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 part of health care.

2. The ACR supports the US Food and Drug Administration (FDA) and United States Pharmacopeia (USP) coordination and standardization of definitions of compounding.

3. The ACR supports compounding as defined by the Pharmacy Compounding Accreditation Board (PCAB) as a means to meet patient drug therapy needs.

4. The ACR supports accreditation of compounding sites by PCAB to ensure patient safety.

5. The ACR opposes compounding when identical medications are commercially and readily available in strength and dosage form to meet patient drug therapy needs.

6. 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.

7. The ACR supports physician authority to compound and administer medications in the office-setting as has been the standard of care for decades and is frequently the only effective therapeutic option for patients suffering from a range of rheumatologic conditions. The immediate compounding of an anesthetic plus a corticosteroid or viscosupplementation gel is a critical process in intra-articular injections and should be made an exception in USP 797.

8. The ACR supports addition of quinacrine to the FDA bulk substances list, in order to maintain access to this drug for the treatment of patients who would benefit from quinacrine. Most patients who are prescribed quinacrine have failed, are intolerant of, or are unable to obtain alternative drugs such as hydroxychloroquine.

9. The ACR opposes regulations and standards that restrict physician access to non-sterile compounded pharmaceuticals by prohibiting the purchase of these materials in bulk for anticipatory use by physicians in a clinical setting.

10. The ACR supports maintaining the 2008 USP 797 standard for sterile compounding, which allows in-office mixture of parenteral drugs for immediate office use.

11. 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.

12. 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 (creation of particular pharmaceutical preparations individualized for specific patients) has always been a part of pharmacy practice; indeed, 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 pharmacy 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. Compounding has historically been done on a small scale for individualized patient needs. Thus, regulation of compounding has always been left to state Boards of Pharmacy (accreditation by the national PCAB is currently available but optional for pharmacies). 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 went from $70 million to $508 million, a 625 percent increase[1]. This has been driven in part by shortages of commercially available products. In addition, improper compounding on a large scale has resulted in major harm to patients, as illustrated by the New England Compounding Center tragedy in 2012[2]. These events have led to increasing scrutiny of compounding.

REGULATION:

Compounding in any setting is subject to definitions and regulations from three sources. The first is state and federal law. However, these laws and regulations generally rely heavily on standards promulgated by USP and the FDA.

While not a government entity, USP works closely with government agencies and regulatory authorities around the world to provide standards of identity, strength, quality, and purity for medicines. USP standards are recognized in a variety of US federal legislation. USP's drug standards are specified in the adulteration and misbranding provisions of the Federal Food, Drug, and Cosmetic Act. The Dietary Supplement Health and Education Act misbranding provision has a role for USP's dietary supplement standards, and more than 200 FDA regulations incorporate USP food ingredient standards[3].

USP has published standards on sterile and non-sterile compounding. These are standards for 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. Thus chapter 797 includes a situation in which a physician mixes two injectable products such as lidocaine and a corticosteroid for injection. The chapter requires mixing in a sterile hood, and manipulation outside a hood is interpreted as inappropriate by many state medical boards. There is an exception provided for immediate use, which generally implies an emergency need. The immediate use provision could be interpreted as a safe harbor for physician mixing of sterile products, depending on the situation and the regulatory authority. USP has proposed revisions to Chapter 797 that threaten this practice, though the revisions have been put on hold due to lack of professional consensus. [4]

The FDA is the third entity with regulatory authority over drug use. 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. This practice is considered manufacturing and thereby falls under the purview of the FDA. Contamination of injectable drugs compounded on a large scale has resulted in major harm to patients.[2]

Therefore, in the Drug Quality and Security Act (DQSA) of 2013 (H.R. 3204), 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 Food Drug and Cosmetic Act are now regulated by FDA, must comply with current good manufacturing practice requirements, and will be inspected by FDA according to a risk-based schedule. Under recent FDA guidance, only patient-specific compounding pursuant to an individual prescription will be exempt from future FDA regulation[5]. 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:

USP Chapter 797 proposed revisions threaten the ability of providers to meet the standard of care for a wide range of musculoskeletal disorders by performing joint and soft tissue injections in the office such as using a preparation of a local anesthetic combined with bicarbonate or a corticosteroid. This procedure is performed safely every day by rheumatologists across the country with exceptionally low risk[6] for the benefit of vast numbers of patients who would otherwise go without effective treatment for painful musculoskeletal disorders. As such, this procedure must be protected.

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.

Draft guidance would also prohibit compounding of drugs not compliant with the use of bulk substances as defined in 21 CFR 207.3(a)(4). Drugs that have niche uses, such as quinacrine for lupus patients, therefore, must be on the bulk substances list in order to be compliant. For the time being, FDA is not taking action on this issue until it makes a final decision on which drugs have sufficient evidence of efficacy to add to the list[7]. As of the approval of this document, quinacrine remains among those under evaluation by the FDA for both the 503a and 503b Bulk Substances list.[7,8]

REFERENCES:

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