AMERICAN COLLEGE OF RHEUMATOLOGY

POSITION STATEMENT

SUBJECT: Compounding of Pharmacologic Agents

PRESENTED BY: Committee on Rheumatologic Care

FOR DISTRIBUTION TO:

Members of the American College of Rheumatology
US Food and Drug Administration
United States Pharmacopeia
Pharmacy Compounding Accreditation Board
Members of Congress

POSITIONS:

1. The American College of Rheumatology (ACR) supports pharmacy compounding pursuant to or in anticipation of a prescription or diagnostic preparation order as an essential aspect of meeting patients' drug therapy needs.

2. The ACR supports the US Food and Drug Administration (FDA), the United States Pharmacopeia (USP), and the Pharmacy Compounding Accreditation Board (PCAB) coordination and standardization of definitions of compounding.

3. The ACR supports appropriate regulations and standards requiring licensure and inspection of all compounding pharmacies and urges state boards of pharmacy and the FDA to identify and take appropriate action against entities that are manufacturing medications in violation of Section 503A under the guise of compounding.

4. The ACR supports physician authority to compound and administer medications in the office setting for the purposes of infusions and intra-articular injections, among others, as the immediate compounding of an anesthetic plus a corticosteroid or viscosupplementation is a critical process standard in rheumatology care.

5. The ACR supports maintaining the current USP 797 standard for sterile in-office mixture of parenteral drugs for immediate office administration within four hours of compounding.

6. The ACR supports physician access to bulk purchase of drugs made in compounding pharmacies for physician use in a clinical setting. Products made for purchase by physicians for in-office use should be clearly marked "for office use" and should not be re-sold to patients for use outside of the office.

7. The ACR supports efforts to keep the regulation of in-office physician compounding under the purview of state medical boards and not state pharmacy boards.

DEFINITIONS AND BACKGROUND:

Pharmaceutical compounding refers to the creation of pharmaceutical preparations individualized for specific patients. Compounding has always been a part of pharmacy practice; for centuries it was the only form of preparing crude medications. As manufacturers of innovative

pharmaceuticals began developing drugs in finished dosage forms, the need for patient-specific compounding gradually diminished to the point that compounding is now considered a specialty practice. Nonetheless, there remains a significant need to prepare individualized drug dosage forms or individualized drug dosages for special needs, such as in veterinary practice and various specialties of medicine such as allergy/immunology, dermatology, etc. Compounding pharmacies can also prepare special dosage forms and flavorings for pediatric use or exclude specific ingredients due to patient allergies and other intolerances. For these reasons, compounding has historically been done on a small scale for individualized patient needs. The regulation of pharmacy-based compounding has always been left to state Boards of Pharmacy. In addition, physicians may sometimes compound and/or store compounded drugs in office settings as regulated by state laws and Boards of Medicine regulations.

Spending by the Medicare Part D program for compounded medicines is rising dramatically. From 2006 to 2015, Medicare Part D spending for compounded drugs grew from $70 million $508 million, a 625 percent increase (1). Consequently, the Office of Inspector General (OIG) initiated investigations into pharmacies compounding these drugs to assess compliance with federal and state regulations. Unfortunately, specific data on Medicare Part D spending on compounded drugs beyond 2015 is not readily available. The Office of Audit Services (OAS) is conducting an audit related to Medicare Part D spending on compounded drugs. This report is scheduled to be released in 2025.

REGULATION:

United States Pharmacopeia:

Laws and regulations that govern compounding generally rely heavily on standards promulgated by the United States Pharmacopeia (USP). While not a government entity, USP works closely with government agencies and regulatory authorities to provide standards of identity, strength, quality, and purity for medicines (3). Because USP is not a government entity, it does not have an enforcement role. However, USP standards are recognized in a variety of federal legislation, including the adulteration and misbranding provisions of the Federal Food Drug and Cosmetic Act. At the state level, compounding is overseen by state boards of pharmacy. Almost all states have laws, regulations, or policies specific to compounding. At least 87 percent of state boards of pharmacy either require full compliance with USP 797 or incorporate USP 797 into their state regulations in some way (4).

USP has published standards on sterile and non-sterile compounding which specify best practices to prevent harm from contaminated or inconsistent formulations. USP chapter 797 (or chapter 800 in the case of hazardous substances such as methotrexate or cyclophosphamide or investigational drugs) specifically addresses standards for compounding of sterile products and defines such to include mixing of two or more commercially manufactured packages of sterile product for administration via injection or infusion. Therefore chapter 797 pertains to the situation in which a physician mixes two injectable products, such as lidocaine and a corticosteroid, for injection.

USP continually reviews and updates its standards and published revisions to chapters 797 and 800 effective November 1, 2023. The USP 797 updates introduce stricter guidelines for compounded sterile preparations (CSPs), emphasizing Beyond Use Dating (BUD), aseptic technique, and hazardous drug handling. The chapter reclassifies CSPs into three categories based on the state of environmental control under which they are compounded, the probability for microbial growth during the time they will be stored, and the time period within which they must be used (5). Revisions also modify the immediate use provision by increasing the time allowed between compounding and administration compared to the previously published compendium. The immediate use provision allows for administration of a CSP within four hours of the start of preparation, so long as certain sterility conditions and personal competencies are met (6). When these conditions are met, compounding of CSPs for immediate administration is not subject to CSP categories. Additional information about USP immediate-use standards can be found in section 1.3 Immediate-Use CSP in USP 797.

State boards of pharmacy are primarily responsible for regulating pharmaceutical compounding and enforcing USP standards. The National Association of Boards of Pharmacies (NABP) has issued model pharmacy rules to assist state boards of pharmacy with the implementation of USP standards (7). The NABP may also award a National Compounding Accreditation for pharmacies that align with applicable USP standards and comply with section 503A of the Federal Food, Drug, and Cosmetic Act (8). Accreditation is also available from the Pharmacy Compounding Accreditation Board (PCAB), part of the Accreditation Commission for Health Care (9). Rheumatologists and rheumatology professionals who engage in compounding are encouraged to review compounding enforcement in their jurisdiction.

FDA Regulation of Bulk Compounding:

Historically, the FDA has concerned itself with the manufacture of drugs and left the regulation of compounding by pharmacists and physicians to the states. However, specialized pharmacy compounders sometimes prepare sterile and non-sterile drugs in bulk in anticipation of recurring demand for sale to physicians and hospitals. Contamination of injectable drugs compounded on a large scale has resulted in major harm to patients in the past as illustrated by the New England Compounding Center tragedy in 2012 (10). Because bulk-compounding is considered manufacturing, it thereby falls under the purview of the FDA

In the Drug Quality and Security Act (DQSA) of 2013, Congress amended the Federal Food, Drug, and Cosmetic Act to clarify FDA jurisdiction over traditional (i.e. patient- specific) compounding, and to provide a regulated (but optional) pathway for "non-traditional" compounders to operate. Section 503A establishes that pharmacies compounding only "patient-specific" drug products made in response to each prescription do not require FDA approval for such products, as they remain exclusively under state-level pharmacy regulation. At the same time, Section 503B created a new category of facilities called "outsourcing facilities" by which non-traditional compounding facilities (i.e. those whose products include "non-patient-specific" large batches) can be explicitly authorized by the FDA while being exempted from certain requirements otherwise imposed on manufacturers.

Outsourcing facilities that register under section 503B of the Food, Drug, and Cosmetic Act must comply with current good manufacturing practice requirements and will be inspected by the FDA according to a risk-based schedule. Under FDA guidance, only patient- specific compounding pursuant to an individual prescription will be exempt from future FDA regulation (11). Compounding for office stock will be prohibited by non-outsourcing facilities. The FDA guidance also limits the ability of hospital pharmacies to anticipate and compound for regular large volume needs and thereby poses problems for larger health-systems.

IMPACT ON RHEUMATOLOGY PATIENTS:

The 2023 USP Chapter 797 immediate-use revisions allowing a 4-hour window between mixing and administration of simple compounded pharmaceuticals better aligns these regulations with routine clinical practice. Rheumatologists often perform joint and soft tissue injections in the office using a preparation of a local anesthetic combined with a corticosteroid and/or viscosupplementation. This procedure is performed safely every day by rheumatologists across the country with exceptionally low risk for the benefit of vast numbers of patients who would otherwise go without effective treatment for painful musculoskeletal disorders (12).

Historically, in a draft guidance, the FDA has indicated its desire for 503B facilities to provide all office-use compounding, which would incentivize pharmacies to register as 503B facilities. However, outsourcing facilities under 503B cannot realistically provide for the needs of all small-scale use by physicians, which may directly affect patient access to necessary medication. The FDA has published a guidance and FAQ document for facilities considering whether to register as an outsourcing facility (13).

Outsourcing facilities which operate under section 503B may not compound a drug that includes a bulk drug substance unless it appears on the 503B bulk drug substances list, or unless the compounded drug appears on FDA's drug shortage list at the time of compounding, distribution and dispensing. Formerly, quinacrine was not included on the 503B bulk substance list, posing a barrier for rheumatology patients needing this therapy. However, as of the approval of this document, quinacrine has been approved as a 503B bulk substance (14). The approval is a victory for rheumatology patients needing treatment with this compounded agent.

Conclusion:

Patients needing access to compounded therapies should be able to expect their treatment is safe, effective, and subject to appropriate oversight. Many rheumatologic patients require treatments which may be subject to compounding regulations, such as infusions or intra-articular injections. The ACR supports FDA regulations and USP guidelines which improve patient safety, while cautioning against the inappropriate application of guidelines intended to regulate higher-risk procedures which may inadvertently impede the care of rheumatologic patients receiving routine and low risk treatments classified as compounding.

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