DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate
Washington, D. C. 20510-6200

OCT 2 2006

Dear Senator Grassley:

Thank you for your letter dated July 13, 2006, to Acting Commissioner Andrew C. von Eschenbach, M.D., of the Food and Drug Administration (FDA or the Agency) and Administrator Mark McClellan of the Centers for Medicare & Medicaid Services (CMS). Your letter expresses concern about the inappropriate pharmacy compounding of inhalation drugs and inquires about FDA and CMS policies related to this practice. This letter responds to your questions regarding the policies of FDA. We understand that CMS has responded in a separate letter to your questions concerning the policies within their purview.

Traditional pharmacy compounding is the combining, mixing, or altering of ingredients in response to a prescription from a licensed practitioner to create a medication tailored to the needs of an individual patient. Traditional compounding typically is used to prepare medications that are not available commercially, such as medication for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children. It involves providing a service in response to a physician's prescription in order to accommodate the specialized need of a particular patient.

FDA believes that traditional pharmacy compounding can play a legitimate role in patient care. Compounded inhalation drugs, however, like all compounded drugs, are not FDA approved, which means that FDA has not verified their safety and effectiveness. FDA shares your concern about the risks associated with the inappropriate compounding of inhalation drugs. In some cases, the processes used to compound these drugs may not prevent contamination or assure that they possess the strength, quality, and purity that they claim to have. Because the patients who use these drugs often have serious underlying health conditions, these poor practices pose special risks. FDA has taken enforcement action against firms engaging in the large-scale manufacture of unapproved inhalation drugs under the guise of traditional compounding. Some of the inhalation drugs produced by these firms were contaminated, were dispensed without prescriptions, and were provided to patients in place of FDA-approved, commercially-available products.

In an effort to work with CMS on this issue of mutual concern, FDA recently commented by letter on proposed revisions to the Medicare reimbursement policy on nebulizer drugs. FDA's letter to CMS (copy enclosed) outlines the risks of compounded inhalation drugs, and explains how reimbursement policies may inadvertently create an incentive for the inappropriate compounding of these drugs. The letter also offers proposed reimbursement alternatives for consideration by CMS.

FDA continues to focus on the inappropriate compounding of inhalation drugs, and offers the following specific responses to the questions in your letter. Your questions are repeated below in bold followed by FDA's response.

> **Question 1. Pharmacies believe that it is the state boards of pharmacy that are responsible for regulating drug compounding; however, given the limitations in oversight by state boards of pharmacy, what is or should be the federal role in the regulation of pharmacy compounding?**

Response: FDA recognizes that some pharmacies mistakenly believe that state boards of pharmacy are solely responsible for regulating drug compounding. State boards of pharmacy are the primary regulators of pharmacies. FDA's position is that the Federal Food, Drug, and Cosmetic (FD&C) Act establishes Agency jurisdiction over "new drugs," drugs which are not generally recognized as safe and effective for their labeled uses. Indeed, FDA has a 90-year history of regulating pharmacies under the FD&C Act and its predecessor laws, and of treating compounded products that are not generally recognized as safe and effective as "new drugs." When it takes enforcement actions relating to compounded drugs, FDA often works in cooperation with the state boards of pharmacy.

As you may be aware, FDA recently took the position in its brief in the *Medical Center Pharmacy* case that compounded drugs are new drugs. As noted in greater detail below, the federal district court judge ruled against FDA on August 30, 2006.

Nevertheless, FDA has long recognized that traditional pharmacy compounding serves an important public health function. Through the exercise of enforcement discretion, FDA historically has not taken enforcement action against pharmacies engaged in traditional compounding. Rather, FDA has directed its enforcement resources toward firms that manufacture large quantities of unapproved new drugs under the guise of traditional compounding, or whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act.

FDA outlines its enforcement policy on pharmacy compounding in its Compliance Policy Guide (CPG) section 460.200 ["Pharmacy Compounding"]. A copy of this CPG is enclosed with this letter. The CPG lists factors that the Agency considers in deciding whether to exercise enforcement discretion with respect to pharmacy compounding. The factors in the CPG are not exhaustive, and FDA may consider other factors in particular cases.

Question 2. Is the FDA considering modifications to its pharmacy compounding compliance guide to further clarify what activities fall under the category of drug manufacturing?

Response: FDA issued its current pharmacy compounding CPG in May 2002, shortly after the Supreme Court ruled in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that section 503A of the FD&C Act restricted constitutionally protected commercial speech. FDA issued the CPG in final form, without opportunity for advance public comment, to fill the regulatory vacuum created by the Supreme Court's decision. With release of the CPG, FDA requested comments and stated that it would review comments submitted to the Agency and revise the CPG, if appropriate. That process is still underway.

Question 3. Does the FDA require additional and/or more explicit authorities to respond to allegations of inappropriate or illegal compounding of inhalation drugs, particularly in light of the district court ruling by Judge Robert Junell in *Medical Center Pharmacy v. Ashcroft,* on May 25, 2006, that compounded drugs are not considered unapproved products under the Food, Drug, and Cosmetic Act?

Response: On August 30, 2006, Judge Junell, issued a written opinion in the *Medical Center Pharmacy* case described above. FDA and its U.S. Department of Justice counsel currently are considering the court's opinion, to gauge its scope and meaning, and to determine whether to appeal the court's ruling.

Question 4. My staff were told that the Medicare reimbursement rate for inhalation drugs is a major driving force for large volume compounding of such drugs, and these large providers can be identified easily by CMS's DME regional carriers. As the agency responsible for oversight of DME suppliers, how often does CMS conduct audits of DME suppliers that provide compounded medications, and how are these audits initiated? Does CMS coordinate with FDA on audits and inspections?

Response: Since this question addresses Medicare reimbursement and CMS audits, FDA defers to CMS for an answer.

Question 5. It appears that one aspect of the solution to addressing some of the problems identified is raising awareness among health care providers who prescribe inhalation drugs of the inappropriate or illegal compounding of such drugs. For example, is the FDA considering alerting physicians by sending out Dear Healthcare Provider letters and/or issuing a public health advisory to advise physicians of how some pharmacies or DME suppliers are manipulating the system to "switch" a patient from a prescribed drug to a compounded drug?

Response: FDA agrees that health care providers must understand the risks associated with compounded inhalation drugs, including the risk of patients being switched to these drugs without their knowledge or consent. Conveying this information was one of FDA's objectives when it recently issued Warning Letters to three firms warning them to stop

manufacturing and distributing thousands of doses of unapproved inhalation drugs under the guise of compounding. The Warning Letters identify a range of serious concerns posed by practices of these firms including inadequate quality control, concerns about potency, and compounding what essentially are copies of FDA-approved, commercially-available drugs without any patient-specific need. FDA also issued a press release advising health care providers, patients, and other members of the public about the health risks connected with the practices of these firms, as well as other firms that likewise compound and distribute mass amounts of unapproved inhalation drugs. Taken together, we expect the press release and the Warning Letters will raise patient and practitioner awareness about this important public health issue.

Question 6. The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology proposed a resolution urging the American Medical Association (AMA) to request that the FDA take enforcement action against pharmacies that are mass manufacturing medications under the guise of compounding and that CMS reconsider paying for these medications. The resolution also calls for education of physicians regarding potential liability, since they are accountable for signing prescriptions for such medications, knowingly or unknowingly. Has FDA spoken with AMA or other professional societies to coordinate an educational campaign on this issue?

Response: An FDA representative attended the AMA's meeting where the resolution proposed by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology was discussed. We understand that the AMA's House of Delegates recommended that the resolution be referred for decision by the AMA's Board of Trustees. FDA will continue to monitor the progress of the resolution and, as appropriate, provide comments. FDA also has spoken with several professional societies regarding compounded drugs. Last October, for example, an FDA representative participated in a panel discussion on compounded inhalation drugs at the annual meeting of the American College of Chest Physicians. FDA welcomes the opportunity to continue to work with professional societies on this matter of mutual interest and concern.

Question 7. CMS staff informed my staff that changing and creating HCPCS codes is labor intensive. However, since the agency cannot distinguish payments for compounded inhalation drugs from payments for brand name or generic drugs, will CMS be considering modifications to how inhalational drugs are reimbursed?

Response: Since this question addresses Medicare reimbursement, specifically, the development of HCPCS codes, FDA defers to CMS for an answer.

Question 8. Patients should be told when they are taking compounded inhalational drugs and why. Who is or should be responsible for ensuring that compounded medications are labeled appropriately so that there is full disclosure regarding the risks and benefits of the drugs that patients are taking?

Response: As you know, compounded drugs do not undergo FDA pre-market approval, which includes review of proposed product labeling. Thus, as a general matter, FDA does not ensure that compounded drugs are properly labeled before they are marketed.

There is no regulatory provision in the FD&C Act that explicitly requires the labeling of a compounded drug to disclose that the drug is compounded and that FDA has not evaluated its safety and effectiveness. As with all drugs, however, compounded drugs are misbranded if their labeling is false or misleading. Compounded drugs are likewise misbranded if their labeling fails to include adequate warnings or if the drugs are "dangerous to health" when used in the manner suggested by their labeling. However, FDA bears the burden of proof in order to apply these misbranding provisions. Further, consistent with the FD&C Act, states may impose additional disclosure requirements on pharmacy-dispensed prescription drugs.

Question 9. Please keep the Committee apprised of FDA's actions related to CHASM's citizen petition.

Response: FDA certainly will keep you informed of action that it takes in response to the Citizen Petition from the Consumer Health Alliance for Safe Medication (CHASM) and will send you a copy of FDA's response when it is released.

Question 10. What is CMS's position on maintaining reimbursement for nebulizers in Medicare Part B but restricting reimbursement for the inhalational drugs to Part D? What is CMS's position on accreditation of compounding pharmacies in order to receive Medicare reimbursement?

Response: Since this question addresses Medicare reimbursement under Parts B and D, and conditions of Medicare reimbursement, FDA defers to CMS for an answer.

Question 11. Has CMS considered requiring a determination of medical necessity for compounded inhalational drugs?

Response: Since this question addresses the determination of medical necessity for purposes of Medicare reimbursement, FDA defers to CMS for an answer.

Thank you again for your concerns about this important issue. If you have further questions, please let us know.

Sincerely,

David W. Boyer
Assistant Commissioner
for Legislation

2 Enclosures

Letter from Steven Silverman, FDA, CDER Office of Compliance, to Medicare on Proposed Revisions to Nebulizers Policy (May 11, 2006)

FDA Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

MAY 11 2006

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RE: Proposed Revisions to Nebulizers Policy
Draft LCD for Nebulizers (DL11499)

Dear Drs. Hughes, Oleck, and Pilley:

Thank you for the opportunity to comment on the proposed revisions to the Medicare nebulizer reimbursement policy. FDA is concerned that the proposed revisions do not distinguish FDA-approved, commercially-manufactured inhalation drugs from unapproved inhalation drugs compounded at pharmacies. Treating these drugs identically may create an incentive for the large-scale compounding of unapproved inhalation drugs. Because compounded inhalation drugs are not reviewed by FDA for safety or efficacy, often are not produced according to good drug manufacturing practice, and typically are not sterile, they may expose patients to unnecessary risk. This is especially the case given that FDA-approved inhalation drugs are readily available to patients.

FDA Is Concerned About Unapproved Compounded Inhalation Drugs.

FDA views traditional compounding as a pharmacy combining, mixing, or altering ingredients pursuant to a valid prescription to create a drug tailored to an individual patient's needs. Traditional compounding typically produces drugs that are not commercially available, such as medication for a patient with an allergy to an FDA-approved product.[1]

FDA believes that a growing number of pharmacies are manufacturing and distributing unapproved inhalation drugs in a manner that goes well beyond traditional compounding. FDA has seen pharmacies compounding millions of doses of inhalation drugs that are often copies of

[1] Appendix A to this letter provides a discussion of FDA's regulatory approach to compounded drugs.

approved, commercially-available products, or that differ from FDA-approved drugs only in terms of dosage, strength, or preservatives. These compounded inhalation drugs may be distributed to patients in multiple states without documented, patient-specific medical need. Many times, physicians do not know that their patients are receiving compounded products. FDA is aware of pharmacies substituting compounded drugs for FDA-approved products, without physician approval.

Compounded drugs are not subject to FDA's drug approval process, which assures drug safety and efficacy, and they often are not produced under the good manufacturing requirements that FDA imposes on commercial drug manufacturers. FDA is concerned that, in some cases, the processes used to compound drugs may not prevent contamination or assure that the drugs possess the strength, quality, and purity reported on their labels. These concerns are underscored by FDA analysis of compounded drugs, as well as enforcement actions by FDA and its state counterparts against contaminated compounded inhalation products. Examples include:

- FDA analyzed samples of compounded inhalation products as part of a compounded drug survey and found that the potency of some samples was below their labeled strength.

- Based on FDA investigative work, the Missouri Board of Pharmacy took enforcement action against a pharmacy that compounded and distributed mass quantities of contaminated albuterol/ipratropium solution to thousands of patients. Despite knowing of the contamination, the pharmacy failed to properly recall the contaminated drugs.

- FDA issued a warning letter to a California pharmacy using commercial-scale manufacturing equipment to compound mass quantities of inhalation drugs, without prescriptions for individually-identified patients. The firm recalled its product due to microbial contamination and a joint FDA/California inspection concluded that the firm was incapable of complying with good drug manufacturing practice.

<u>The Proposed Policy Changes May Promote Compounding of Unapproved Inhalation Drugs.</u>

TriCenturion's March 25, 2006, "Dear Physician" letter asks for comments on four proposed policy changes, the first of which provides: "Payment for levalbuterol will be based on the allowance for albuterol." There is one FDA-approved levalbuterol product. But the proposed policy would reimburse all levalbuterol products, including unapproved compounded products, at the same rate.

This policy may encourage pharmacies to compound unapproved levalbuterol products, rather than dispense the FDA-approved drug. The cost to pharmacies of dispensing unapproved, compounded drugs is generally much lower than the cost of dispensing FDA-approved drugs. Hence the profits from these compounded inhalation drugs are correspondingly higher than profits from FDA-approved drugs. Pharmacies can compound inhalation drugs inexpensively because these drugs do not undergo FDA's approval process, they often are not produced according to good drug manufacturing practice, and they generally are not sterile. FDA does not favor reimbursement policies that foster the compounding of inhalation drug that may pose risks not found in the approved products with which they compete.

The second proposed policy change provides that "[p]ayment for DuoNeb will be based on the allowance for separate unit dose vials of albuterol and ipratropium." As with the first proposed

policy change, FDA is concerned that this new policy will promote compounding of unapproved inhalation drugs. DuoNeb is the only FDA-approved product that contains both albuterol and ipratropium. Reimbursing DuoNeb based on the allowance for separate units of albuterol and ipratropium encourages compounding pharmacies to steer patients towards compounded albuterol/ipratropium combinations that are inexpensive to produce. As with compounded levalbuterol, pharmacies are able to make these compounded combinations less expensively because they do not undergo FDA approval, they often are not produced according to good drug manufacturing practice, and they generally are not sterile. While these deficiencies lower the production cost of the compounded products, they may put patients at risk.

Additionally, the draft proposed LCD for Nebulizers that is attached to the TriCenturion letter includes specific statements that could promote the inappropriate compounding of drugs. For example, the proposed policy states:

> The medical necessity for administering albuterol and ipratropium in a non-compounded combined unit dose preparation (J7620) has not been established [emphasis supplied].

By asserting that the medical necessity for non-compounded combinations has not been established, this statement suggests that the medical necessity for administering compounded albuterol and ipratropium in a combined unit dose preparation *has* been established, which is not the case.

Consistent with its concerns about compounded inhalation products, FDA recommends that CMS consider limiting reimbursement of inhalation drugs to FDA-approved products, unless there is documented, patient-specific medical need for a compounded product. Additionally, CMS might consider reimbursing compounded drugs at a lower rate than FDA-approved inhalation drugs, because the compounded drugs generally are much less expensive to produce. In order to distinguish reimbursement claims for FDA-approved inhalation drugs from reimbursement claims for unapproved, compounded drugs, these drugs should be assigned different codes.

Conclusion

Thank you for the opportunity to provide FDA's views on the compounding of unapproved inhalation drugs and how the proposed Medicare reimbursement policy for nebulizers may encourage inappropriate compounding. If you have any questions, please feel free to contact me at (301) 827-8910.

Sincerely yours,

Steven Silverman, Acting Deputy Director
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance

Appendix A – FDA's Regulatory Approach to Compounded Drugs

Under the Federal Food, Drug, and Cosmetic Act (FDCA), a "new drug" may not be legally manufactured or sold in the United States unless it has been pre-approved by FDA as safe and effective for its intended uses. *See* 21 U.S.C. §§ 321(g) and (p), 352, 353(b), and 355. When a pharmacist compounds a prescription drug, by definition, he or she creates a "new drug" under federal law because the compounded product is not "generally recognized, among experts . . . as safe and effective." *See* 21 U.S.C. §§ 321(p). In virtually all instances, compounded drugs have not been approved by FDA as safe and effective and thus are unapproved drugs.

FDA has long recognized, however, that traditional pharmacy compounding serves an important public health function by meeting the specialized medical needs of individual patients for whom commercially available approved drugs are inadequate or inappropriate. Accordingly, FDA historically has not taken enforcement actions against pharmacies engaged in the traditional practice of pharmacy. Rather, FDA has directed its enforcement resources against establishments that produce large quantities of unapproved new drugs under the guise of traditional compounding, and establishments whose activities result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002), which is attached to this letter. The CPG lists factors that the agency considers in deciding whether to exercise its enforcement discretion with respect to pharmacy compounding. These factors help differentiate the traditional practice of pharmacy compounding from the large-scale manufacture of unapproved new drugs. They further address compounding that presents a threat to the public health or to the drug approval process (such as compounding drugs that are commercially available, FDA-approved drugs).

Attachment: Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002).

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

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.

[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.

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.[2]

[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

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.

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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).

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.

Issued: 3/16/1992
Reissued: 5/29/2002

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.