostreptomycin sulfate: All drug products containing dihydrostreptomycin
sulfate.
Dipyrone: All drug products containing dipyrone.
Encainide hydrochloride: All drug products containing encainide hydrochloride.
Fenfluramine hydrochloride: All drug products containing fenfluramine hydrochloride.
Flosequinan: All drug products containing flosequinan.
Gelatin: All intravenous drug products containing gelatin.
Glycerol, iodinated: All drug products containing iodinated glycerol.
Gonadotropin, chorionic: All drug products containing chorionic gonadotropins of
animal origin.
Grepafloxacin: All drug products containing grepafloxacin.
Mepazine: All drug products containing mepazine hydrochloride or mepazine
acetate.
Metabromsalan: All drug products containing metabromsalan.
Methamphetamine hydrochloride: All parenteral drug products containing
methamphetamine hydrochloride.
Methapyrilene: All drug products containing methapyrilene.
Methopholine: All drug products containing methopholine.
Mibefradil dihydrochloride: All drug products containing mibefradil dihydrochloride.

Nitrofurazone: All drug products containing nitrofurazone (except topical drug products formulated for dermatalogic application).
Nomifensine maleate: All drug products containing nomifensine maleate.
Oxyphenisatin: All drug products containing oxyphenisatin.
Oxyphenisatin acetate: All drug products containing oxyphenisatin acetate.
Phenacetin: All drug products containing phenacetin.
Phenformin hydrochloride: All drug products containing phenformin hydrochloride.
Pipamazine: All drug products containing pipamazine.
Potassium arsenite: All drug products containing potassium arsenite.
Potassium chloride: All solid oral dosage form drug products containing potassium chloride that supply 100 milligrams or more of potassium per dosage unit (except for controlled-release dosage forms and those products formulated for preparation of solution prior to ingestion).
Povidone: All intravenous drug products containing povidone.
Reserpine: All oral dosage form drug products containing more than 1 milligram of reserpine.
Sparteine sulfate: All drug products containing sparteine sulfate.
Sulfadimethoxine: All drug products containing sulfadimethoxine.
Sulfathiazole: All drug products containing sulfathiazole (except those formulated for vaginal use).
Suprofen: All drug products containing suprofen (except ophthalmic solutions).
Sweet spirits of nitre: All drug products containing sweet spirits of nitre.
Temafloxacin hydrochloride: All drug products containing temafloxacin.
Terfenadine: All drug products containing terfenadine.
3,3',4',5-tetrachlorosalicylanilide: All drug products containing 3,3',4',5-tetrachlorosalicylanilide.
Tetracycline: All liquid oral drug products formulated for pediatric use containing tetracycline in a concentration greater than 25 milligrams/milliliter.
Ticrynafen: All drug products containing ticrynafen.
Tribromsalan: All drug products containing tribromsalan.
Trichloroethane: All aerosol drug products intended for inhalation containing trichloroethane.
Troglitazone: All drug products containing troglitazone.

Urethane: All drug products containing urethane.
Vinyl chloride: All aerosol drug products containing vinyl chloride.
Zirconium: All aerosol drug products containing zirconium.
Zomepirac sodium: All drug products containing zomepirac sodium.

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[1] This guidance has been prepared by the Office of Regulatory Policy and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] With respect to such activities, 21 U.S.C. 360(g)(1) exempts retail pharmacies from the registration requirements of the Act. The exemption applies to "Pharmacies" that operate in accordance with state law and dispense drugs "upon prescriptions of practitioners licensed to administer such drugs to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail" (emphasis added). See also 21 U.S.C. §§ 374(a)(2) (exempting pharmacies that meet the foregoing criteria from certain inspection provisions) and 353(b)(2) (exempting drugs dispensed by filling a valid prescription from certain misbranding provisions).

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Hypertext created: June 3, 2002 (tc)