Compounding pharmaceuticals for investigational use

Q: Despite the vast increase in the array of pharmaceutical products in recent years, there are still many cases in which we find we must compound pharmaceuticals. These situations may involve patients with rare or life-threatening conditions, special patient populations (such as children), and drug shortages. Compounded products are also sometimes requested for investigational use. What regulations and issues relate to the compounding of pharmaceutical products for investigational use?

A: Compounding requests may involve a single prescription for a specific patient or an order for an investigational product. At the University of Michigan Health System (UMHS), if a pharmaceutical-grade chemical is used to prepare a pharmaceutical product for a single patient, there is no requirement for institutional review board (IRB) approval or an investigational new drug (IND) application. If a raw chemical is not pharmaceutical grade, whether or not the proposed use is for research, UMHS requires the physician to contact FDA to determine if an IND is required. The compounded pharmaceutical product is considered an investigational product for experimental use if it is to be used for multiple patients with a specific disease for research purposes. IRB approval is required to ensure that the research meets ethical and safety standards. Informed consent must be obtained from subjects before the product is administered. In addition, FDA may require the investigator to submit an IND application.

Federal Guidance. Section 127 of the Food and Drug Administration Modernization Act of 1997 added section 503A to the Food, Drug and Cosmetic Act to clarify the status of pharmacy compounding under Federal Law. However, in April 2002, the Supreme Court in Thompson v. Western States Medical Center, No. 01-344, ruled that section 503A is invalid because it contained unconstitutional restrictions on commercial speech (prohibitions on soliciting prescriptions for and advertising specific compounded drugs). In the absence of this regulation, the FDA Compliance Policy Guide on Pharmacy Compounding (Sec 460.200) was enacted to provide guidance to drug compounders. This guidance states that traditional compounding of reasonable quantities of a drug for an individual patient upon receipt of a valid prescription from a licensed practitioner is acceptable. The FDA considers enforcement action when a pharmacy engages in activities that are normally associated with a drug manufacturer and violates the Food Drug and Cosmetic Act provisions concerning good manufacturing practices, labeling of drugs with directions for use, and approval of drugs under a new drug application. Specific situations in which FDA considers enforcement action include, but are not limited to: compounding in anticipation of receiving prescriptions (except in very limited quantities); compounding drugs that were withdrawn from the market for safety reasons (list published in the Code of Federal Regulations); compounding drugs, without an IND application, from bulk active ingredients that are not components of FDA-approved drugs; compounding drug products that are copies of commercially available FDA-approved products; or compounding for third parties for resale to patients. Receiving, storing or using drug substances that are not guaranteed to meet official compendia requirements or for which written assurance that they have been made in a FDA-registered facility could also warrant action.

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The Management Consultation column gives readers an opportunity to obtain advice on common management problems from pharmacists practicing in health systems.

AHIP readers are invited to submit questions for this column. Selected questions will be forwarded to one or two experts in the field, who will prepare brief responses for publication. Questions should be narrow in scope, such that they can be answered in approximately 500 words. Responses will be sent to the inquirer before publication. Readers are also invited to comment on the answers of consultants; such comments will be considered for the Letters column.

Suggestions for topics should be submitted to AJHP, 7272 Wisconsin Avenue, Bethesda, MD 20814 (301-657-3000 or ajhp@ashp.org).

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The use of the compounded product may need to be reviewed by FDA to determine if an IND application is necessary. If FDA determines that an IND application is required for the experimental use of a compounded pharmaceutical product, the licensed prescriber (the principal investigator) must submit an IND application that includes, among other items, a section describing the composition, manufacture, and control of the drug substance and the drug product. The pharmacist can be a key contributor to this component of the IND.

State laws regarding the compounding of a pharmaceutical product may vary. In Michigan, the use of a compounded pharmaceutical product prepared by a state-registered pharmacy is legal, provided the product is dispensed pursuant to a prescription for an individual patient. A bulk-compounded product cannot be distributed to other facilities for dispensing to patients without a manufacturing license.

Practice at UMHS. UMHS consists of 865 licensed beds in three inpatient facilities. The ambulatory care centers at UMHS handle approximately 1.5 million visits annually. The Investigational Drug Service (IDS), a component of the pharmacy department, currently manages 260 protocols involving an investigational drug. The practices of IDS are defined by hospital-approved policies and procedures that are in accordance with the ASHP Guidelines on Clinical Drug Research, the Code of Federal Regulations, and FDA’s guidelines on good clinical practice. Most protocols are drug company or National Cancer Institute sponsored, so the drugs being studied arrive in the IDS pharmacy already packaged by the sponsor for final preparation and dispensing. Some protocols are investigator initiated and may involve manufactured drug products. However, for approximately 5% of protocols, compounding from a raw chemical by the IDS pharmacy staff is necessary. While this percentage is low, the complexities surrounding the compounding of these products can be great. To streamline the process and to ensure continuity in the services provided, guidelines for selecting raw chemicals for use in preparing or compounding a pharmaceutical product were developed. The guidelines establish a process for determining if and how the chemical should be used.

IDS will consider compounding a pharmaceutical product from a raw chemical only if an acceptable commercial product does not exist. In addition, the compounded product will only be prepared once published data supporting the use of the chemical have been evaluated by a pharmacist. The literature assists the pharmacist in evaluating the appropriateness of ingredients and the drug delivery system before the product is prepared. Major points considered in this assessment include risk versus benefit to the patient, an evaluation of the route of administration, and short-term and long-term toxicities (particularly with respect to possible contaminants).

When agreeing to compound a pharmaceutical product, the IDS pharmacist considers available resources, including personnel, because some products may require a special process or special equipment. The compounded product is prepared by a pharmacist or under the direct supervision of a pharmacist. The actual ingredients, quantities used, and methods of preparation are described on a formulation record to ensure consistent reproduction of the product for future doses. This record also allows for documentation of who prepared the product and how the product should be packaged and states the expiration date as described by USP-NF. The final product is assayed to ensure quality control. Inhouse resources or licensed external facilities may perform this assay. Preparation of a pharmaceutical product for injection also requires that steps be in place to ensure that the product is sterile, pyrogen free, and of an acceptable pH. In addition, guidelines in USP-NF must be followed.

Sources of the active ingredients for compounding a pharmaceutical product are defined in USP-NF and may include a manufactured drug product or a raw chemical or substance. A manufactured drug product (e.g., aspirin) must come from a container labeled with a lot number and expiration date. If a chemical or substance is the active ingredient, a USP- or NF-grade chemical or substance prepared by a manufacturer registered with FDA is preferred. A chemical or substance labeled as USP or NF grade is considered pharmaceutical grade and is acceptable for use in patients, unless it also bears the term “reagent” or “reagent grade.” If a USP- or NF-grade chemical or substance is not available, a high-quality chemical or substance may be an option. High-quality sources that can be considered are analytical reagent grade, American Chemical Society grade, or Food Chemicals Codex grade.

For chemicals or substances that are not purchased from a registered drug manufacturer, the pharmacist should assess the product by establishing purity and safety. This assessment includes evaluating the certificate of analysis (which lists impurities and contaminants), the manufacturer’s reputation, and the reliability of the source. An impurity is any component of a drug substance (excluding water) that is not the chemical entity defined as the drug substance. UMHS has recommendations for the maximum allowable contaminants in a chemical or substance that is not USP or NF grade to...
be used in compounding a pharmaceutical product. At UMHS, it is suggested that the percent content of heavy metals (cadmium, silver, copper, molybdenum, lead, mercury, bismuth, arsenic, antimony, and tin) be <0.001%. In addition, ordinary impurities (species that are innocuous by virtue of having no significant undesirable biological activity in the amounts present) should not exceed 2%. Organic volatile impurities should be within the following limits: benzene, <2 µg/g; chloroform, <60 µg/g; 1,4-dioxane, <380 µg/g; trichloroethylene, <80 µg/g; and methylene chloride, <600 µg/g. The pharmacist should consider all contaminants and inert ingredients, taking into account the amounts that would be administered to a patient in the final product. When an IND application is filed, FDA reviews the amounts of impurities and contaminants and determines what is acceptable on a case-by-case basis.

Upon receipt of a chemical, the expiration date as labeled by the manufacturer, the date received, and the date opened are noted on the container. The chemical is discarded on or before the manufacturer’s expiration date. All containers of chemicals that do not have a manufacturer’s expiration date are discarded one year after opening, unless an appropriate USP assay can be performed to determine stability, as required by the Joint Commission on Accreditation of Healthcare Organizations.

**Conclusion.** Compounding of investigational drugs from raw substances or chemicals is an area that is not well defined. Guidance for pharmacists on how to handle requests for compounding investigational products from chemicals is limited to the requirement of obtaining an IND application when the bulk active ingredient is not a component of a FDA-approved drug. Institutions should have guidelines for such situations and should adhere to the current FDA compliance guide for pharmacy compounding and the Code of Federal Regulations. A pharmacist’s assessment of the clinical situation, the raw materials to be used, and the preparation methods is critical.

2. 21 C.F.R. §216.24.
3. 21 C.F.R. §312.23.

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