CORAR

Council on Radionuclides and Radiopharmaceuticals, Inc.

3911 Campolindo Drive
Moraga, CA 94556-1551
(925) 283-1850
Fax: (925) 283-1850
E-mail: corar@silcon.com

Henry H Kramer, Ph D., FACNP
Executive Director

January 10, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5360 Fishers Lane
Rockville, Maryland 20857

Re: Docket No. 02D-0242: Compliance Policy Guides Manual Section 460.200, "Pharmacy Compounding"

Dear Sir or Madam:

The Council on Radionuclides and Radiopharmaceuticals (CORAR) appreciates the opportunity to make comments on the Food and Drug Administration's (FDA) Compliance Policy Guides Manual Section 460.200, "Pharmacy Compounding" First, CORAR would like to commend the FDA for its attention to this issue and for clarifying the boundaries of permissible pharmaceutical and radiopharmaceutical compounding, and to dispel the confusion on this subject as a result of the United States Supreme Court's decision to uphold the Ninth Circuit's decision to invalidate section 503A of the FDC [1] and the FDA's revocation of the Compliance Policy Guide (CPG) Section 7132.16, delineating the FDA's enforcement policy on pharmacy compounding. CORAR believes that the new CPG will go a long way toward ensuring that radiopharmaceuticals are prepared and compounded in a manner that guarantees their effectiveness, safety, and purity.

CORAR is an industry association of manufacturers of radiopharmaceuticals, radionuclides, radiochemical and other radioactive products used primarily in medicine and life science research. The member companies of CORAR supply vitally important radiopharmaceuticals and radioactive material to physicians and research facilities throughout the world. Radiopharmaceuticals are used in over 15 million medical diagnostic and therapeutic procedures per year in the U.S.

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1 See FDC Act § 503A. The 10th Circuit Court of Appeals invalidated this section on constitutional grounds. 238 F.3d 1090 (10th Cir. 2001). The U.S. Supreme Court upheld the Ninth Circuit's decision (Thompson v. Western States Medical Center, 535 U.S. 357 (2002).

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While section 503A of the FDC did not apply to radiopharmaceuticals, CORAR is pleased that this new CPG appears to apply to all pharmaceuticals, including radiopharmaceuticals. CORAR would urge the FDA to consider developing additional guidance that clarifies Agency positions concerning nuclear pharmacy activities as related to the compounding of radiopharmaceuticals.

FDA has historically made an exception from the New Drug Application (NDA) requirement for radiopharmaceuticals prepared within the normal practice of pharmacy. Specifically, that prohibited compounding does not include preparation of a drug consistent with the manufacturer's directions contained in the approved product labeling or other manufacturer directions consistent with that labeling which result in a final radioactive drug product that is of the same quality and purity as that produced with adherence to the product labeling. This exception is based on the fact that the manufacturer has already presented extensive clinical and non-clinical data on pharmacology, toxicology, adverse events, and radiation safety demonstrating that the finished product, prepared in that manner, is safe. The manufacturer has also presented clinical data showing that the product, prepared in that manner, is effective for its labeled indication. This exception should not apply if a pharmacist deviates from the manufacturer's instructions. A separate NDA should be required, unless the changed product falls within the "compounding exception." CORAR urges the Agency to enforce prohibitions against deviations from the manufacturer's labeling or instructions.

CORAR is concerned with any deviation by a nuclear pharmacy that involves exceeding the recommended total maximum radioactivity so that the vial can be used in a greater number of patients (i.e., "vial splitting"). In this case there is no longer any assurance that the manufacturer's data applies or that the conclusion that the product is safe and effective is still valid. Specifically, with regard to vial splitting, the manufacturer of an approved radiopharmaceutical has determined the relative quantities of radioactive and other components that result in the optimum diagnostic performance, stability, and has conducted safety and effectiveness testing using that formulation. A nuclear pharmacist typically does not have information on how the relative quantities of components were determined and what the effect of changing them will be. For example, increasing the radioactivity beyond the manufacturer's recommendations can compromise the ability of the radioisotopes to bind to the carrier in the correct proportions. Moreover, if a vial is split so that each patient receives only a fraction of the recommended dose of the carrier, the amount of carrier may be insufficient for each patient. Either of these results may compromise the diagnostic performance of the drug.

We do not, of course, believe that a nuclear pharmacist may never deviate from the manufacturer's instructions without obtaining an NDA. However, in order to avoid the NDA requirement, such deviations must necessarily be subject to the restrictions on compounding within the practice of pharmacy. Under, FDA Compliance Policy Guides, pharmacy preparation of an FDA-approved, commercially available drug product including a radiopharmaceutical, with deviations that make the compound slightly different from the commercial product, is only permissible where the compound is prepared in small quantities. The CPG goes on to say "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.

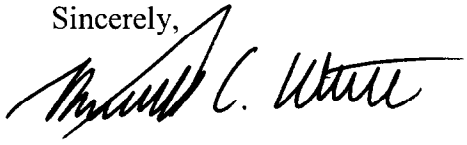
CORAR strongly supports the above language and the requirement that the compounding of commercially available drug products, including radiopharmaceuticals be done only pursuant to a prescription or patient-specific order, and there is patient-by-patient consultation between the physician and pharmacist that results in documentation that substantiates the medical need for the particular variation of the compound. Such a requirement was previously detailed in FDA, Compliance Policy Guide (CPG) 7132.16 at 4 (1992), which was rescinded in January 1999, but still relied on by the Agency. FDA has stated that radiopharmaceutical compounding that is inconsistent with this or other requirements of CPG 7132.16 "results in products that are considered unapproved new drugs under section 505 of the Act." Letter from Lana Ogram, FDA, to CORAR, July 26, 2000 (Attachment 1).

In summary, CORAR believes that preparation of a radiopharmaceutical in a manner that deviates materially beyond the manufacturer's labeling or instructions, including exceeding recommended activity in order to split vials, may violate section 505 of the FDC Act and may compromise the diagnostic performance of the drug to the detriment of the patient. Where deviations are made, they must comply with the restrictions on drug product compounding including radiopharmaceutical compounding contained in FDA's Compliance Policy Guides, as referenced above.

In conclusion, CORAR strongly urges the Agency to resist any calls to weaken the CPG, specifically any efforts to ease the documentation burden required for the compounding of drug products that are commercially available in the market place or that are essentially copies of commercially available FDA-approved drug products. We support and commend the Agency for publishing the Compliance Policy Guides for "Pharmacy Compounding" and look forward to working with the Agency to develop future guidance specific to nuclear pharmacy and other nuclear medicine related issues.

Again, thank you for the opportunity to comment.

Sincerely,



Richard C. White

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 26 2000

William A. Ehmig, Chairman
Committee on Health Care
Council on Radionuclides and Radiopharmaceuticals
3911 Campolindo Drive
Moraga, CA 94556-1551

Dear Mr. Ehmig,

This is in response to your letter of March 16, 1999 in which you provided information on your concerns regarding the situation brought to our attention by DuPont Pharmaceutical Company. In DuPont's letter, they alleged that Custom Care Pharmacy of Tampa, Florida is compounding Thallium-201, a commercially available proprietary drug, in a manner that allegedly violates FDA rules and regulations governing the practice of compounding by a licensed pharmacist. You requested that FDA evaluate the merits of the DuPont allegations and provide CORAR with FDA's interpretations of the laws and regulations governing the compounding of a commercially available drug product by a licensed pharmacist.

Background - Section 503A

As you know, President Clinton signed the FDA Modernization Act (FDAMA, Pub. L. 105-115) into law on November 21, 1997. Section 127 of FDAMA, which added section 503A to the Federal Food, Drug, and Cosmetic Act (the act), clarifies the status of pharmacy compounding under Federal law. Under section 503A of the act, drug products that are compounded by a pharmacist or physician for an identified individual patient and that conform to other requirements in section 503A are exempted from three provisions of the act (1) section 501(a)(2)(B)(concerning the good manufacturing practice requirements); (2) section 502(f)(1)(concerning the labeling of drugs with adequate directions for use); and (3) section 505 (concerning the approval of drugs under new drug or abbreviated new drug applications).

In response to your concerns regarding the compounding of Thallium-201, section 503A(e)(2) states that section 503A does not apply to radiopharmaceuticals. Therefore, radiopharmaceuticals are not eligible for the statutory exemptions provided by section 503A referenced above.

The legislative history of FDAMA states that section 503A was not intended to "change or otherwise affect current law with respect

to radiopharmaceuticals." H. Rep. No. 105-399, 105th Cong., 1st Sess. 95 (1997). At the time section 503A was enacted, "current law" did not provide a statutory exemption for compounded drugs (including radiopharmaceuticals) from the adulteration, misbranding, and new drug provisions of the act. *See Professionals and Patients for Customized Care v. Shalala*, 847 F. Supp. 1359, 1364 (S.D. Tex. 1994) (drugs "compounded in pharmacies are not exempt from the adulteration, misbranding, and new drug provisions"), *aff'd* 56 F.3d 592 (5th Cir. 1995). See H. Rep. No. 106-619, at 118 (2000) (House Appropriations Committee Report reaffirming this interpretation, copy enclosed.)

Agency Enforcement Policy

Whether one can compound Thallium-201 depends on how FDA exercises its enforcement discretion in accordance with the agency's enforcement policies. At this time, the agency is evaluating radiopharmaceutical compounding according to the enforcement policies in place at the time of the enactment of section 503A. These enforcement policies are set out in the agency's 1992 Compliance Policy Guide on pharmacy compounding (CPG 7132.16) and the 1984 Nuclear Pharmacy Guideline. The agency is currently reexamining these documents in light of FDAMA and intends to issue new guidance on the compounding of radiopharmaceuticals. Until that guidance is issued, we will rely on the enforcement policies articulated before FDAMA that are described, in part, below.

CPG 7132.16 established the agency's policy of focusing enforcement resources on drug manufacturing activities that are operating under the guise of pharmacy compounding rather than on traditional pharmacy compounding activities. The CPG identifies certain factors to assist the agency in distinguishing between traditional pharmacy compounding and manufacturing. One such factor is whether the pharmacy engages in regular or inordinate compounding of drug products that are "essentially generic copies of commercially available, FDA-approved products." The CPG states that it may be appropriate to compound a small quantity of a drug that is only slightly different from a commercially available FDA-approved drug. However, in these circumstances, "patient-by-patient consultation between physician and pharmacist must result in documentation that substantiates the medical need for the particular variation." Another factor identified in the CPG associated with commercial manufacturing is the practice of "offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale." Compounding that is consistent with the activities of commercial manufacturing under the CPG results in products that are considered unapproved new drugs under section 505 of the act.

This is the regulatory framework that we are using to evaluate the compounding of radiopharmaceuticals. We are using this framework to determine, on a case-by-case basis, whether an enforcement action is warranted to address violations of the act. We have inspected the facility you cited in your letter and have identified some issues associated with their practices that we are continuing to pursue. We have issued a letter to Custom Care outlining, as we have for you, the requirements of the act and our enforcement policies regarding the compounding of radiopharmaceuticals. We are awaiting their response.

Thank you for bringing these concerns to our attention. If you need further information or have additional questions, please contact George Scott at (301) 827-7312.

Sincerely,

Lana Ogram
Director, Division of Prescription
Drug Compliance and Surveillance
Office of Compliance
Center for Drug Evaluation and Research

Enclosure