COMMONWEALTH OF VIRGINIA

Meeting of the Board of Pharmacy

Perimeter Center, 9960 Mayland Drive, Second Floor
Henrico, Virginia 23233

(804) 367-4456 (Tel)
(804) 527-4472(Fax)

Tentative Agenda of Meeting
Compounding Workgroup

July 31, 2014

9:00AM

TOPIC **PAGES**

Call to Order: Jody H. Allen, Chairman

- Welcome & Introductions
- Reading of Emergency Evacuation Script

Call for Public Comment

Background Materials

o HB1035 with Enactment Clause to Form Workgroup	1-4
o Other Applicable Sections of Law	5-9
o Guidance Document 110-36	10-18
o *Quality Standards for Large Scale Sterile Compounding Facilities*	19-51
o *CGMP-USP <797> Crosswalk*	52-81
o Copy of Letter to VSEPS regarding Repackaging of Avastin	82-83
o *Understanding the New Proposed USP Chapter <800>*	84-86
o Information from FDA website on Compounding	87-92

Brief Overview of Federal Compounding Allowances – Caroline Juran

- o Drug Quality and Security Act
- o 503A, 503B, 503C of the Federal Food & Drug Cosmetic Act
- o Compounding Drugs for Human Use verses Animal Use
- o Repackaging verses Compounding

Compounding Performed in Pharmacies

- o Consider amending Guidance Document 110-36
  - Quality Assurance
    - Surface sampling - a practice used to determine cleaning procedures are adequate, but only required on a yearly basis
    - Proper media fill incubation requirements depending on media used
    - Are facilities decreasing CFU growth by improper incubation procedures?
    - Certifications for employees
  - Beyond Use Dating (BUDs)
    - Repackaging a MDV into single dose units
    - Removing SDV from an ISO Class 5 area
    - Clarification on BUDs references able to be used and quantity

- Use of dispensing pins (spikes) and relation to sterility concerns
- Irrigations (bladder/wound) for patient home use
- Review of USP <51> in Guidance Document 110-36 93
- When is it Required to Use a Closed System Transfer Device
- Federal prohibition for pharmacies to provide compounded drugs for human use for office administration
- New allowance for pharmacies to provide compounded drugs for animal use in limited capacity to veterinarians for dispensing

Compounding Performed in Physician Offices

- Mixing, Diluting, and Reconstituting Drugs for Administration
- Use of a Pharmacist in Physician's Office to Mix, Dilute, and Reconstitute or Compound

Compounding Performed in Outsourcing Facilities

- Status of Implementation of Federal Law, e.g., Guidance, Regulations, MOU
- Virginia Legislative Proposal to License Outsourcing Facilities

Miscellaneous Topics

- Responsibility of Individual Facilities/Buying Groups when obtaining Compounded Drugs from a Pharmacy or Outsourcing Facility
- Institutional Responsibilities to Ensure Sterility/Stability of All Products Obtained from these Facilities
- Status USP Chapter <800> 94

Adjournment

******The workgroup will have a working lunch at approximately 12pm.*****

Compounding Workgroup Members:

Jody H. Allen, PharmD, Committee Chairman, Board of Pharmacy member
Ellen Shinaberry, PharmD, Chairman of the Board of Pharmacy
Crady Adams, RPh, Board of Pharmacy member
Jim Rutkowski, Assistant Attorney General, Counsel to Board of Pharmacy
Syed Salman Ali, MD, Board of Medicine member
Brian Mitchell, MD, Representing Medical Society of Virginia
Sarah Colgan, PharmD, Representing Virginia Society of Health-System Pharmacists
Kelly Gattschalk, DVM, Board of Veterinary Medicine member
Jamin Engel, PharmD, participating at the request of Board of Pharmacy Chairman
Eric Kastango, RPh, Principal-CEO, Clinical IQ, LLC, USP expert for the Board of Pharmacy
Steve Escobar, DVM, Representing Virginia Veterinary Medicine Association
Alexander Pytlarz, Representing Virginia Pharmacists Association
Alan Wagner, MD, Representing Virginia Society of Eye Physicians and Surgeons
Jaime Hoyle, Esq., Chief Deputy Director, Department of Health Professions
Elaine Yeatts, Senior Policy Analyst, Department of Health Professions
Caroline Juran, RPh, Executive Director, Board of Pharmacy
Sammy Johnson, RPh, Deputy Executive Director, Board of Pharmacy

Alternate members:

James T. May, III, MD, Representing Medical Society of Virginia
Bobby Ison, RPh, Representing Virginia Society of Health-System Pharmacists
Mark Johnson, DVM, Chairman of the Board of Veterinary Medicine member
Claudia True, DVM, Representing Virginia Veterinary Medicine Association
William Harp, MD, Executive Director, Board of Medicine
Chris Currin, RPh, Representing Virginia Pharmacists Association
David Brown, DC, Director, Department of Health Professions

VIRGINIA ACTS OF ASSEMBLY -- 2014 SESSION

CHAPTER 147

An Act to amend and reenact §§ 54.1-3301 and 54.1-3410.2 of the Code of Virginia, relating to veterinarians; dispensing compounded drug products.

[H 1035]

Approved March 5, 2014

Be it enacted by the General Assembly of Virginia:

1. That §§ 54.1-3301 and 54.1-3410.2 of the Code of Virginia are amended and reenacted as follows:

§ 54.1-3301. Exceptions.

This chapter shall not be construed to:

1. Interfere with any legally qualified practitioner of dentistry, or veterinary medicine or any physician acting on behalf of the Virginia Department of Health or local health departments, in the compounding of his prescriptions or the purchase and possession of drugs as he may require;

2. Prevent any legally qualified practitioner of dentistry, or veterinary medicine or any prescriber, as defined in § 54.1-3401, acting on behalf of the Virginia Department of Health or local health departments, from administering or supplying to his patients the medicines that he deems proper under the conditions of § 54.1-3303 or from causing drugs to be administered or dispensed pursuant to §§ 32.1-42.1 and 54.1-3408, *except that a veterinarian shall only be authorized to dispense a compounded drug, distributed from a pharmacy, when (i) the animal is his own patient, (ii) the animal is a companion animal as defined in regulations promulgated by the Board of Veterinary Medicine, (iii) the quantity dispensed is no more than a 72-hour supply, (iv) the compounded drug is for the treatment of an emergency condition, and (v) timely access to a compounding pharmacy is not available, as determined by the prescribing veterinarian*;

3. Prohibit the sale by merchants and retail dealers of proprietary medicines as defined in Chapter 34 (§ 54.1-3400 et seq.) of this title;

4. Prevent the operation of automated drug dispensing systems in hospitals pursuant to Chapter 34 (§ 54.1-3400 et seq.) of this title;

5. Prohibit the employment of ancillary personnel to assist a pharmacist as provided in the regulations of the Board;

6. Interfere with any legally qualified practitioner of medicine, osteopathy, or podiatry from purchasing, possessing or administering controlled substances to his own patients or providing controlled substances to his own patients in a bona fide medical emergency or providing manufacturers' professional samples to his own patients;

7. Interfere with any legally qualified practitioner of optometry, certified or licensed to use diagnostic pharmaceutical agents, from purchasing, possessing or administering those controlled substances as specified in § 54.1-3221 or interfere with any legally qualified practitioner of optometry certified to prescribe therapeutic pharmaceutical agents from purchasing, possessing, or administering to his own patients those controlled substances as specified in § 54.1-3222 and the TPA formulary, providing manufacturers' samples of these drugs to his own patients, or dispensing, administering, or selling ophthalmic devices as authorized in § 54.1-3204;

8. Interfere with any physician assistant with prescriptive authority receiving and dispensing to his own patients manufacturers' professional samples of controlled substances and devices that he is authorized, in compliance with the provisions of § 54.1-2952.1, to prescribe according to his practice setting and a written agreement with a physician or podiatrist;

9. Interfere with any licensed nurse practitioner with prescriptive authority receiving and dispensing to his own patients manufacturers' professional samples of controlled substances and devices that he is authorized, in compliance with the provisions of § 54.1-2957.01, to prescribe according to his practice setting and a written or electronic agreement with a physician;

10. Interfere with any legally qualified practitioner of medicine or osteopathy participating in an indigent patient program offered by a pharmaceutical manufacturer in which the practitioner sends a prescription for one of his own patients to the manufacturer, and the manufacturer donates a stock bottle of the prescription drug ordered at no cost to the practitioner or patient. The practitioner may dispense such medication at no cost to the patient without holding a license to dispense from the Board of Pharmacy. However, the container in which the drug is dispensed shall be labeled in accordance with the requirements of § 54.1-3410, and, unless directed otherwise by the practitioner or the patient, shall meet standards for special packaging as set forth in § 54.1-3426 and Board of Pharmacy regulations. In lieu of dispensing directly to the patient, a practitioner may transfer the donated drug with a valid prescription to a pharmacy for dispensing to the patient. The practitioner or pharmacy participating in

the program shall not use the donated drug for any purpose other than dispensing to the patient for whom it was originally donated, except as authorized by the donating manufacturer for another patient meeting that manufacturer's requirements for the indigent patient program. Neither the practitioner nor the pharmacy shall charge the patient for any medication provided through a manufacturer's indigent patient program pursuant to this subdivision. A participating pharmacy, including a pharmacy participating in bulk donation programs, may charge a reasonable dispensing or administrative fee to offset the cost of dispensing, not to exceed the actual costs of such dispensing. However, if the patient is unable to pay such fee, the dispensing or administrative fee shall be waived;

11. Interfere with any legally qualified practitioner of medicine or osteopathy from providing controlled substances to his own patients in a free clinic without charge when such controlled substances are donated by an entity other than a pharmaceutical manufacturer as authorized by subdivision 10. The practitioner shall first obtain a controlled substances registration from the Board and shall comply with the labeling and packaging requirements of this chapter and the Board's regulations; or

12. Prevent any pharmacist from providing free health care to an underserved population in Virginia who (i) does not regularly practice pharmacy in Virginia, (ii) holds a current valid license or certificate to practice pharmacy in another state, territory, district or possession of the United States, (iii) volunteers to provide free health care to an underserved area of this Commonwealth under the auspices of a publicly supported all volunteer, nonprofit organization that sponsors the provision of health care to populations of underserved people, (iv) files a copy of the license or certificate issued in such other jurisdiction with the Board, (v) notifies the Board at least five business days prior to the voluntary provision of services of the dates and location of such service, and (vi) acknowledges, in writing, that such licensure exemption shall only be valid, in compliance with the Board's regulations, during the limited period that such free health care is made available through the volunteer, nonprofit organization on the dates and at the location filed with the Board. The Board may deny the right to practice in Virginia to any pharmacist whose license has been previously suspended or revoked, who has been convicted of a felony or who is otherwise found to be in violation of applicable laws or regulations. However, the Board shall allow a pharmacist who meets the above criteria to provide volunteer services without prior notice for a period of up to three days, provided the nonprofit organization verifies that the practitioner has a valid, unrestricted license in another state.

This section shall not be construed as exempting any person from the licensure, registration, permitting and record keeping requirements of this chapter or Chapter 34 of this title.

§ 54.1-3410.2. Compounding; pharmacists' authority to compound under certain conditions; labeling and record maintenance requirements.

A. A pharmacist may engage in compounding of drug products when the dispensing of such compounded products is (i) pursuant to valid prescriptions for specific patients and (ii) consistent with the provisions of § 54.1-3303 relating to the issuance of prescriptions and the dispensing of drugs.

Pharmacists shall label all compounded drug products that are dispensed pursuant to a prescription in accordance with this chapter and the Board's regulations, and shall include on the labeling an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding.

B. A pharmacist may also engage in compounding of drug products in anticipation of receipt of prescriptions based on a routine, regularly observed prescribing pattern.

Pharmacists shall label all products compounded prior to dispensing with (i) the name and strength of the compounded medication or a list of the active ingredients and strengths; (ii) the pharmacy's assigned control number that corresponds with the compounding record; (iii) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (iv) the quantity.

C. In accordance with the conditions set forth in subsections A and B, pharmacists shall not distribute compounded drug products for subsequent distribution or sale to other persons or to commercial entities, including distribution to pharmacies or other entities under common ownership or control with the facility in which such compounding takes place*; however, a pharmacist may distribute to a veterinarian in accordance with federal law.*

Compounded products for companion animals, as defined in regulations promulgated by the Board of Veterinary Medicine, and distributed by a pharmacy to a veterinarian for further distribution or sale to his own patients shall be limited to drugs necessary to treat an emergent condition when timely access to a compounding pharmacy is not available as determined by the prescribing veterinarian.

A pharmacist may, however, deliver compounded products dispensed pursuant to valid prescriptions to alternate delivery locations pursuant to § 54.1-3420.2.

A pharmacist may also provide compounded products to practitioners of medicine, osteopathy, podiatry, dentistry, or veterinary medicine to administer to their patients in the course of their professional practice, either personally or under their direct and immediate supervision.

Pharmacists shall label all compounded products distributed to practitioners *other than veterinarians* for administration to their patients with (i) the statement "For Administering in Prescriber Practice Location Only"; (ii) the name and strength of the compounded medication or list of the active

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ingredients and strengths; (iii) the facility's control number; (iv) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; ~~and~~ (v) *the name and address of the pharmacy; and (vi) the* quantity.

Pharmacists shall label all compounded products for companion animals, as defined in regulations promulgated by the Board of Veterinary Medicine, and distributed to a veterinarian for either further distribution or sale to his own patient or administration to his own patient with (a) the name and strength of the compounded medication or list of the active ingredients and strengths; (b) the facility's control number; (c) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; (d) the name and address of the pharmacy; and (e) the quantity.

D. Pharmacists shall personally perform or personally supervise the compounding process, which shall include a final check for accuracy and conformity to the formula of the product being prepared, correct ingredients and calculations, accurate and precise measurements, appropriate conditions and procedures, and appearance of the final product.

E. Pharmacists shall ensure compliance with USP-NF standards for both sterile and non-sterile compounding.

F. Pharmacists may use bulk drug substances in compounding when such bulk drug substances:

1. Comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if such monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding; or are drug substances that are components of drugs approved by the FDA for use in the United States; or are otherwise approved by the FDA;

2. Are manufactured by an establishment that is registered by the FDA; or

3. Are distributed by a licensed wholesale distributor or registered nonresident wholesale distributor, or are distributed by a supplier otherwise approved by the FDA to distribute bulk drug substances if the pharmacist can establish purity and safety by reasonable means, such as lot analysis, manufacturer reputation, or reliability of the source.

G. Pharmacists may compound using ingredients that are not considered drug products in accordance with the USP-NF standards and guidance on pharmacy compounding.

H. Pharmacists shall not engage in the following:

1. The compounding for human use of a drug product that has been withdrawn or removed from the market by the FDA because such drug product or a component of such drug product has been found to be unsafe. However, this prohibition shall be limited to the scope of the FDA withdrawal;

2. The regular compounding or the compounding of inordinate amounts of any drug products that are essentially copies of commercially available drug products. However, this prohibition shall not include (i) the compounding of any commercially available product when there is a change in the product ordered by the prescriber for an individual patient, (ii) the compounding of a commercially manufactured drug only during times when the product is not available from the manufacturer or supplier, (iii) the compounding of a commercially manufactured drug whose manufacturer has notified the FDA that the drug is unavailable due to a current drug shortage, (iv) the compounding of a commercially manufactured drug when the prescriber has indicated in the oral or written prescription for an individual patient that there is an emergent need for a drug that is not readily available within the time medically necessary, or (v) the mixing of two or more commercially available products regardless of whether the end product is a commercially available product; or

3. The compounding of inordinate amounts of any preparation in cases in which there is no observed historical pattern of prescriptions and dispensing to support an expectation of receiving a valid prescription for the preparation. The compounding of an inordinate amount of a preparation in such cases shall constitute manufacturing of drugs.

I. Pharmacists shall maintain records of all compounded drug products as part of the prescription, formula record, formula book, or other log or record. Records may be maintained electronically, manually, in a combination of both, or by any other readily retrievable method.

1. In addition to other requirements for prescription records, records for products compounded pursuant to a prescription order for a single patient where only manufacturers' finished products are used as components shall include the name and quantity of all components, the date of compounding and dispensing, the prescription number or other identifier of the prescription order, the total quantity of finished product, the signature or initials of the pharmacist or pharmacy technician performing the compounding, and the signature or initials of the pharmacist responsible for supervising the pharmacy technician and verifying the accuracy and integrity of compounded products.

2. In addition to the requirements of subdivision I 1, records for products compounded in bulk or batch in advance of dispensing or when bulk drug substances are used shall include: the generic name and the name of the manufacturer of each component or the brand name of each component; the manufacturer's lot number and expiration date for each component or when the original manufacturer's lot number and expiration date are unknown, the source of acquisition of the component; the assigned lot number if subdivided, the unit or package size and the number of units or packages prepared; and the beyond-use date. The criteria for establishing the beyond-use date shall be available for inspection

by the Board.

3. A complete compounding formula listing all procedures, necessary equipment, necessary environmental considerations, and other factors in detail shall be maintained where such instructions are necessary to replicate a compounded product or where the compounding is difficult or complex and must be done by a certain process in order to ensure the integrity of the finished product.

4. A formal written quality assurance plan shall be maintained that describes specific monitoring and evaluation of compounding activities in accordance with USP-NF standards. Records shall be maintained showing compliance with monitoring and evaluation requirements of the plan to include training and initial and periodic competence assessment of personnel involved in compounding, monitoring of environmental controls and equipment calibration, and any end-product testing, if applicable.

J. Practitioners who may lawfully compound drugs for administering or dispensing to their own patients pursuant to §§ 54.1-3301, 54.1-3304, and 54.1-3304.1 shall comply with all provisions of this section and the relevant Board regulations.

K. Every pharmacist-in-charge or owner of a permitted pharmacy or a registered nonresident pharmacy engaging in sterile compounding shall notify the Board of its intention to dispense or otherwise deliver a sterile compounded drug product into the Commonwealth. Upon renewal of its permit or registration, a pharmacy or nonresident pharmacy shall notify the Board of its intention to continue dispensing or otherwise delivering sterile compounded drug products into the Commonwealth. Failure to provide notification to the Board shall constitute a violation of Chapter 33 (§ 54.1-3300 et seq.) or Chapter 34 (§ 54.1-3400 et seq.). The Board shall maintain this information in a manner that will allow the production of a list identifying all such sterile compounding pharmacies.

2. That the Board of Pharmacy shall convene a workgroup to include representatives of the Board of Veterinary Medicine, the Board of Medicine, and stakeholders to include the Virginia Pharmacists Association, Virginia Society of Health-System Pharmacists, Virginia Veterinary Medicine Association, and the Virginia Society of Eye Physicians and Surgeons. The workgroup shall explore and clarify issues related to the compounding of drugs for human and animal use. The work group shall provide a report to the Chairmen of the House of Delegates' Committee on Health, Welfare and Institutions and the Senate Committee on Education and Health by November 1, 2014.

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from *The Drug Control Act,* July 1, 2014

§54.1-3401

"Compounding" means the combining of two or more ingredients to fabricate such ingredients into a single preparation and includes the mixing, assembling, packaging, or labeling of a drug or device (i) by a pharmacist, or within a permitted pharmacy, pursuant to a valid prescription issued for a medicinal or therapeutic purpose in the context of a bona fide practitioner-patient-pharmacist relationship, or in expectation of receiving a valid prescription based on observed historical patterns of prescribing and dispensing; (ii) by a practitioner of medicine, osteopathy, podiatry, dentistry, or veterinary medicine as an incident to his administering or dispensing, if authorized to dispense, a controlled substance in the course of his professional practice; or (iii) for the purpose of, or as incident to, research, teaching, or chemical analysis and not for sale or for dispensing. The mixing, diluting, or reconstituting of a manufacturer's product drugs for the purpose of administration to a patient, when performed by a practitioner of medicine or osteopathy licensed under Chapter 29 (§ 54.1-2900 et seq.), a person supervised by such practitioner pursuant to subdivision A 6 or A 19 of § 54.1-2901, or a person supervised by such practitioner or a licensed nurse practitioner or physician assistant pursuant to subdivision A 4 of § 54.1-2901 shall not be considered compounding.

from *Regulations Governing the Practice of Medicine, Osteopathy, Podiatry and Chiropractic,* Virginia Board of Medicine, September 25, 2013

Part IX. Mixing, Diluting or Reconstituting of Drugs for Administration.

18VAC85-20-400. Requirements for immediate-use sterile mixing, diluting or reconstituting.

A. For the purposes of this chapter, the mixing, diluting, or reconstituting of sterile manufactured drug products when there is no direct contact contamination and administration begins within 10 hours of the completion time of preparation shall be considered immediate-use with the exception of drugs in fat emulsion for which immediate use shall be one hour. If manufacturers' instructions or any other accepted standard specifies or indicates an appropriate time between preparation and administration of less than 10 hours, the mixing, diluting or reconstituting shall be in accordance with the lesser time. No direct contact contamination means that there is no contamination from touch, gloves, bare skin or secretions from the mouth or nose. Emergency drugs used in the practice of anesthesiology and administration of allergens may exceed 10 hours after completion of the preparation, provided administration does not exceed the specified expiration date of a multiple use vial and there is compliance with all other requirements of this section.

B. Doctors of medicine or osteopathic medicine who engage in immediate-use mixing, diluting or reconstituting shall:

1. Utilize the practices and principles of disinfection techniques, aseptic manipulations and solution compatibility in immediate-use mixing, diluting or reconstituting;

2. Ensure that all personnel under their supervision who are involved in immediate-use mixing, diluting or reconstituting are appropriately and properly trained in and utilize the practices and principles of disinfection techniques, aseptic manipulations and solution compatibility;

3. Establish and implement procedures for verification of the accuracy of the product that has been mixed, diluted, or reconstituted to include a second check performed by a doctor of medicine or osteopathic medicine or a pharmacist, or by a physician assistant or a registered nurse who has been specifically trained pursuant to subdivision 2 of this subsection in immediate-use mixing, diluting or reconstituting. Mixing, diluting or reconstituting that is performed by a doctor of medicine or osteopathic medicine, a pharmacist, or by a specifically trained physician assistant or registered nurse or mixing, diluting or reconstituting of vaccines does not require a second check;

4. Provide a designated, sanitary work space and equipment appropriate for aseptic manipulations;

5. Document or ensure that personnel under his supervision documents in the patient record or other readily retrievable record that identifies the patient; the names of drugs mixed, diluted or reconstituted; and the date of administration; and

6. Develop and maintain written policies and procedures to be followed in mixing, diluting or reconstituting of sterile products and for the training of personnel.

C. Any mixing, diluting or reconstituting of drug products that are hazardous to personnel shall be performed consistent with requirements of all applicable federal and state laws and regulations for safety and air quality, to include but not be limited to those of the Occupational Safety and Health Administration (OSHA). For the purposes of this chapter, Appendix A of the National Institute for Occupational Safety and Health publication (NIOSH Publication No. 2004-165), Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings is incorporated by reference for the list of hazardous drug products and can be found at www.cdc.gov/niosh/docs/2004-165.

18VAC85-20-410. Requirements for low-, medium- or high-risk sterile mixing, diluting or reconstituting.

A. Any mixing, diluting or reconstituting of sterile products that does not meet the criteria for immediate-use as set forth in 18VAC85-20-400 A shall be defined as low-, medium-, or high-risk compounding under the definitions of Chapter 797 of the U.S. Pharmacopeia (USP).

B. Until July 1, 2007, all low-, medium-, or high-risk mixing, diluting or reconstituting of sterile products shall comply with the standards for immediate-use mixing, diluting or reconstituting as specified in 18VAC85-20-400. Beginning July 1, 2007, doctors of medicine or osteopathic medicine who engage in low-, medium-, or high-risk mixing, diluting or reconstituting of sterile products shall comply with all applicable requirements of the USP Chapter 797. Subsequent changes to the USP Chapter 797 shall apply within one year of the official announcement by USP.

C. A current copy, in any published format, of USP Chapter 797 shall be maintained at the location where low-, medium- or high-risk mixing, diluting or reconstituting of sterile products is performed.

18VAC85-20-420. Responsibilities of doctors who mix, dilute or reconstitute drugs in their practices.

A. Doctors of medicine or osteopathic medicine who delegate the mixing, diluting or reconstituting of sterile drug products for administration retain responsibility for patient care and shall monitor and document any adverse responses to the drugs.

B. Doctors who engage in the mixing, diluting or reconstituting of sterile drug products in their practices shall disclose this information to the board in a manner prescribed by the board and are subject to unannounced inspections by the board or its agents.

from *The Pharmacy Act*, July 1, 2014

§ 54.1-3304.1. Authority to license and regulate practitioners.

The Board of Pharmacy shall have the authority to license and regulate the dispensing of controlled substances by practitioners of the healing arts.

(1988, c. 904, § 54-524.34:2; 1989, c. 510.)

from *Regulations for Practitioners of the Healing Arts to Sell Controlled Substances*, August, 2, 2013

18VAC110-30-40. Acts to be performed by the licensee.

A. The selection of the controlled substance from the stock, any preparation or packaging of a controlled substance or the preparation of a label for a controlled substance to be transferred to a patient shall be the personal responsibility of the licensee.

1. Any compounding of a controlled substance shall be personally performed by the licensee or a registered pharmacy technician under the supervision of the licensee.

2. A licensee may supervise one person who may be present in the storage and selling area to assist in performance of pharmacy technician tasks, as set forth § 54.1-3321 of the Code of Virginia, provided such person is either:

a. A pharmacy technician registered with the board; or

b. A licensed nurse or physician assistant who has received training in technician tasks consistent with training required for pharmacy technicians.

3. Unless using one of the board-approved training courses for pharmacy technicians, a licensee who uses a nurse or physician assistant to perform pharmacy technician tasks shall develop and maintain a training manual and shall document that such licensee has successfully completed general training in the following areas:

a. The entry of prescription information and drug history into a data system or other recordkeeping system;

b. The preparation of prescription labels or patient information;

c. The removal of the drug to be dispensed from inventory;

d. The counting or measuring of the drug to be dispensed to include pharmacy calculations;

e. The packaging and labeling of the drug to be dispensed and the repackaging thereof;

f. The stocking or loading of automated dispensing devices or other devices used in the dispensing process, if applicable; and

g. Applicable laws and regulations related to dispensing.

4. A licensee who employs or uses pharmacy technicians, licensed nurses or physician assistants to assist in the storage and selling area shall develop and maintain a site-specific training program and manual for training to work in that practice. The program shall include training consistent with that specific practice to include, but not be limited to, training in proper use of site-specific computer programs and equipment, proper use of other equipment used in the practice in performing technician duties, and pharmacy calculations consistent with the duties in that practice.

5. A licensee shall maintain documentation of successful completion of the site-specific training program for each pharmacy technician, nurse or physician assistant for the duration of the employment and for a period of two years from date of termination of employment. Documentation for currently employed persons shall be maintained on site or at another location where the records are readily retrievable upon request for inspection. After employment is terminated, such documentation may be maintained at an off-site location where it is retrievable upon request.

B. Prior to the dispensing, the licensee shall:

1. Conduct a prospective drug review and offer to counsel a patient in accordance with provisions of § 54.1-3319 of the Code of Virginia; and

2. Inspect the prescription product to verify its accuracy in all respects, and place his initials on the record of sale as certification of the accuracy of, and the responsibility for, the entire transaction.

C. If the record of sale is maintained in an automated data processing system as provided in 18VAC110-30-200, the licensee shall personally place his initials with each entry of a sale as a certification of the accuracy of, and the responsibility for, the entire transaction.

Virginia Board of Pharmacy

COMPLIANCE WITH USP STANDARDS FOR COMPOUNDING

§54.1-3410.2 requires pharmacies performing sterile or non-sterile compounding to comply with USP Standards. USP standards for sterile and non-sterile compounding may be found in the current editions of the USP-NF. In accordance with 18VAC110-20-170, the Board requires a pharmacy to maintain references consistent with the pharmacy's scope of practice and with public safety.

USP Chapter 795 lists the requirements for non-sterile compounding including information about the compounding environment, equipment, stability criteria and beyond-use dating and records. USP Chapter 797 lists requirements for policies and procedures, training and evaluation of personnel performing sterile compounding, determining risk levels and the physical standards for the sterile compounding area. The Board expects that the requirements of Chapters 795 and 797 will be found in compliance at time of inspection.

The terms "annually" and "semiannually" as used in USP Chapters 795 and 797 are defined to mean every 12 months and every 6 months, respectively. Records associated with annual and semiannual requirements shall be maintained in accordance with USP standards. Such records may be maintained as an electronic image that provides an exact image of the document that is clearly legible provided such electronic image is retrievable and made available at the time of inspection or audit by the Board or an authorized agent.

1. ***Where may information regarding USP-NF standards for compounding be located?***

   A subscription to the current version of "USP on Compounding: A Guide for the Compounding Practitioner" may be purchased at http://www.usp.org/store/products-services/usp-compounding This guide provides access to all compounding-related General Chapters from the USP-NF and is updated with the release of each new USP-NF edition and supplement. The latest edition, USP 36- NF 31, published on November 1, 2012 becomes official May 1, 2013.

2. ***Does the law require compliance only with Chapter <797>?***

   No, the law requires compliance with all applicable chapters within USP-NF. Regarding sterile compounding, pharmacists should pay particularly close attention to General Chapters: <1> Injections, <51> Antimicrobial Effectiveness Testing, <71> Sterility Testing, <85> Bacterial Endotoxin Testing, and <797> Pharmaceutical Compounding- Sterile Preparations.

3. ***In the absence of sterility testing, what beyond use dates (BUDs) must be used?***

   When sterility testing has not been performed, the assigned BUD must not exceed the following allowances:

	Controlled Room	Refrigerator	Freezer

	Temperature		
Low-risk	48 hours	14 days	45 days
Medium-risk	30 hours	9 days	45 days
High-risk	24 hours	3 days	45 days

4. ***Is it appropriate to assign a BUD of 90 days in the absence of sterility testing if there is literature indicating the stability of the drug is assured for 90 days?***
   No, it is inappropriate and a violation of law to assign a BUD which exceeds the USP default BUDs in the absence of sterility testing. Drug stability should not be confused with drug sterility.

5. ***What is skip lot testing and may skip lot testing be used to perform sterility testing of compounded sterile products?***

   Skip lot testing is a process that only tests a fraction of the drugs compounded. It is NOT appropriate for sterility testing. It may only be used for ensuring consistency and drug strength (potency). Because skip lot testing is complex and requires a robust program, it may not be possible for a pharmacy to properly implement. Information regarding skip lot testing may be accessed at http://www.itl.nist.gov/div898/handbook/pmc/section2/pmc27.htm

6. ***How may a hospital pharmacy "batch-producing" limited quantity of CSPs for IN-HOUSE use extend the BUD past the default dating in Chapter <797>?***

   EACH BATCH must undergo sterility testing in accordance with USP Chapter <71> in order to extend the BUD past the default dating in Chapter <797> and the appropriate documentation to support an extended BUD must be kept on file for presentation upon inspection.

7. ***Do batches less than 25 require sterility testing to be performed?***

   No, however, the batches may not be assigned a BUD which exceeds the default BUDs in USP Chapter <797>. The chapter requires sterility testing according to USP <71> before CSPs are dispensed or administered when:
   - high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages (e.g., ampuls, bags, syringes, vials) or
   - in multiple-dose vials (MDVs) for administration to multiple patients or
   - CSPs that are exposed longer than 12 hours at 2 to 8 C and longer than 6 hours at warmer than 8 C before they are sterilized.

8. ***How often must the primary engineering control, e.g., laminar airflow workbench and secondary engineering control, e.g., ante and buffer rooms be certified?***

   Certification of the primary and secondary engineering controls shall be performed no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. The certification must be performed no later than *the last day of the sixth month*, following the previous certification.
   ***Note- this guidance reflects a change to Major Deficiencies 22 and 23 in Guidance Document 110-9 which was amended at the March 2013 full board meeting.

9. Must compounding personnel who work in multiple pharmacies, to include pharmacy interns on rotations, pass a media-fill test at each pharmacy where they will prepare CSPs?

Yes, all compounding personnel working in multiple pharmacies, to include pharmacy interns on rotations, must pass a media-fill test at each pharmacy prior to performing sterile compounding.

10. How often must media-fill testing be performed?

Media-fill testing of all compounding personnel shall be performed initially prior to beginning sterile compounding and at least annually thereafter for low and medium-risk compounding, and semiannually for high-risk level compounding. ***Note - the terms "annually" and "semi-annually" are defined within this guidance document to mean every 12 months and every 6 months, respectively.

11. If compounding personnel fail a media-fill test, may they continue preparing compounded sterile products?

No, compounding personnel who failed a media-fill test may not be allowed to prepare compounded sterile products (low, medium, or high-risk) prior to retraining and receipt of a passing media-fill test. ***Note- this guidance reflects a change to Major Deficiency 26a in Guidance Document 110-9 which was amended at the March 2013 full board meeting.

12. Because batches less than 25 do not require sterility testing to be performed, may the CSP which may have been autoclaved be assigned an extended BUD based on stability data?

Yes, sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units. The board would expect to see that biological indicators are used with each autoclave batch and that the cycle time and temperature were recorded on a log or printer tape directly from the autoclave.

13. Does USP-NF address how long a CSP may hang for infusion?

No, USP-NF does not address how long a CSP may hang for infusion. Refer to facility policy on this issue. USP-NF, however, does require the administration of CSPs to begin prior to the assigned BUD.

14. May a pharmacist repackage Avastin for office administration not pursuant to a patient-specific prescription?

No. While pharmacists may repackage a drug product when dispensing a drug pursuant to patient-specific prescription, a pharmacist may not repackage a drug for another entity. The board has historically interpreted the repackaging of a drug for distribution purposes as an act restricted to a manufacturer, defined in Va Code §54.1-3401. This interpretation appears consistent with recent warning letters from the US Food and Drug Administration (FDA). The allowance in Va Code §54.1-3401 for a pharmacist to provide compounded drugs to a physician for office administration does not apply. Repackaging Avastin does not constitute compounding as it does not involve the mixing of two of more substances.

15. May a pharmacist repackage Avastin pursuant to a patient-specific prescription?

Yes, a pharmacist may repackage a drug as part of the dispensing process pursuant to a patient-specific prescription.

16. What concepts, at a minimum, should be taken into consideration when performing sterility testing of CSPs?

- Maintain a written policy and procedure manual clearly identifying sterility testing procedures used by the pharmacy and processes for assigning BUDs.
- Prior to using an outside testing company to perform sterility testing, evaluate the company to determine if it performs testing in full compliance with USP Chapter <71>. This may be done by reviewing 483 reports issued by the FDA to the testing company and which may be available on the FDA website. Alternatively, request copies of the 483 reports directly from the testing company. The observed deficiencies noted on the 483 reports will assist the pharmacist in evaluating the testing company's level of compliance. Also, request written documentation from the testing company which explains the sterility testing processes used and how it complies with USP Chapter <71> in its totality. This documentation should contain, at a minimum, specific details regarding the method of testing, method suitability associated with each sterility testing process to ensure the drug being tested will not interfere with the test, identification of testing method (membrane filtration is the preferred method of testing), two growth media, and number of days of incubation. Have this documentation readily available for inspector review.
- When performing sterility testing in-house, document in the written policy and procedure manual, at a minimum, specific details regarding the method of testing, method suitability associated with each sterility testing process to ensure the drug being tested will not interfere with the test, identification of two growth media, and number of days of incubation.
- Vendors providing products for in-house testing must describe all conditions and limitations to their testing products. Ensure the appropriate filtration volume and sample size is being tested.
- When determining an appropriate sterility testing process, note that the preferred method per USP is membrane filtration. The Board strongly recommends that written documentation justifying the use of direct inoculation be available for inspection
- Ensure the sterility testing incorporates two media for growth.
- The sample size used for testing must comply with USP Chapter <71>, tables 2 and 3.
- Maintain robust recordkeeping, e.g., chart the dates, temperatures, growth associated with the two media incubations, and employee signatures. Do not simply indicate "no growth" without indicating which growth media was used and the number of days incubated.

17. Must sterility testing be performed on all batches of CSPs?

Sterility testing is not required of low and medium-risk level batched CSPs if the BUDs do not exceed the default BUDs found in USP Chapter <797>. If the low or medium-risk level batched CSP is to be assigned an extended BUD, then sterility testing must be performed. Sterility testing must always be performed of high-risk level CSPs in batches greater than 25. See Response to Q#7

18. What is the definition of a "batch"?

USP does not currently define the term "batch". In 21CFR210.3, FDA defines "batch" to mean a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

19. *How should a dilution or stock bag for pediatrics be treated?*

USP does not currently address this issue, however, the Board advises that the dilution or stock bag should be treated as a single dose container/vial with the remains being discarded within 6 hours of compounding.

20. What concepts, at a minimum, should be taken into consideration when determining drug stability?

Pharmacists should use professional judgment to determine appropriate references of chemical stability information. When relying on information in studies, pharmacists should have at least two articles which justify the assigned stability. If stability is determined by extrapolating information from a reference source, then the pharmacist must ensure that the drug stability in the reference source is not concentration dependent. The process used by the pharmacist to determine drug stability should be well-documented and maintained for inspector review.

21. What are some important considerations regarding membrane filtration and filter integrity testing, aka bubble point testing?

Membrane filtration may be accomplished using a 0.22 micron filter. It is important to note that sterility testing cannot be accomplished by simply performing membrane filtration. Filter integrity testing, also known as a bubble point test, must be performed to verify that the filter was successful in its application. Smaller disc filters may have filter volume limitations which must be taken into consideration. Because it is known that filtration has not always been successful in preventing the passing through of microorganisms, pharmacists must always build quality processes into their sterile compounding to minimize the risk and the introduction of contamination.

22. What are some best practices for performing required media fill testing and gloved fingertip sampling?

Persons performing high-risk level CSPs must successfully pass media-fill testing prior to initially compounding sterile products and semi-annually (within 6 months of the last testing). Persons performing low or medium-risk level CSPs must successfully pass media-fill testing prior to initially compounding sterile products and annually (within 12 months of the last testing). Persons who fail a media-fill test may not perform sterile compounding prior to retraining and receipt of a passing media-fill test.

Media fill testing should mimic the most challenging sterile compounding activity performed by those persons. Robust documentation regarding the media-fill testing process and individual testing must be maintained which documents, at a minimum, the media growth to include lot

and expiration date, number of days in incubator, incubator temperature, name of person being tested, dates testing performed, results of growth. Blanks in the form used to document media fill testing should be evaluated and corrected to ensure an accurate testing process.

Glove finger tip testing verifies the person can properly don gloves without contaminating them and is routinely disinfecting them. To improve compliance with required testing, pharmacists should consider performing media-fill testing and glove finger tip testing around the same time that environments are being certified. Employees who use isolators must also perform gloved fingertip sampling by donning sterile gloves within the ISO Class 5 main chamber and testing those gloves.

23. How often must air and surface sampling be performed?

USP requires air and surface sampling to be performed "periodically". The Board advises that air and surface sampling should be performed at least annually. Air sampling shall be conducted using volumetric air sampling equipment and the appropriate media (bacterial sampling for all risk levels and fungi sampling for high-risk level compounding operations). It may be performed by pharmacy personnel or outsourced.

24. What minimally should be taken into consideration when having primary and secondary engineering controls certified?

Certification and testing of primary (LAFWs, BSCs, CAIs and CACIs) and secondary engineering controls (buffer and ante areas) shall be performed by a qualified individual no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006) shall be used. Pharmacists shall request written documentation from the certifying company explaining how the company's certifying processes fully comply with these standards. This shall include written acknowledgement that certification testing will be performed under dynamic conditions. Certifications issued shall specifically indicate the ISO standard for each primary and secondary engineering control and not simply indicate "passed".

25. What minimally should be taken into consideration when compounding multidose vials?

Multidose vials of CSPs must comply with USP Chapter <51>. It must be determined that the preservative being used is bacteriostatic, fungistatic, effective at maintaining sterility for 28 days, and does not interact with the drug. Antimicrobial preservatives cannot be used as a substitute for good compounding practices.

26. What BUDs are recommended for non-sterile compounded products?

USP Chapter <795> makes the following recommendations for assigned BUDs of non-sterile compounded products:

Nonaqueous formulations - The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.
Water-Containing Oral Formulations - The BUD is not later than 14 days when stored at controlled cold temperatures.

Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations – The BUD is not later than 30 days.

These maximum BUDs are recommended for nonsterile compounded drug preparations in the absence of stability information that is applicable to a specific drug or preparation. The BUD shall not be later than the expiration date on the container of any component.

27. May a non-sterile compounded product be assigned an extended BUD beyond the recommendations in USP Chapter <795>?

The Board advises that non-sterile compounded products should not be assigned an extended BUD unless the pharmacist maintains full documentation to justify the appropriateness of the extended BUD.

28. Under what conditions may a glove box be used to perform sterile compounding?

The glove box, referred to as an isolator (CAI/CACI) in Chapter <797>, must be placed in an ISO 7 buffer area UNLESS it meets all of the following conditions listed in USP Chapter 797:

- The isolator shall provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
- Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.
- Not more than 3520 particles (0.5 μm and larger) per m^3 shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.[8]

It is incumbent upon the compounding personnel to obtain documentation from the manufacturer that the CAI/CACI will meet this standard when located in environments where the background particle counts exceed ISO Class 8 for 0.5-μm and larger particles. When isolators are used for sterile compounding, the recovery time to achieve ISO Class 5 air quality shall be documented and internal procedures developed to ensure that adequate recovery time is allowed after material transfer before and during compounding operations.

If the primary engineering control (PEC) is a CAI or CACI that does not meet the requirements above or is a LAFW or BSC that cannot be located within an ISO Class 7 buffer area, then only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician order for a specific patient may be prepared, and administration of the CSP shall commence within 12 hours of preparation or as recommended in the manufacturer's package insert, whichever is less.

The weighing of chemicals must occur in at least ISO Class 8 conditions. An isolator used to compound hazardous drugs (with exception of "low volume") must be located in a separate negative pressure room and exhausted outside.

29. May hazardous sterile products be compounded in the same hood as non-hazardous sterile drugs?

Originally adopted: June 8, 2004
Revised: June 7, 2005, June 5, 2006, June 4, 2008, June 12, 2012, October 1, 2012, July 17, 2013, March 26, 2014

No. Hazardous sterile products may not be compounded in the same hood as non-hazardous CSPs.

30. Under what conditions may hazardous drugs be compounded in a cleanroom with positive air pressure?

USP allows a "low volume" of hazardous CSPs to be compounded in a cleanroom with positive air pressure, however, USP does not currently define the term "low volume". The "low volume" hazardous CSPs must be compounded under two tiers of containment, the isolator or biologic safety cabinet and closed system transfer device.

31. Must a compounding pharmacy using Schedule II powders comply with the perpetual inventory requirements of Regulation 18VAC110-20-240?

Yes.

32. Must bladder irrigation fluids and irrigations for wounds be prepared in a sterile manner in compliance with USP-NF requirements?

Yes. USP Chapter <797> states that for the purposes of the chapter, a compounded sterile product includes any of the following: compounded biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals, including but not limited to the following dosage forms that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

33. May a pharmacist provide a compounded drug to another pharmacy or veterinarian who will then dispense the drug to his client?

No. Va Code §54.1-3410.2 indicates pharmacists shall not distribute compounded drug products for subsequent distribution or sale to other persons or to commercial entities, including distribution to pharmacies or other entities under common ownership or control with the facility in which such compounding takes place.

VA Code §54.1-3410.2 does authorize pharmacists to provide compounded drug to practitioners of medicine, osteopathy, podiatry, dentistry, or veterinary medicine to administer to their patients in the course of their professional practice, either personally or under their direct and immediate supervision. The compounded drug must be labeled with (i) the statement "For Administering in Prescriber Practice Location Only"; (ii) the name and strength of the compounded medication or list of the active ingredients and strengths; (iii) the facility's control number; (iv) an appropriate beyond-use date as determined by the pharmacist in compliance with USP-NF standards for pharmacy compounding; and (v) quantity.

34. May a prescriber or patient obtain a compounded sterile product from an out-of-state pharmacy that is not registered by the Virginia Board of Pharmacy as a nonresident pharmacy?

Originally adopted: June 8, 2004
Revised: June 7, 2005, June 5, 2006, June 4, 2008, June 12, 2012, October 1, 2012, July 17, 2013, March 26, 2014

No, only nonresident pharmacies registered by the Virginia Board of Pharmacy may ship compounded sterile products into Virginia. Verification of registration may be determined at https://secure01.virginiainteractive.org/dhp/cgi-bin/search_publicdb.cgi by searching the business name and choosing the occupation of "non-resident pharmacy".

Quality Standards for Large Scale Sterile Compounding Facilities

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Introduction

Legislation has established a new regulatory category for pharmaceutical compounders that supply healthcare providers with prepared non-patient specific medicines for use in hospitals, offices and clinics. These "outsourcing facilities" will be subject to more rigorous quality and safety standards modeled after the Current Good Manufacturing Practices (CGMPs)[1] that apply to pharmaceutical manufacturers. In light of the new law, this paper reviews the differences between traditional and outsourced compounding and describes the key CGMP provisions that are critical to ensuring drug quality and patient safety when compounding occurs at a larger scale. The scope and magnitude of sterile compounding has changed dramatically over the past three decades and includes many large scale commercial compounding operations providing compounded sterile preparations (CSPs) without the traditional benefit of a patient-specific prescription. This sector has outgrown existing traditional compounding standards of practice necessary to ensure product quality and sterility as well as added capacity. While outsourcing facilities will be subject to CGMPs, all large scale sterile compounding should meet more rigorous quality standards regardless of participation in the new regulatory category.

The Emergence of the Outsourced Compounding Sector

Pharmacy compounding is the historical cornerstone of the pharmacy profession. According to a 1949 text, it is the "task in which all the scientific knowledge, professional skill and sense of responsibility . . . must find their expression and justification."[2] Traditionally, compounding is the extemporaneous preparation and dispensing of medications in various dosage forms to meet the medical needs of patients pursuant to a prescription written by an authorized prescriber. The pharmacy profession, most notably hospital pharmacy, has redefined itself over time, and its focus has moved from production and distribution to clinical patient management.* As

* This transformation was fostered by the 1985 Hilton Head invitational consensus-conference facilitated by the American Society of Health-System Pharmacists (formerly known as the American Society of Hospital Pharmacists) which shifted departmental pharmacy practice from the provision of discrete clinical services (e.g., aminoglycoside pharmacokinetic dosing services) to a comprehensive clinical enterprise where pharmacists take on a larger role in the safe and appropriate use of medications. Examples of the services currently provided by pharmacy

the institutional practice of pharmacy shifted away from compounding, commercial business enterprises found opportunities to fill this void.[3] Examples include manufacturers of automated medication dispensing cabinets and pharmacies specializing in extemporaneous compounding.

Drug manufacturers were some of the first to enter the outsourced compounding space specifically to service the hospital market. In July 1982, Baxter Healthcare began operations of the Travenol Regional Compounding Center (TRC) business,[4] first opening a center in Morton Grove, Illinois and later adding a second in Bridgeport, New Jersey. The TRC program was designed to operate on a large scale to transform commercially available drug powders and concentrates into dosage packages suitable for immediate administration to patients† without further aseptic manipulation at hospitals or other provider sites. Baxter and other companies that followed their approach argued that this service was an extension of the hospital's compounding operation.

Though a commercial success, the TRC program drew the attention of the FDA, which alleged that the TRC activities violated the Food, Drug and Cosmetic Act (FDCA). FDA believed the drug packages produced at the TRCs were new drugs, which must be separately tested for safety and efficacy,[5] and further that Baxter was creating new dosage forms of other pharmaceutical companies' proprietary medications. Subsequently, they intervened, issuing a consent decree that prohibited Baxter from providing these services without significant financial and punitive penalties.[6] As a result, Baxter closed these operations.

Hospitals, however, were still looking to outsource the compounding of certain products, such as parenteral nutrition. The preparation of parenteral nutrition is complex and requires specialized facilities that maintain optimal states of environmental control, trained personnel and costly equipment. In all but the biggest hospitals, the cost associated with compounding parenteral nutrition using these systems was prohibitive. In 1991, Central Admixture Pharmacy Services (CAPS), a division of B Braun Medical, started to provide hospitals with ready-to-use, patient-specific bags of parenteral nutrition.[7] This allowed hospitals that did not have the

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departments include anticoagulation dosing services, immunization tracking and administration and recently, new prescribing roles.

† Many drugs are not produced by drug manufacturers in the final form needed for patient administration. They are purchased in either lyophilized (freeze-dried) or liquid concentrate form. Hospitals have commonly responded to the need to prepare these drugs for administration to patients by operating their own centralized drug preparation programs for the reconstitution, dilution, and repackaging, of drugs.

resources to prepare this type of compounded sterile preparation (CSP) to purchase them on an as needed basis, freeing up both fiscal and human resources.

The CAPS locations providing this service were state licensed pharmacies. Since nutrition was one of Baxter's core products (they manufactured or distributed various parenteral nutrition components such as amino acids, dextrose, water and fat emulsions and offered a state of art automated compounding device that improved the safety profile of preparing these complex formulations), they wanted to re-enter the outsourced compounding business. Baxter sought and received FDA permission to provide compounding services but with the provisos that the Baxter facilities (then known as the COMPASS program which later became PharMEDium when divested by Baxter)[8] be registered with the FDA, employ pharmacists and pharmacy technicians, and meet a limited number of quality requirements from the CGMPs – the robust quality requirements for commercial pharmaceutical manufacturing – dictated by the FDA. Baxter was also required to provide these compounded solutions of parenteral nutrition in a patient-specific manner. (Personal Communication, John L. Quick-former Corporate VP of Quality and Regulatory Affairs, Baxter Healthcare, May 2, 2014). The FDA never formalized these expectations in a Compliance Policy Guide or any other written document.[9] At about the same time, the FDA required the CAPS program facilities to become registered establishments, so they operated as both licensed pharmacies and FDA registered establishments.

Over time, COMPASS and CAPS expanded their extemporaneous compounding services to include non-patient-specific cardioplegia, anesthesia syringes, antibiotics and narcotic dosage forms. The FDA exercised its enforcement discretion with these companies allowing them to provide these non-patient specific doses since they were under the purview of the Agency, however there was an expectation that these organizations had the ability to ultimately track the compounded medication to the patients for which they were used.[10,11]

In addition to outsourced compounding for hospitals, a second market began to emerge to serve physician office practices and ambulatory care clinics looking for certain medication doses to keep on site for use in those entities. In some cases these drugs were in short supply from the pharmaceutical companies, in other cases pharmacies identified commonly-prescribed compounded dosage forms and marketed their ability to supply them to prescribers regionally or nationally.

While COMPASS and CAPS had mainly prepared new dosage forms from packaged FDA-approved medicines, the new compounders entering this new market were

producing large quantities of non-patient-specific sterile injectable drugs from non-sterile bulk chemicals and they were not registered with the FDA. Compounding sterile preparations from non-sterile ingredients is a high risk activity that requires significantly more rigorous controls to ensure the quality and sterility of the final formulation versus those required by compounders using only commercially available FDA approved products as their starting materials.

Additional factors continued to drive demand for outsourced sterile preparation services. New standards for sterile compounding issued by the United States Pharmacopeial Convention (USP) – discussed below – presented compliance challenges for pharmacies, despite the fact that these standards were considered minimum practice for sterile compounding as early as 1995 in USP Chapter <1206>, Sterile Drugs for Home Use (which was replaced in 2004 by the new USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations).

Federal attention to the changing landscape of pharmaceutical compounding grew throughout this period. In the 1990s, the FDA became increasingly concerned with the expansion of this sector and grappled with how to appropriately regulate larger-scale compounding pharmacies that were operating like manufacturers. In 1992, the FDA published a non-binding Compliance Policy Guidance 460.200 that established nine criteria that the Agency used to determine when a pharmacy preparing large quantities of non-patient specific medications exceeded the traditional activities of a pharmacy and should be regulated under CGMPs. The compounding pharmacy industry, led by organizations like the Professional Compounding Centers of America (PCCA) and the International Academy of Compounding Pharmacists (IACP), battled with the FDA over their perceived right to compound medications to meet the growing demand for sterile injectable drugs, which included those kept in stock in physician office practices.[12]

In 1997 this regulatory gap prompted Congress to modify Section 503A of the FDCA to create a safe harbor for pharmacists who were compounding medications pursuant to physician's order. The Food and Drug Administration Modernization Act (FDAMA) section 127 amended the FDCA by adding section 503A (21 U.S.C. 353a), which governs the application of Federal law to pharmacy compounding. Under section 503A(a) of the act, a compounded drug product is a drug product made in response to, or in limited quantities in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounded drug products are exempt from three key provisions of the act:

1. *Adulteration* provision of section 501(a)(2)(21 U.S.C. 351(a)(2)(B)) (current good manufacturing practice [CGMP] requirements);

2. *Misbranding* provision of section 502(f)(1) (21 U.S.C. 352(f)(1)) (labeling of drugs with adequate directions for use);

3. New drug provision of section 505 (21 U.S.C. 355) (...use of drugs under Investigational New Drug Applications (INDs), New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs).[13]

This law was almost immediately challenged by various compounding pharmacists who argued that the inclusion of a prohibition on advertising and promotion was an unconstitutional violation of free speech. A decision in the United States Court of Appeals for the Ninth Circuit held that the restriction on advertising and promotion was unconstitutional and further that the unconstitutional provision was not severable from the rest of section 503A.[14] The Supreme Court reviewed the case and in 2002 affirmed the ruling of unconstitutionality, but did not review the question of severability.[15] Following this decision the FDA assumed that section 503A was not enforceable and issued a second Compliance Policy Guide on how it would use its underlying authority to control certain compounding activities.[16] In 2008, the United States Court of Appeals for the Fifth Circuit held that the restriction on advertising and promotion *was* severable and thus that the rest of section 503A was enforceable.[17] These conflicting rulings resulted in inconsistent legal status of the law in different parts of the country and affected the FDA's perception of its authority to regulate pharmacies that they believed were acting more like manufacturers.

Compounding Quality Failures and Patient Harm

Alongside growth of the compounding sector and oversight challenges came high-profile incidents of contaminated drugs harming patients. The 1980s and 1990s saw a number of cases of contaminated sterile preparations involving eye drops,[18] parenteral nutrition solutions[19] and cardioplegia.[20] Because of these tragic and well-publicized sterile compounding failures, some FDA officials suggested banning certain types of pharmacy compounding under the FDA's discretionary authority to regulate

compounded preparations as unapproved new drugs under the adulteration and misbranding provisions of the FD&C Act. The following summarizes the FDA perspective at that time:

> "Generally, FDA will defer to state authorities regarding less significant violations of the Act related to pharmacy compounding of human drugs. 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."[21]

One of the first major catastrophic compounding incidents occurred in 2001 when a generic sterile injectable drug went into short supply after the pharmaceutical company production line was shut down due to CGMP compliance deficiencies. The drug, betamethasone injectable suspension, was compounded by a community pharmacy and one lot of 60 vials was not terminally sterilized. The result was distribution of vials contaminated with a highly pathogenic gram negative microorganism.[22] Several patients were hospitalized and treated and three patients died as a result of the contamination.

The 2012 national fungal meningitis outbreak linked to contaminated medications prepared by the New England Compounding Center brought widespread attention to compounding quality. As of October 23, 2013, when the Centers for Disease Control and Prevention (CDC) last updated their data, the total adverse event case count was 751, with 64 deaths.[23] But while larger than other outbreaks, this was not an isolated event. Between January 2000 and 2012, eleven other outbreaks were identified, involving 207 infected patients and 17 deaths after exposure to other contaminated compounded drugs.[24] The past several years have also seen harm caused by other errors, such as super-potency. Three patients died in 2007 after receiving a dose of colchicine made by a compounding pharmacy that was eight-times stronger than the labeled concentration.[25]

In recent years the FDA has increased its inspections of compounding pharmacies and registered establishments that were known to have had quality issues or that in the Agency's opinion posed a potential risk to patient safety. Since 2012, over 90 pharmacies have been inspected by the FDA and many were issued inspection reports known as "483s" which document and communicate observed conditions that may constitute violations of the FD&C Act.[26]

Compounding Quality Standards

The incidences of injuries and deaths to patients during the late 1980s and early 1990s from pharmacy compounded injections, ophthalmic solutions and organ transplant baths became a call to action[27,28] prompting US-based professional and standards organizations to develop better quality guidelines.

In the early 1990s, both the American Society of Health-System Pharmacists‡ (ASHP) and the USP issued voluntary standards for sterile compounding. ASHP published a Technical Assistance Bulletin (TAB) to help pharmacists and pharmacy technicians produce sterile preparations of higher quality.[29] Both the ASHP TAB and USP Chapter <1206>, Sterile Drug for Home Use, served as a foundation for USP General Chapter <797>§ issued in 2004 — the first U. S. national practice standard for sterile compounding that was enforceable by the U. S. Food and Drug Administration (FDA) and the State Boards of Pharmacy. Chapter <797> was developed by an expert General Committee, now called the Compounding Expert Committee (2010-2015), which updates the standard as needed.

The objective of Chapter <797> is to describe conditions and practices to prevent harm, including death, to patients that could result from:

(1) microbial contamination (nonsterility),

(2) excessive bacterial endotoxins,

(3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles** (see "official" and "article" in the General Notices and Requirements) or 10% for nonofficial articles,

(4) unintended chemical and physical contaminants and

(5) ingredients of inappropriate quality in CSPs.

‡ Then called the American Society of Hospital Pharmacists

§ USP sets standards in its drug and drug dosage form monographs, General Chapters numbered lower than 1000, and General Notices, which are legally enforceable under the 1938 FD&C Act by FDA, state regulatory boards, Joint Commission, etc., but USP per se lacks enforcement authority.

** An article is a substance and an official article is an article that is recognized in USP or NF via monograph

Importantly, USP Chapter <797> describes *minimum* practice and quality standards for CSPs of drugs and nutrients based on current scientific information and best known sterile compounding practices.[30] The Chapter was never intended to describe the quality system requirements for large scale compounding practices described previously that are outside the traditional compounding role of pharmacists as defined Section 503A. Chapter <797> was last revised in June 2008. Its next revision – expected in the coming year or two – should reflect advances of science and industry understanding of best practices learned over the past several years, as well as lessons learned from the national fungal meningitis contamination event. These standards have historically been intended for traditional pharmacy compounding practices only. The quality system described in USP General Chapter <797> was not created to ensure drug quality and patient safety at the scales of large compounding facilities.

USP Chapter <797> - Good But Not Sufficient for Large Scale Compounding

USP General Chapter <797> has advanced compounding practice and describes a standardized compounding quality system as well as the expectations for personnel who compound and the processes needed to engender a quality CSP. But the Chapter leaves room for pharmacists and pharmacy technicians to exercise professional discretion. Unfortunately this discretion has at times resulted in a lack of compliance with standards of practice.[31] Additionally, lack of critical oversight by state boards of pharmacy, failure of accreditation organizations to establish an expectation of compliance and inadequate knowledge and expertise explain the profession's slow pace of adoption of effective compounding quality systems. In 2007, one study showed that only one in six pharmacists was prepared for sterile compounding work.[32] The results of a 2013 national survey of compliance with USP General Chapter <797> has showed little to no significant improvement in the overall scores of participating organizations over time despite the extensive and protracted educational efforts of professional and private organizations since 2004.[33]

The misapplication of professional discretion relative to sterile compounding practice has at times yielded inconsistent quality. This presents a much greater public threat when compounders operate on a large scale and their products can reach hundreds of patients across the country. Preparing medicines in large volumes necessitates much more robust quality assurance practices, such as those described under CGMPs. For

example, one element central to the CGMP approach is the focus upon building quality into the overall process and the prevention of problems. Quality is consistently producing products or services that the customer wants while simultaneously decreasing errors. Though quality can represent a measurement at a defined instance, it is better explained as a dynamic process leading to continual improvement of the output to customers over time. Systematic evaluation and elimination of variability within a manufacturing process is a cornerstone of predictable quality outcomes. The practice of large scale sterile compounding is no different and the absence of these concepts in large scale compounding was starkly illustrated by the national fungal meningitis outbreak and other such events.[34]

The current Chapter <797> does not adequately address large scale sterile compounding, whether it is done at an outsourcing facility without prescriptions, or at a large compounding pharmacy that aggregates many prescriptions and produces high volumes of sterile drugs. While the later example of compounding may be considered patient-specific – a criteria commonly used to differentiate traditional from non-traditional compounding – the sheer volume of drugs made by these prescription aggregator pharmacy operations most certainly exceed the *traditional* patient-specific compounding practices that Chapter <797> was intended to cover. Despite this, many large scale pharmacies that dispense patient-specific formulations will continue to operate under state board of pharmacy oversight, and therefore will still only be required to meet USP Chapter <797> or other similar standards set by the state.

USP Chapter <797> is currently under revision. The USP Compounding Expert Committee should add a more robust set of quality requirements to Chapter <797> to address high volume compounding pharmacy practices. Though it may be challenging to develop metrics based on volume and scale of production, they are nonetheless needed – the risk of patient exposure to potentially unidentified safety problems at high volume compounding pharmacies demands it. More robust sterile compounding quality systems must be adopted for all outsourcing facilities as well as for large scale compounding pharmacies that remain under state oversight.

Current Good Manufacturing Practices

Compounding pharmacies that meet federal requirements under 503A are not required to establish drug efficacy and safety, obtain FDA approval, or comply with manufacturing and labeling standards. This assumes that compounded drugs are

prepared as result of (or in limited quantities in anticipation of) the receipt of a valid prescription for an identified patient.

In contrast, drug manufacturers prepare large amounts of identical medicines for wide distribution. The pharmaceutical industry, unlike pharmacies that compound medication, is subject to rigorous regulations – CGMPs[††] – that are enforced by the FDA and define and safeguard critical aspects employed in the manufacture of all drugs. CGMPs are minimum guidelines for practice in the manufacture, processing, packing or holding of drug products to be administered to humans or animals. Their purpose is to ensure that all pharmaceutical products are produced in such a manner as to ensure consistent quality and integrity. CGMPs establish the "what to do" not the specific elements of "how to do." In addition to the CGMPs, the FDA has published a Guidance for Industry document titled "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice." That document reflects the Agency's current thinking about the specific application of CGMPs to sterile production.

Exhibit 1 compares traditional pharmacy compounding, large scale compounding, and manufacturing based on certain central attributes. Large scale outsourced compounding shares elements of both categories. But as the scale of production grows, so does the public health risk when quality errors occur, underscoring the need for robust quality system requirements.

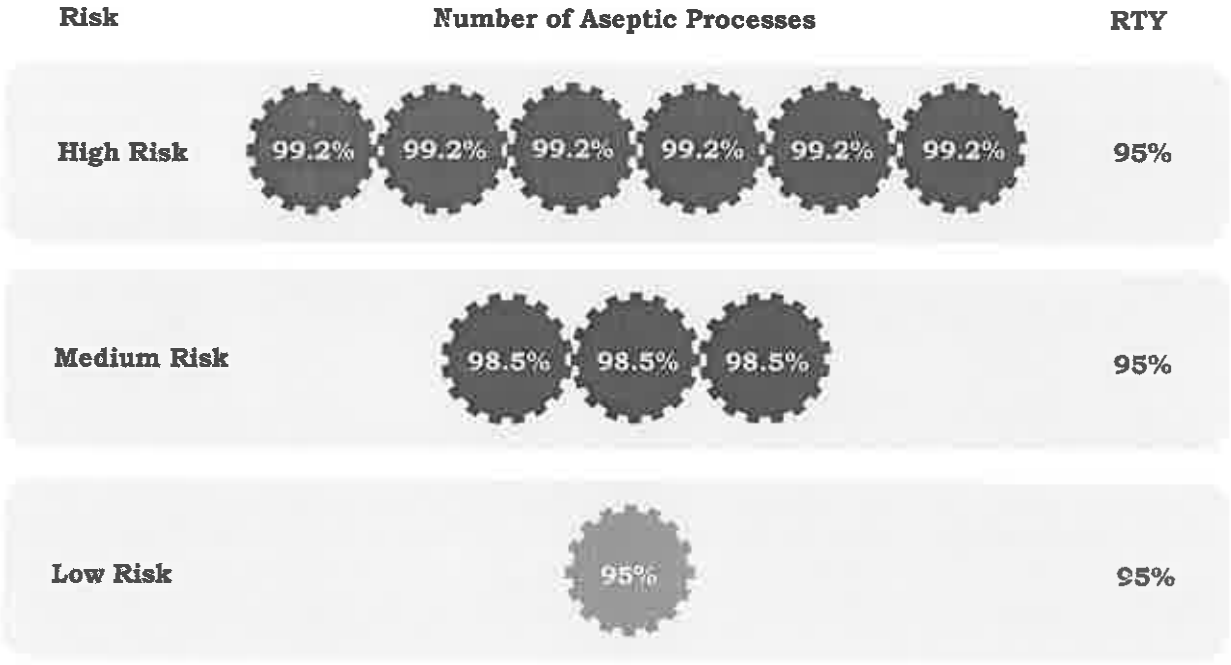
[††] 21 Code of Federal Regulations (CFRs) Part 210 and 211

Exhibit 1: Comparison of Traditional and Large Scale Compounding with Drug Manufacturing[35]

Attribute	Traditional Compounding	Large Scale Outsourced Compounding	Drug Manufacturing
Who is the Customer?	The patient upon receipt of a valid prescription from an authorized prescriber.	Hospitals, home infusion entities and prescribers.	Pharmacies, wholesalers and prescribers upon receipt of an order.
Therapeutic Paradigm	Matches drug to patient at the time of receipt of valid prescription.	Matches drug to customer requirement. Customers match drug to patient at the time of receipt of a valid prescription.	Matches patient to drug based on FDA approved indications.
Public Health Risk from Deviations in Quality System (Contamination or Ingredient Error)	Can be limited or significant: Typically only one patient is exposed when drug is prepared in response to a specific patient prescription. But large scale batch compounding, even when in anticipation of a prescription, increases the risk of exposure when errors occur.	Significant: Drug is produced in larger volumes than a traditional pharmacy but less than traditional manufacturing.	Significant: Drug is mass produced in response to market demand.
Main Regulatory Oversight	State Board of Pharmacy Rules and Regulations.	US Food and Drug Administration.	US Food and Drug Administration.
Published Quality System	USP General Chapter <797> Pharmaceutical Compounding-Sterile Preparations.	21 Code of Federal Regulations Parts 210 and 211 (CGMPs) and anticipated guidance.	21 Code of Federal Regulations Parts 210 and 211 (CGMPs).
Degree of Enforcement	Low to moderate: 21 states require compliance with the published quality system.	High: FDA is inspecting all establishments registering as outsourcing facilities.	High: All registered establishments can expect to be periodically inspected.

Strong quality systems are important for high-volume compounding, but also for higher risk compounding activities such as compounding sterile drugs from non-sterile bulk ingredients. The concept of Rolled Throughput Yield (RTY) is a helpful way to understand this. RTY is the probability that a single unit can pass through a series of process steps free of defects. The fewer the number of steps, the lower the potential for defects or points of failure. As the number of units in a batch increases or the number of steps in a process increases, the greater the chance of error, thus the precision of the process must improve. Exhibit 2 below represents three different processes and their relative risk based on the complexity of the relative compounding or manufacturing processes.

Exhibit 2: Rolled Throughput Yield (RTY). As a process becomes more complex, the accuracy and precision of each process step needs to improve



In low and medium-risk level compounding as defined by USP Chapter <797>, compounders use FDA approved, commercially available, sterile release materials (e.g., medications and diluents), sterile components (e.g., tubing, syringes and needles) and packaging (e.g., empty IV bags, cassettes and elastomeric devices) as starting materials. During the aseptic processing of low and medium-risk level CSPs, the sterility of the materials, components and packaging is maintained by using proper aseptic technique — highly technical work that requires meticulous attention to detail.

In high-risk compounding as described in Chapter <797>, *nonsterile* materials, components or packaging and the final product are required to undergo some form of individual sterilization (filtration, steam, dry-heat or irradiation) prior to being compounded and subsequently released for use by patients. However, USP Chapter <797> only requires sterility testing according to USP Chapter <71> for batches of 25 or more or when the default beyond-use dates (BUDs) set based on risk-level in USP Chapter <797>, are exceeded. Otherwise compounders rely solely on careful aseptic processing to ensure sterility when manipulating commercially available, FDA approved sterile drugs and solutions. According to the FDA's guidance on drugs produced by aseptic processing:

> "Any manual or mechanical manipulation of the sterilized drug, components, containers or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. A terminally sterilized drug product, on the other hand, undergoes final sterilization in a sealed container, thus limiting the potential for error."‡‡ [36]

CGMP contains rigorous requirements for terminal sterilization, as discussed below. High-risk compounding involves numerous steps, each with a higher degree of complexity and therefore the precision, accuracy and effectiveness of each step must be more robust in order to ensure a predictable and acceptable outcome. Each individual process requires validation and control, as each can introduce error that could result in a contaminated medicine.

Exhibit 3 provides a comparison of selected quality system requirement attributes of CGMPs and USP General Chapter <797> that illustrates key differences between these standards.

‡‡ According to the FDA, nearly all drugs recalled due to nonsterility or lack of sterility assurance in the period spanning 1980-2000 were produced via aseptic processing

Exhibit 3: Comparison of Selected Quality System Requirement Attributes of CGMPs and USP General Chapter <797>

Quality System Requirement	CGMP	USP General Chapter <797>
Engineering Control Smoke Studies To Assess Proper Air Flow	Yes[§§]	Yes
Inbound Component ID Test	Yes	No[***]
Stability Testing of Formulation via Stability Indicating Method to Assign Expiration / Beyond-Use Date	Yes	No[†††]
Sterility Testing as Release Test (USP General Chapter <71>)	Yes	Limited[‡‡‡]
Cleaning Validation	Yes	No
Continuous Particle Count	Yes	No
Use of Sterile Disinfectants	Yes	Only Isopropyl Alcohol
Environmental Monitoring During Production	Yes (Air, surface, personnel)	No
Frequency of Environmental Monitoring	Daily (Air, surface, personnel)	Air-twice yearly Surface-routinely Personnel-initially and 1-2 /year
Sterile Garb	Yes	Only sterile gloves
Reserve Samples	Yes	No

§§ Critical to demonstrate that unidirectional first-air is delivered from the HEPA filter through the critical site and out of the device without refluxing or rollout into the critical site.
*** There is no requirement for direct testing of bulk non-sterile active pharmaceutical ingredients (API). Certificate of Analysis from FDA registered supplier is acceptable if component is part of a FDA approved drug.
††† Peer-reviewed literature acceptable
‡‡‡ Only w/extended dating & High-Risk batches > 25

Drug Quality and Security Act

In 2013, Congress passed the Drug Quality and Security Act, which was signed into law by President Obama on November 27. Title I of the Act addresses compounding and eliminates the unconstitutional provisions of Section 503A of the FDCA, effectively reinstating Section 503A as a safe harbor for traditional compounding practices. Though it exempts traditional compounders from complying with CGMPs, it does require compliance with general chapters on compounding (specifically Chapters <795> and <797> as well as other applicable USP chapters).[37]

The law also creates a new section of the FD&C Act - Section 503B - that recognizes pharmacies that engage in the manufacture and shipment of larger quantities of compounded drugs without prescriptions. These organizations, called outsourcing facilities, may receive exemptions from the drug approvals and labeling requirements of the FDCA if they voluntarily register with the Agency. Under the law such facilities are subject to the CGMPs, risk-based inspections and other standards to be defined by the agency with guidance from the FDA Pharmacy Compounding Advisory Committee.

As of this writing, over forty establishments have voluntarily registered with the FDA as Section 503B facilities. The FDA has yet to issue specific CGMP guidance for 503B facilities, but has indicated they will do so.[38] Lack of guidance creates a compliance challenge for 503B registrants.

In addition to the application of the CGMPs, additional guidance should be offered by the Agency similar to that in the FDA Aseptic Processing Guidance Document.

The section below describes key CGMP concepts that should be applied by 503B facilities, given their larger scale and non-patient specific operations, to ensure drug quality and patient safety. In addition, the appendix to this paper contains a crosswalk between the CGMPs and USP General Chapter <797> Pharmaceutical Compounding - Sterile Preparations, highlighting the detailed differences between these two quality standards.

Key CGMP Concepts for 503B Outsourcing Facilities

The central tenet articulated in the CGMP regulations and in robust modern-day quality systems is that quality must be built into the product and that testing alone cannot be relied upon to ensure quality. This Quality by Design[39] concept has been missing from the compounding regulatory schema that were intended for traditional pharmacy activities, not large scale compounding.

Through the lifecycle of a compounded sterile medication from receipt of raw materials to the point of administration, there are several key areas where the CGMPs provide a more robust way to ensure product quality and patient safety compared to USP General Chapter <797>, especially when large quantities of sterile products are made.

They are:

1. CGMP Mindset

CGMPs are a set of requirements from the U.S. FDA that serve as the cornerstone for assuring quality. This regulation is considered the premier quality model and has been adopted globally in the pharmaceutical industry. The "CGMP Mindset" is a term used to describe a desired attitude and vigilant adherence to detail that is harmonized with a set of actions and behaviors in the manufacturing process. This mindset must be fostered by organizational culture that embraces CGMP compliance, provides clear, understandable, consistent direction to all employees and decreases production errors and costs.

Another driver of the CGMP mindset is the dynamic tension that the FDA creates through their inspection process. The Agency holds organizational leadership accountable for complying with the CGMPs. A healthy respect for oversight has been absent in pharmacy compounding but is beginning to gain traction in state-based inspection models conducted by some State Boards of Pharmacy.

2. An Autonomous Quality Unit (QU)

The Quality Unit (QU) within a drug manufacturing operation is responsible for ensuring that the various operations associated with all systems are appropriately

planned, approved, conducted and monitored. The QU must review production records to ensure that no errors have occurred and has the authority to reject any product. In properly managed CGMP programs, manufacturing error and deviation rates are low. When mistakes are made or deviations occur, a robust quality system facilitates effective error tracing. Quality Units typically have no production responsibilities thereby insulating quality decision-makers from either financial or production pressures. Their decisions to accept or reject products are based instead upon a comprehensive set of predetermined specifications. This type of organizational check and balance is not an absolute expectation of USP General Chapter <797>. The Chapter states "when time and personnel availability so permit, compounding manipulations and procedures are separated from post compounding quality inspection and review before CSPs are dispensed."

3. Receipt and Release of Non-Sterile Ingredients, Materials, Supplies and Packaging

Confirming the identity and quality of starting materials is fundamental to building quality into the manufacturing process. Allowing ingredients, supplies and packaging that may not meet predefined specifications into production potentially introduces variability that may affect drug quality and patient safety. 503B entities need to establish a process to receive, evaluate and release non-sterile ingredients, materials, supplies and package components against predetermined acceptance specifications. This includes identity testing and assessing the degree of bioburden – the type and amount of microbial contamination present before sterilization. The microbiological quality of active pharmaceutical ingredients (APIs) and other components will have an impact on the effectiveness of sterilization methods.

USP General Chapter <797> does not identify specific requirements to determine this quality parameter stating "nonsterile active ingredients and added substances or excipients for CSPs should preferably be official General or NF articles. When nonofficial ingredients are used, they shall be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identity, quality and purity in relation to the intended use in a particular CSP."

Relying on a certificate of analysis for bulk APIs used in a larger-scale production process is not sufficient as API repackagers are not required to perform any qualitative assessment of these substances. USP General Chapters on compounding do not adequately address this regulatory gap. Analysis of bulk substances must be

performed to verify their identity and quality. Materials that fail to meet all pre-defined specifications must be rejected. Vendors of bulk APIs, other ingredients and components need to be qualified by the 503B entity and appropriately registered with the FDA. In addition, a system must be developed and maintained to track the lot numbers of non-sterile ingredients, materials, supplies and packaging components based on the date received ensuring they are used on a first in/first out basis.

4. Receipt and Release of Sterile Ingredients, Materials, Supplies and Packaging

Some 503B entities use only FDA approved, commercially available, sterile ingredients, materials, supplies and packaging in their operation, which have already undergone the necessary release testing by the original manufacturer. Despite the known quality of these items, 503B entities of this type must ensure the pedigree of their ingredients, materials, supplies and packaging. Mechanisms must be established to obtain certificates of analysis from the original manufacturers to confirm ingredient identity and the sterility. Predetermined specifications for all sterile ingredients, packaging and components must be developed and used to release these items. Should any of the material fail to meet these predetermined specifications, they must be rejected.

5. Buildings and Facilities and Environmental Monitoring

Any quality manufactured medication must be produced in a suitable environment that controls the risk of contamination and error. The CGMPs describe the critical elements of a suitable environment; but the specific criteria required are dependent on the organization's processes and must focus on the anticipated exposure of the materials, components and packaging to the immediate environment during each processing step. The buildings and facilities should be of suitable size for the activities performed and constructed of suitable materials and in a manner to facilitate cleaning, maintenance and proper operations. A well-designed, one-way flow of traffic for personnel, materials and equipment will reduce the risk of processing errors. All areas of a sterile production must be maintained in a strict and sanitary manner to prevent infestation, cross-contamination or damage to incoming / in-process materials and finished products.

Each of the defined areas of operation in an aseptic processing facility must be controlled for suitable air quality depending on the nature of the operation, equipment

and products. This involves ensuring microbiological and particle contaminants do not exceed set minimum levels, such as those in ISO§§§ classifications for air cleanliness. Air quality should be measured during initial qualification studies performed under as-built, static conditions, but ongoing sampling must also occur during routine aseptic operations to ensure an environmental state of control. Frequent sampling under dynamic operating conditions facilitates the early identification of drift from a state of control and permits timely investigation and remedial action before product quality is compromised.

The environmental sampling program described in the current USP General Chapter <797> is considered inadequate for traditional pharmacy sterile compounding practices and is grossly inadequate for large scale compounding outsourced operations. The limited data collection required is insufficient to establish a microbial state of control, and it is certainly not able to detect any drift from that state of control in a timely fashion.

The quality of the environment and the interaction of human operators with the product during aseptic filling operations can affect the microbial quality of product being manufactured. The elements of comprehensive environmental monitoring program must include air sampling, surface sampling and personnel sampling (e.g., sterile gloves and other sterile garb) during each compounding session. 503B facilities must monitor both viable and non-viable particle counts during any aseptic processing procedures, which is the expectation under CGMPs. Environmental monitoring data also must be considered in conjunction of other quality data for product release.

Organizations must respond to data indicating an unfavorable trend away from the state of control. The FDA 4803 observations from the inspection of New England Compounding Center (NECC) showed that NECC was conducting more frequent environmental monitoring than what was required in Chapter <797>, but they failed to act upon that troubling data to eliminate the presence of unacceptable levels of microbial bioburden.[40]

6. Standard Operating Procedures (SOPs)

In order to ensure process uniformity within an organization and maintain it consistently, standard operating procedures are critical. Properly designed SOPs

§§§ ISO (International Organization for Standardization) is a large developer of widely-used voluntary international standards.

clearly articulate the steps to ensure product consistency and quality. To develop effective SOPs that meet an organization's requirements, consensus must be achieved between production and quality control units and there must be an understanding of the activities necessary to consistently bring about the desired outcome. Though SOPs are required by Chapter <797>, compliance has been imperfect. The detailed process understanding needed to write SOPs is often lacking in organizations that function out of verbal tradition rather than from a well-defined and disciplined quality system. Unfortunately this paradigm is all too common within pharmacy compounding operations and it represents a failure of leadership. For example, only 48% of pharmacies surveyed in 2013 responded that they had a detailed written policy and procedure on all aspects of surface and viable air sampling which includes preparation of plates, labeling of plates according to the Environmental Sampling Plan, reading plates; documentation of result as well as procedure for sending them to contracted lab (in the event that is applicable).[41]

Subsequent to the development of detailed SOPs, is training of staff in the SOPs. Compounding staff must also be involved in the ongoing development and revision of SOPs. SOPs can and should be living documents that are refined continually as potential points of failure are identified. In a true quality system, the staff is encouraged to identify instances of "close calls" where mistakes were almost made. As issues and variances are identified, solutions are found and tested. When solutions are successful, the changes to the SOP are made permanent and the personnel are again retrained. This type of process and these expectations are self-evident in organizations that comply with CGMPs.

7. Personnel Training, Qualification and Monitoring

The personnel working in an aseptic processing area are the greatest source of both microbial and particulate contamination. Traditional pharmacy compounding is almost exclusively a manual process involving a significant human presence. This presence creates an increased risk in large scale compounding operations, as a greater number of products may be affected by contamination introduced by humans.

USP General Chapter <797> requires that "Compounding personnel are adequately skilled, educated, instructed and trained to correctly perform and document the following activities in their sterile compounding duties:

a. perform antiseptic hand cleansing and disinfection of non-sterile compounding surfaces;

b. select and appropriately don protective garb;

c. maintain or achieve sterility of CSPs in ISO Class 5 (see Table 1) PEC devices and protect personnel and compounding environments from contamination by radioactive, cytotoxic and chemotoxic drugs

d. identify, weigh and measure ingredients; and

e. manipulate sterile products aseptically, sterilize high-risk level CSPs and label and quality inspect CSPs."

These requirements for traditional compounding practices lack the qualitative and quantitative specificity and rigor needed for large scale compounding operations. For example, proper sterile garbing is critical to preventing microbial contamination, especially for entities that produce large scale batched products. USP General Chapter <797> describes the minimum garbing requirements but does not provide any qualitative guidance on this topic. In CGMP facilities, operators working in the aseptic processing area may not have any exposed skin and personnel in critical processing areas (e.g., ISO 5) must be vigilant about how they move and work within the critical filling zones.

Ideally, any aseptic processing procedures must minimize the presence of humans and maximize the use of automated equipment that has been validated to not add bioburden to the process. CGMP manufacturing operations have worked diligently to automate aseptic processing as much as possible, greatly reducing the risk of contamination. These commercial scale manufacturers employ automated sterilization / decontamination cycles to eliminate contamination from inbound ingredients, materials, supplies and packaging. USP General Chapter <797> relies on a manual decontamination and there is no requirement to validate the effectiveness of that decontamination.

Chapter <797> lacks a clear and comprehensive list of personnel training core elements. By contrast, the FDA Aseptic Processing Guidance used in the CGMP context states "Appropriate training should be conducted before an individual is permitted to enter the aseptic manufacturing area. Fundamental training topics should include aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazards posed by a non-sterile drug product and the specific written procedures covering aseptic manufacturing area operations. After initial training, personnel should participate regularly in an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to

written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and aseptic technique during manufacturing operations."

8. Stability Program and Expiration Dating

CGMPs require a program to determine the stability characteristics and shelf-life for each product. Chapter <797>, however, does not provide sufficient guidance for 503B facilities on robust methodology for establishing compounded drug stability and beyond-use dates (i.e. expiration dates). In fact, the Chapter permits individuals to use their professional judgment to assign this critical date. Chapter <797> states:

> "To ensure consistent practices in determining and assigning beyond-use dating (BUDs), the compounding facility should have written policies and procedures governing the determination of the BUDs for all compounded products. When attempting to predict a theoretical BUD, a compounded or an admixed preparation should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components."
>
> "Compounding personnel who assign BUDs to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to determine a conservative and safe BUD."

503B facilities must have a more robust stability program that uses appropriate and validated methods and procedures to determine the stability characteristics of the manufactured product and to establish appropriate storage conditions and expiration dates. Stability is specific to the ingredients, materials and containers used in the manufacturing process and must be demonstrated through objective qualitative and quantitative data derived by validated scientific tests.

Some compounders use contract testing laboratories to conduct stability studies, but the methods and procedures used by contract testing laboratories have recently come under scrutiny. Several contract testing laboratories were issued 483s by the FDA calling into the question the veracity of the systems needed to support compounding practices when drug strength, sterility and endotoxin testing is required.[42]

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Under a CGMP model, an organization's stability program is fully articulated within the organization's standard operating procedures. SOPs will describe the sample size, test intervals, storage conditions and test methods to determine stability, as well as the number of batches to evaluate each the formulations manufactured.

9. Cleaning and Disinfecting; Equipment Use Logs

Under CGMP regulations, facilities and equipment must be qualified, calibrated, cleaned and maintained to prevent contamination and mix-ups. Properly maintaining facilities and equipment is critical to ensure suitability and fitness of use. USP General Chapter <797> states the importance of cleaning and disinfecting, but it lacks specificity. Additional detail is necessary to describe proper cleaning and disinfection activities as well as how to inspect for adequacy.

As required under CGMP, only sterile chemical agents should be used to clean and disinfect facilities where sterile products are manufactured and these agents must be validated against the microbial bioburden of the facility to determine their effectiveness. USP General Chapter <797> does not require validated cleaning methods, but relies on limited environmental sampling alone to demonstrate that microbial bioburden is being appropriately controlled.

As a subset of cleaning and disinfecting procedures, all equipment (e.g., primary engineering controls, autoclaves, pumps, scales and other items that influence the quality of the product) must have operating SOP, maintenance, cleaning and use logs. Equipment must also be properly identified for tracking purposes – each product batch record must document the equipment used.

10. Process Validation

The effectiveness of any procedure used to sterilize or assure the quality / stability of a manufactured product must be established through process validation. Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities that take place over the lifecycle of the product and process.[43] Although Chapter <797> requires that "sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging," it lacks specific guidance in how to determine that this standard has been met.

Each 503B entity must establish validated methods to ensure quality and sterility within their processes and not merely rely on documentation provided by companies that sell bulk chemicals and other services to the compounding industry. Quality cannot be adequately assured merely by in-process and finished-product checks, which is the present-day model used under Chapter <797>.

11. Equipment Calibration, Validation and Preventative Maintenance System

A robust process validation system requires a clear understanding of how equipment will be used to achieve the quality, integrity, strength and sterility of each batch. Each piece of processing equipment used in batch manufacturing must be shown to be operating within its predetermined specifications.

A fundamental failure discovered in many compounding contamination events is the ineffective and improper use of equipment and procedures to terminally sterilize the CSPs. These critical quality assurance procedures were not validated and the sterility of the final product was not assured.

SOPs must define a calibration program that identifies the necessary steps to ensure the precision and accuracy of equipment. This includes all production and laboratory equipment that perform quantitative measurements, such as balances, thermometers, pipettes and temperature sensing devices in autoclaves or dry-heat ovens. Each piece of equipment or group of equipment requires a calibration log that specifies the frequency of calibration, points where calibration is checked and its acceptable operating range. Calibrated equipment should be tagged or labeled to show who performed the calibration, the date of the calibration and the scheduled date of the next calibration.

12. Area Clearance and Label Accountability System

This quality system element prevents product mix-ups and mislabeling. Area clearance applies to procurement, control and segregation of supplies and components and documentation throughout the manufacturing process. To reduce the risk of error, the manufacturing of a specific formulation occurs in a segregated area with assigned personnel working on only one formulation at a time. Strict control of all product labels must be in place to prevent errors in product labeling. This concept is not described in USP General Chapter <797>.

Area clearance and a label accountability program is a required element of the organization's SOPs. Whenever product is labeled, it must be performed in a cleared area free from label materials or documentation from other batches. An individual different from the person preparing the formulation should examine the labels to assure that the correct label is affixed to its corresponding product and that it properly identifies the product. This individual must also reconcile the quantity of labels issued vs. the quantity of labels used. Any discrepancies in the label reconciliation process must be fully investigated before the batch released. Any excess batch labels should be destroyed to prevent mislabeling.

Labels need to be stored in a manner to prevent mix-up and within a labeling area or room where labels are inspected prior to performing the labeling operation. An area clearance should be conducted to assure that all labels from the previous labeling operation are removed before bringing in the next batch to be labeled.

13. Change Control

Change control is another well-known CGMP concept that focuses on managing change to prevent unintended consequences. The system must manage the end-to-end change control process including initiating, reviewing, approving, distributing and storing the history of changes in procedures, processes, testing, formulations and other critical tasks that can impact product quality or regulatory filings. It captures the relevant information about the objective, nature and scope of change. A well-managed change control program can provide evidence of CGMP compliance to the FDA. A 503B entity would require a robust change control policy to ensure drug quality and patient safety. The CGMP regulations provide for change control primarily through the assigned responsibilities of the quality unit. Effective change control activities (e.g., quality planning and control of revisions to specifications, process parameters, procedures) are key components of any quality system.

14. Finished Product Release System

Required under CGMPs, a finished product release system assures that each batch of product conforms to predetermined specifications. Written procedures for the release of finished products must include an established sampling plan for testing the completed batch of finished product. Products failing to meet established specifications must be rejected. Products that can be reprocessed must again be sampled, tested and meet the established specifications before release. All products

need to be quarantined according to written procedures until released by the quality unit.

USP General Chapter <797> does not require a formal finished product release system. The standard does require sterility testing, but only when the default beyond-use dating of compounded medications made from sterile ingredients is exceeded; and for high-risk CSPs, such as those made from non-sterile bulk ingredients, and only for batches of larger than 25.

15. Operational Variances and Complaint System/Corrective and Preventive Action (CAPA)

A compliance system that tracks and trends feedback to improve the manufacturing process is a cornerstone of CGMP quality systems. A Corrective and Preventive Action (CAPA) system focuses on the systematic investigation of discrepancies (failures and/or deviations) in an attempt to prevent their reoccurrence (corrective action) as well as eliminate the cause of potential nonconforming product and other quality problems (preventive action).

To ensure that corrective and preventive actions are effective, failures must be systematically investigated and corrective actions must be standardized and integrated into the SOPs.

Performance feedback may be manufacturing process data on operational variances, or may come from customer complaints. A robust CAPA system must include a written SOP about how complaints are handled as well as a written record of each complaint. If the complaint requires an investigation, the investigation must be documented and made readily available in the CAPA record.

Summary

The uninterrupted availability of sterile formulations is an important part of delivering comprehensive pharmaceutical care to patients. The passage of the Drug Quality and Security Act provides the FDA, USP, State Boards of Pharmacy and various stakeholders with the opportunity to rethink the resources, standards and requirements necessary to ensure availability of manufactured/compounded drug

with suitable quality for patient safety. USP General Chapter <797> provides minimum practice and quality standards for traditional pharmacy sterile compounding activities. It does not describe nor was it intended to describe an appropriate quality system for large scale compounding activities. Producing large scale sterile batches requires a higher degree of discipline consistent with the approach described in the Current Good Manufacturing Practices. As Chapter <797> is revised, it should also address large scale sterile compounding activities and identify higher quality standards where necessary, even for compounders that ultimately link drugs to individual patient prescriptions. The description of key GMP concepts for large scale compounding listed in this paper may be useful in that effort. Regardless of the standard applied, a robust, detailed timely quality oversight process is required to drive meaningful compliance. The state boards of pharmacy are working to ensure that their inspectors are adequately skilled, educated and trained to enforce the requirements of Chapter <797>.[44] Large scale operations working within the provisions of Section 503B of the Drug Quality and Security Act must be regulated and inspected by the U.S. Food and Drug Administration. The FDA and State Boards of Pharmacy must work together to identify non-traditional compounding facilities that have not registered with the FDA as a 503B entity in order to ensure that they receive appropriate regulatory oversight. Only when all compounding facilities are held fully accountable to appropriate quality systems can drug quality and patient safety be assured.

Authors

Eric S. Kastango, MBA, RPh, FASHP
President/CEO, Clinical IQ, LLC and CriticalPoint, LLC

Katherine H. Douglass, MS, RN, APN,C, CRNI
Vice President, CriticalPoint, LLC

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This paper was peer-reviewed by

James Agalloco, BE Chem Eng., MS, MBA
President, Agalloco & Associates
Belle Mead, NJ

Patricia C. Kienle, RPh, MPA, FASHP
Director, Accreditation and Medication Safety
Cardinal Health Innovative Delivery Solutions

David W. Newton, B.S. Pharm., Ph.D., FAPhA,
Professor
Department of Biopharmaceutical Sciences
Bernard J. Dunn School of Pharmacy
Shenandoah University

John L. Quick, BS, MBA
President, Quick & Associates
Genoa City, WI

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Subpart B - Organization and Personnel		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.22 Responsibilities of Quality Control Unit	(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.	**No**
	(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.	**No**
	(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.	**No**
	(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.	**No**
211.25 Personnel Qualifications	(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.	**No explicit requirement is stated in the USP chapter**

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Subpart B - Organization and Personnel		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.28 Personnel responsibilities	(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.	**Yes, however the only sterile garb required is sterile gloves. CGMPs expect personnel to be completely covered (no exposed skin) and be wearing sterile garb**
	(b) Personnel shall practice good sanitation and health habits.	**Yes**
	(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.	**Yes**
	(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.	**Yes**
211.34 Consultants	Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.	**No**
Subpart C-Buildings and Facilities		
211.42 Design and construction features	(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.	**Yes**

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Subpart C-Buildings and Facilities		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.42 Design and construction features *(continued)*	(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:	**Yes, however the rigor required by CGMPs are not clearly stated in USP Chapter <797>**
	(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;	**No**
	(2) Holding rejected components, drug product containers, closures, and labeling before disposition;	**No**
	(3) Storage of released components, drug product containers, closures, and labeling;	**No**
	(4) Storage of in-process materials;	**No**
	(5) Manufacturing and processing operations;	**No**
	(6) Packaging and labeling operations;	**No**
	(7) Quarantine storage before release of drug products;	**No**
	(8) Storage of drug products after release;	**Yes**
	(9) Control and laboratory operations;	**No**
	(10) Aseptic processing, which includes as appropriate:	**Yes**
	(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;	**Yes**
	(ii) Temperature and humidity controls;	**No-Temperature only**
	(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;(iv) A system for monitoring environmental conditions;	**Yes** **No**

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Subpart C-Buildings and Facilities		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.42 Design and construction features *(continued)*	(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions; (vi) A system for maintaining any equipment used to control the aseptic conditions.	**Yes, but less stringent** **Yes, but minimal**
	(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.	**No**
211.44 Lighting	Adequate lighting shall be provided in all areas	**Yes**
211.46 Ventilation, air filtration, air heating and cooling	(a) Adequate ventilation shall be provided	**Yes**
	(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.	**Yes**
	(c) Air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.	**Yes**
	(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use	**No**
211.48 Plumbing	(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.	**No**
	(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.	**No**
211.50 Sewage and refuse	Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.	**No**
211.52 Washing and toilet facilities	Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.	**Yes**

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Subpart C-Buildings and Facilities		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.56 Sanitation	(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.	**No**
	(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.	**Yes**
	(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).	**No**
	(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.	**No**
211.58 Maintenance	Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.	**Not specifically**
Subpart D-Equipment		
211.63 Equipment design, size, and location	Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.	**Not specifically**
211.65 Equipment construction	(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.	**No**
	(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug	**No**

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Subpart D-Equipment		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.65 Equipment construction *(continued)*	products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.	**No**
211.67 Equipment cleaning and maintenance	(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:	**Not specifically**
	(1) Assignment of responsibility for cleaning and maintaining equipment;	**Yes**
	(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;	
	(4) Removal or obliteration of previous batch identification;	**No**
	(5) Protection of clean equipment from contamination prior to use;	**No**
	(6) Inspection of equipment for cleanliness immediately before use.	**No**
	(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.	**Yes**
211.68 Automatic, mechanical, and electronic equipment	(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.	**Yes however the rigor required by CGMPs are not clearly stated in USP Chapter <797>**
	(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be	**No**

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Subpart D-Equipment		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.68 Automatic, mechanical, and electronic equipment *(continued)*	checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.	**No**
	(c) Such automated equipment used for performance of operations addressed by §§ 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections relating to the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section, and one person checks that the equipment properly performed the operation.	**No**
211.72 Filters	Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may be used when it is not possible to manufacture such products without the use of these filters. If use of a fiber releasing filter is necessary, an additional nonfiber-releasing filter having a maximum nominal pore size rating of 0.2 micron (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. The use of an asbestos containing filter is prohibited.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
Subpart E-Control of Components and Drug Product Containers and Closures		
211.80 General requirements	(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.	**Yes however the rigor required by CGMPs is not clearly stated in USP 797**

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Subpart E-Control of Components and Drug Product Containers and Closures		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.80 General requirements *(continued)*	(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.	**No**
	(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).	**No**
211.82 Receipt and storage of untested components, drug product containers, and closures	(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.	**No**
	(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of § 211.80.	**No**
211.84 Testing and approval or rejection of components, drug product containers, and closures	(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.	**No**
	(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by § 211.170.	**No**
	(c) Samples shall be collected in accordance with the following procedures: (1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component. (2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures. (3) Sterile equipment and aseptic sampling techniques shall be used when necessary. (4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing. (5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was	**No**

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Subpart E-Control of Components and Drug Product Containers and Closures		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.84 Testing and approval or rejection of components, drug product containers, and closures *(continued)*	taken, the date on which the sample was taken, and the name of the person who collected the sample. (6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.	**No**
	(d) Samples shall be examined and tested as follows: (1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.	**No**
	(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. (3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals. (4) When appropriate, components shall be microscopically examined. (5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination. (6) Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.	**No**
	(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.	**No**

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Subpart E-Control of Components and Drug Product Containers and Closures		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.86 Use of approved components, drug product containers, and closures	Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate	**No**
211.87 Retesting of approved components, drug product containers, and closures	Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with § 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure	**No**
211.89 Rejected components, drug product containers, and closures	Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable	**No**
211.94 Drug product containers and closures	(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.	**No**
	(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.100 Written procedures; deviations	(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**

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Subpart F-Production and Process Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.100 Written procedures; deviations *(continued)*	(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.101 Charge-in of components	Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess: (a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient. (b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information: (1) Component name or item code; (2) Receiving or control number; (3) Weight or measure in new container; (4) Batch for which component was dispensed, including its product name, strength, and lot #.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that: (1) The component was released by the quality control unit; (2) The weight or measure is correct as stated in the batch production records; (3) The containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under § 211.68, only one person is needed to assure paragraphs (c)(1), (c)(2), and (c)(3) of this section. (d) Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under § 211.68, only verified by one person.	**Yes however the rigor required by CGMPs are not clearly stated in USP Chapter <797>**
211.103 Calculation of yield	Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person, or, if the yield is calculated by automated equipment under § 211.68, be independently verified by one person.	**No**

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Subpart F-Production and Process Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.105 Equipment identification	(a) Production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.	**No**
	(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.	**No**
211.110 Sampling and testing of in-process materials and drug products	(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate: (1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; (5) Clarity, completeness, or pH of solutions. (6) Bioburden Testing	**Yes however the rigor required by CGMPs are not clearly stated in USP Chapter <797>**
	(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.	**No**
	(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.	**No**
	(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.	**No**

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Subpart F-Production and Process Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.111 Time limitations on production	When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.	**No**
211.113 Control of microbiological contamination	(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.	**No**
	(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.115 Reprocessing	(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.	**No**
	(b) Reprocessing shall not be performed without the review and approval of the quality control unit	**No**
Subpart G-Packaging and Labeling Control		
211.122 Materials examination and usage criteria	(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they is unsuitable.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.	**No**
	(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.	**No**
	(e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.	**No**

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Subpart G-Packaging and Labeling Control		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.122 Materials examination and usage criteria *(continued)*	(f) Use of gang printing of labeling for different drug products or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.	**No**
	(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures: (1) Dedication of labeling and packaging lines to each different strength of each different drug product. (2) Use of appropriate electronic or electromechanical equipment to conduct a 100- percent examination for correct labeling during or after completion of finishing operations; or (3) Use of visual inspection to conduct a 100- percent examination for correct labeling during or after completion of finishing operations for hand- applied labeling. Such examination shall be performed by one person and independently verified by a second person.	**No**
	(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.	**No**
211.125 Labeling issuance	(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.	**No**
	(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.	**No**
	(c) Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with § 211.192. Labeling reconciliation is waived for cut or roll labeling if a 100-percent examination for correct labeling is performed in accordance with § 211.122(g)(2).	**No**
	(d) All excess labeling bearing lot or control numbers shall be destroyed.	**No**
	(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.	**No**
	(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.	**No**

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Subpart G-Packaging and Labeling Control		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.130 Packaging and labeling operations	There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features: (a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.	**No**
	(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.	**No**
	(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.	**No**
	(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.	**No**
	(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.	**No**
211.132 Tamper-resistant packaging requirements for over-the-counter (OTC) human drug products		**No**
211.134 Drug product inspection	(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) Results of these examinations shall be recorded in the batch production or control records	**No**

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Subpart G-Packaging and Labeling Control		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.137 Expiration dating	(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in § 211.166.	**Referred to beyond-use dating. Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in §211.166.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.	**No**
	(d) Expiration dates shall appear on labeling in accordance with the requirements of § 201.17 of this chapter.	**Yes, beyond use dates (BUDs)**
	(e) Homeopathic drug products shall be exempt from the requirements of this section.	**No**
	(f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section	
	(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product	
	(h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.	

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Subpart H-Holding and Distribution		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.142 Warehousing procedures	Written procedures describing the warehousing of drug products shall be established and followed. They shall include: (a) Quarantine of drug products before release by the quality control unit.	**No**
	(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.150 Distribution procedures	Written procedures shall be established, and followed, describing the distribution of drug products. They shall include: (a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary	**No**
Subpart I-Laboratory Controls		
211.160 General requirements	(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.	**No**

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Subpart I-Laboratory Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.160 General requirements *(continued)*	(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:	**No**
	(1) Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.	**No**
	(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.	**No**
	(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.	**No**
	(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used	**Yes**
211.165 Testing and release for distribution	(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.	**No**
	(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.	**No**

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Subpart I-Laboratory Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.165 Testing and release for distribution *(continued)*	(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.	**No**
	(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with § 211.194(a)(2).	**No**
	(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.	**No**
211.166 Stability testing	(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include: (1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability; (2) Storage conditions for samples retained for testing; (3) Reliable, meaningful, and specific test methods; (4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed; (5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.	**No**

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Subpart I-Laboratory Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.166 Stability testing *(continued)*	(c) For homeopathic drug products, the requirements of this section are as follows: (1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.	**No**
	(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.	**No**
	(d) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.	**No**
211.167 Special testing requirements	(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.	**No**
	(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed	**No**
211.170 Reserve Samples	a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows: (1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient	**No**

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Subpart I-Laboratory Controls		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.170 Reserve samples *(continued)*	(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with § 211.192. The results of examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows: (1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product. (2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for: (i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or (ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days. (3) For an OTC drug product that is exempt for bearing an expiration date under § 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed	**No**
211.173 Laboratory animals		**No**
211.176 Penicillin contamination	If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference.	**No**

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Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.180 General requirements	(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the batch.	**No, however state pharmacy laws may dictate record retention of batch records, prescription files.**
	(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.	**No**
	(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.	**No, however state pharmacy laws may dictate record retention of batch records, prescription files.**
	d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.	**No, however state pharmacy laws may dictate record retention of batch records, prescription files.**
	(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for: (1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch. (2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product. (f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §§ 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or	**No**

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Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.180 General requirements *(continued)*	any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration	**No**
211.182 Equipment cleaning and use log	A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under § 211.68, just the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.184 Component, drug product container, closure, and labeling records	These records shall include the following: (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in § 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) The results of any test or examination performed (including those performed as required by § 211.82(a), § 211.84(d), or §211.122(a)) and the conclusions derived therefrom.	**No**
	(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.	**No**
	(d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with §§ 211.122(c) and 211.130(c).	**No**
	(e) The disposition of rejected components, drug product containers, closure, and labeling	**No**

CGMP - USP <797> Crosswalk

Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.186 Master production and control records	(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.	**No**
	b) Master production and control records shall include: (1) The name and strength of the product and a description of the dosage form; (2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit; (3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic; (4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records; (5) A statement concerning any calculated excess of component; (6) A statement of theoretical weight or measure at appropriate phases of processing; (7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to § 211.192 is required;	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>** **No** **No** **No** **No** **No** **No**
211.186 Master production and control records *(continued)*	(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling; (9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>** **No**
211.188 Batch production and control records	Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include: (a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;	**No**

CGMP - USP <797> Crosswalk

Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.188 Batch production and control records *(continued)*	(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including: (1) Dates; (2) Identity of individual major equipment and lines used; (3) Specific identification of each batch of component or in-process material used; (4) Weights and measures of components used in the course of processing; (5) In-process and laboratory control results; (6) Inspection of the packaging and labeling area before and after use; (7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing; (8) Complete labeling control records, including specimens or copies of all labeling used; (9) Description of drug product containers and closures; (10) Any sampling performed; (11) Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under § 211.68, the identification of the person checking the significant step performed by the automated equipment. (12) Any investigation made according to § 211.192. (13) Results of examinations made in accordance with § 211.134.	**No**
211.192 Production record review	All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and followup	**No**

CGMP - USP <797> Crosswalk

Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.194 Laboratory records	(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows: (1) A description of the sample received for testing with identification of source (location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing. (2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,{2} or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use. {2} Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201-3301. (3) A statement of the weight or measure of sample used for each test, where appropriate. (4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested. (5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors. (6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested. (7) The initials or signature of the person who performs each test and the date(s) the tests were performed. (8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.	**No**

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Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.194 Laboratory records *(continued)*	(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method. (c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions. (d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by § 211.160(b)(4). (e) Complete records shall be maintained of all stability testing performed in accordance with § 211.166.	**No**
211.196 Distribution records	Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.198 Complaint files	(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with § 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with § 310.305 of this chapter.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
	(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under § 211.137, such written records shall be maintained for 3 years after distribution of the drug product.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**

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Subpart J-Records and Reports		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.198 Complaint files *(continued)*	(1) The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant. (2) Where an investigation under § 211.192 is conducted, the written record shall include the findings of the investigation and followup. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with § 211.180(c). (3) Where an investigation under § 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.	
Subpart K-Returned and Salvaged Drug Products		
211.204 Returned drug products	Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of § 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**
211.208 Drug Product Salvaging	Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**

CGMP - USP <797> Crosswalk

Subpart K-Returned and Salvaged Drug Products		Is this requirement of 21 CFR 211 required in USP Chapter <797>?
211.208 Drug Product Salvaging *(continued)*	of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.	**Yes however the rigor required by CGMPs is not clearly stated in USP Chapter <797>**

COMMONWEALTH of VIRGINIA

David E. Brown, D.C.
Director

Department of Health Professions
Perimeter Center
9960 Mayland Drive, Suite 300
Henrico, Virginia 23233-1463

www.dhp.virginia.gov
TEL (804) 367- 4400
FAX (804) 527- 4475

Board of Pharmacy
(tel) (804) 367-4456
(fax) 804-527-4472

March 21, 2013

Alan L. Wagner, MD, FACS
Virginia Society of Eye Physicians and Surgeons
PO Box 3268
Glen Allen, VA 23058-3268

Dear Dr. Wagner:

I am writing in response to your letter sent to the Board of Pharmacy on March 11, 2013 wherein you indicate several members of the Virginia Society of Eye Physicians and Surgeons have expressed concern regarding access to compounded medications used in ophthalmology practices. Specifically, you state that these members report that the Board of Pharmacy is instructing some compounding pharmacies it has inspected to require prescriptions for each individual patient for compounded medications like intravitreal Avastin. You further indicate that retinal specialists are concerned that requiring individual prescriptions, rather than larger orders based on historical prescribing/administering patterns is impractical and could create barriers to the patient and doctor to effectively administer Avastin in a timely and efficient manner. You request the Board to review its interpretations of relevant laws and regulations and express concerns for possible increased cost for wasted doses.

Please note that the referenced practice by which pharmacies supply physicians with Avastin for an off-label use involves repackaging the manufactured drug product into smaller volume syringes. It does not constitute compounding as defined in Va Code §54.1-3401. While pharmacists may repackage a drug product when dispensing a drug pursuant to a individual prescription, a pharmacist may not repackage drug solely for distribution purposes. The board has historically interpreted the repackaging of a drug for distribution purposes as an act restricted to a manufacturer, defined in Va Code §54.1-3401. This interpretation appears consistent with recent warning letters from the US Food and Drug Administration (FDA).

The excerpt below is taken from a warning letter from the FDA to Infupharma, LLC dated July 30, 2012:

> "Our investigators found that your firm has a contract with another pharmacy to repack Avastin from sterile injectable single-use vials into sterile injectable 1 mL single-use syringes and to repack human chorionic gonadotropin (HCG) multi-use vials into single-use syringes for further distribution. FDA does not consider your practice of repackaging and distributing Avastin and HCG without prescriptions for resale to other entities to constitute the regular course of a pharmacy's business of dispensing and selling drugs at retail.

> FDA regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product and pursuant to valid prescriptions, to be within the practice of pharmacy. Processing and repacking (including repackaging) of approved drugs without valid prescriptions or for resale by other pharmacies or entities, however, exceed the traditional practice of pharmacy. Consequently, your firm is subject to the CGMP requirements for finished pharmaceuticals as described in Section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)] and Title 21 Code of Federal Regulations Parts 210 and 211 (21 CFR 210 & 211)."

As you may be aware, the FDA alerted health care professionals in 2011 "that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections." This alert followed a cluster of eye infections resulting from administration of Avastin, repackaged in a Florida pharmacy. Some of the at least twelve affected patients lost all remaining vision in that eye due to the endophthalmitis. The alert also mentioned that while some physicians prescribe Avastin for this off-label use, there is a FDA-approved drug for this indication. Additionally, on March 18, 2013, the FDA announced that Clinical Specialites, a compounding pharmacy in Georgia, was issuing a voluntary recall of repackaged Avastin due to reports of five intra-ocular infections resulting from repackaged Avastin.

It is the patient risk, exemplified in these two instances, associated with pharmacies repackaging Avastin not pursuant to individual prescriptions, but in large quantities intended to be stored in a prescriber's office for an extended period of time that is most concerning to the Board. Repackaging sterile products not pursuant to individual prescriptions must be performed by a manufacturer complying with CGMP requirements. However, the law does not prohibit a pharmacist from repackaging Avastin pursuant to an individual prescription.

I hope this information assists you in understanding the issues surrounding pharmacies repackaging Avastin. Please feel free to contact me at (804) 367-4456 or pharmbd@dhp.virginia.gov should you have additional questions.

Sincerely,

Caroline D. Juran
Executive Director

Cc: The Honorable William A. Hazel, Jr.
Dianne L. Reynolds-Cane, MD, Director, DHP
Board of Medicine
Medical Society of Virginia
Virginia Pharmacists Association

Photo courtesy of Luci A. Power, MS, RPh, Power Enterprises.

By Luci A. Power, MS, RPh; Eric S. Kastango, MBA, RPh, FASHP; Kate Douglass, MS, RN, APN,C, CRNI; and Patricia C. Kienle, RPh, MPA, FASHP

Understanding the **New Proposed USP Chapter <800>**

Each year, approximately eight million US health care workers are potentially exposed to hazardous drugs (HDs).[1] The subject of worker exposure to HDs (ie, chemotherapy, antineoplastics, cytotoxics, etc) has been discussed since the early 1970s, when chemotherapy was mixed on countertops or in horizontal laminar airflow workbenches that blew HD-contaminated air into the room, directly at compounding personnel. In 2004, the National Institute of Occupational Safety and Health (NIOSH) published the NIOSH Alert, Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings, 11 months after the publication of the 2004 version of USP Chapter <797>. In the 2008 revision of USP Chapter <797>, a specific section was devoted to the preparation of hazardous drugs, which defined several key requirements, including[2]:

1. Appropriate primary and secondary engineering controls to ensure sterility and drug containment
2. The use of personal protective equipment (PPE), regardless of engineering control employed
3. Training of compounding personnel to include at least the following:
   - Safe aseptic manipulation practices;
   - Negative pressure techniques when utilizing a biological safety cabinet (BSC) or compounding aseptic containment isolator (CACI);
   - Correct use of closed system drug-transfer devices (CSTDs);
   - Containment, cleanup, and disposal procedures for breakages and spills; and
   - Treatment of personnel contact and inhalation exposure
4. Training of personnel who perform routine custodial waste removal and cleaning activities in storage and preparation areas for HDs in appropriate procedures to protect themselves and prevent contamination.

These requirements are limited, however, as they do not address the full scope of HD exposure. Not all HDs are sterile; as such, the hazards of non-sterile compounding require delineation as well.

New Proposed USP <800>

On March 28, 2014, USP posted the new proposed *General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings* on their Web site (available at http://www.usp.org/usp-nf/notices/compounding-notice).[3] This chapter identifies the requirements for receipt, storage, mixing, preparing, compounding, dispensing, and administering HDs to properly protect patients, health care personnel, and the environment. General Chapter <800> was published electronically in the May–June issue of *Pharmacopeial Forum* (PF). Public review and comments will be accepted through July 31, 2014.

An important strategy to minimize occupational exposure to HDs is to ensure containment to as low a limit as reasonably achievable (ALARA). The concept of ALARA, a radiation safety principle, can be borrowed for use related to HD containment. As defined in Title 10, Section 20.1003 of the Code of Federal Regulations (10 CFR 20.1003),

> *ALARA is an acronym for "as low as (is) reasonably achievable," which means making every reasonable effort to maintain exposures to ionizing radiation as far below the dose limits as practical, consistent with the purpose for which the licensed activity is undertaken, taking into account the state of technology, the economics of improvements in relation to state of technology, the economics of improvements in relation to benefits to the public health and safety, and other societal and socioeconomic considerations, and in relation to utilization of nuclear energy and licensed materials in the public interest.*[4]

By replacing the references to radiation and nuclear energy with the term HDs, the ALARA principle accurately explains the essence of proposed chapter <800>. Adopting the strategies laid out in USP <800> will enable hospitals to ensure that health care workers manipulating HDs are exposed only to amounts of contamination in line with the concept of ALARA.

Proposed USP Chapter <800> identifies the requirements for receipt, storage, mixing, preparing, compounding, dispensing, and administering hazardous drugs to properly protect patients, health care personnel, and the environment.

Understanding Hazardous Drug Exposure

Since the first reported HD exposures, one of the roadblocks to achieving HD safety compliance has been the lack of documented evidence that HDs cause harm to health care workers. There is no clear, reportable number of deaths of health care workers who have developed cancer as a result of handling HDs at the workplace; few registries exist in the US that track employment, cancer outcomes, or reproductive outcomes of health care workers exposed to HDs, so accurate counts remain elusive. While to date there is no conclusive proof of the link between HD exposure and cancer in health care workers, the data on reproductive risk, notable biological marker effects, and recent specific chromosomal aberrations is too much to ignore.

In 2010, an investigative reporter, Carol Smith, endeavored to put a human face on the problem by recounting the tribulations of Sue Crump, a Seattle-area pharmacist who died at age 55 of pancreatic cancer.[5] The reporter chronicled Crump's experience mixing chemotherapy in hospital settings, which Crump believed was a causative factor in her cancer. The impact of this report resulted in the Washington State legislature passing two HD rules in 2012, one detailing handling requirements and the other requiring a registry to track workers who handle HDs and adverse events they had experienced.[6,7] Certainly this is a positive development, and underscores the need for additional resources to track occupational exposure and cancer throughout the US.

Also in 2010, two important studies were published in the *Journal of Occupational and Environmental Medicine*. The first study, partially funded by NIOSH, evaluated antineoplastic drug exposure of health care workers at three university-based US health care centers, and reported continuing surface contamination in pharmacy and nursing areas despite HD handling guidelines.[8] The second study reported damage to health care workers' chromosomes that are linked to secondary cancers in treated patients, specifically tAML (acute myeloid leukemia with gene translocation) and tMDS (myelodysplastic syndromes with gene translocation).[9] These studies prompted NIOSH, OSHA, and TJC to jointly draft a letter discussing the safe use of HDs, which was sent on April 8, 2011 to all US hospitals.[10] Its message was to remind hospital and health care employers that HDs, such as antineoplastic drugs, pose serious health risks to workers when proper handling precautions are not followed.

Exposure to HDs, both directly and indirectly, is an occupational hazard for a large number of health care workers, **and it is vital that everyone who is at risk educate themselves about Chapter <800> and the actions they can take to protect themselves.**

TABLE 1

Comparison of USP <797> and New Proposed USP <800>[18]

USP <797> Pharmaceutical Compounding—Sterile Preparations	Proposed General Chapter USP <800> Hazardous Drugs—Handling in Healthcare Settings
Applies to sterile compounding only	Applies to sterile and non-sterile compounding
Applies from receipt of inventory up to start of drug administration	Applies from receipt of inventory through drug administration
All HDs should be stored separately in an area with 12 ACPH and 0.01" w.c. negative to adjacent space	Antineoplastic HDs must be stored separately from non-HDs in an area with 12 ACPH and 0.01" w.c. negative to adjacent space unless coated, final-manufactured dosage forms are clearly labeled as HDs and safety strategies are detailed in policies and procedures
Exemption for low-volume compounding	No low-volume exemption
CSTD use is a *should*	CSTD use is a *shall* during administration, when dosage form permits
Defines PECs for HD sterile compounding	Defines PECs for non-sterile and sterile HD compounding Allows manipulation of HDs that do not produce aerosols (eg, coated tablets or capsules) outside of C-PEC
Prohibits SCA for HD compounding Requires BSC to be housed in ISO class 7 room air that is 0.01" w.c. negative	Permits SCA for HDs provided CACI/BSC in area that has 12 ACPH and 0.01" W.C. negative; maximum BUD 12 hours
Does not require environmental and medical surveillance	Requires environmental and medical surveillance

ACPH = air changes for hour; BSC = biological safety cabinet; BUD = beyond-use date; C-PEC = containment primary engineering control; CACI = compounding aseptic containment isolators; HD = hazardous drug; PECs = primary engineering controls; SCA = segregated compounding area; w.c. = water column.

NIOSH Hazardous Drug Handling Guidance

After the 2010 article on pharmacist Sue Crump was published, OSHA noted, "Although this is an important safety and health issue, OSHA has not considered a standard to specifically address hazardous drugs in the health care setting."[5] In fact, OSHA has not addressed this topic since posting their 1995 HD handling guidance document to the Web in 1999.[11,12] Although many hospital leaders rely on the OSHA Web site for information on HDs in the workplace, the site contains little information detailing surface contamination studies and no information on the use of CSTDs.

Many states operate their own OSHA programs, and some states are following Washington's lead in this effort. Maryland[13] and North Carolina[14] have action in progress, and California passed an HD bill in October 2013.[15] However, because state OSHA initiatives all vary somewhat, state rules may not ensure the consistency of practice standards necessary to effectively deal with the problem of HD exposure in the health care setting.

Hundreds of studies have been published discussing HD exposure since the 2004 NIOSH Alert. The NIOSH Web site maintains a list of all the studies related to HD exposure (available at http://www.cdc.gov/niosh/topics/antineoplastic/pubs.html).

While limited evidence exists in the literature concerning occupational cancer related to antineoplastic agents,[16] adverse effects on fertility and reproductive health continue to be identified in a number of studies, mainly in female nurses.[17]

USP Chapter <800> provides extensive and consistent position statements on all aspects of HD handling; thus, adopting the requirements in USP <800> will improve and standardize practice nationwide. **TABLE 1**[18] highlights some of the major differences between the current requirements in USP Chapter <797> and the proposed version of USP Chapter <800>.

(Continues on page 24)

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Summary

Exposure to HDs, both directly and indirectly, is an occupational hazard for a large number of health care workers, and it is vital that everyone who is at risk educate themselves about Chapter <800> and the actions they can take to protect themselves. Do the strategies detailed in the new proposed chapter reduce exposures to HDs as low as reasonably achievable? To weigh in, please visit the USP Web site to download and read the proposed chapter. This is your opportunity to submit feedback and constructive suggestions to the expert committee to help strengthen the chapter and properly protect yourself and your colleagues from contamination. ■

Luci A. Power, MS, RPh, is an independent lecturer and consultant on pharmacy IV and hazardous drug systems. For over 25 years, she was with the department of pharmaceutical services at the University of California Medical Center in San Francisco, serving in various capacities. Luci is a primary author of both the 1985 and 1990 ASHP Technical Assistance Bulletins on Handling Cytotoxic and Hazardous Drugs, lead author of the 2006 ASHP Guidelines on Handling Hazardous Drugs, and first author of the ASHP Safe Handling of Hazardous Drugs Video Training Program. Luci is an original member of the National Institute for Occupational Safety and Health (NIOSH) working group on hazardous drugs and an author of the 2004 NIOSH Alert: Preventing Occupational Exposures to Antineoplastics and Other Hazardous Drugs in Health Care Settings. She is also a Compounding with Hazardous Drugs Expert Panel member.

Eric S. Kastango, MBA, RPh, FASHP, is the president, CEO, and owner of Clinical IQ, LLC, a provider of customized process and educational strategies for the pharmaceutical, medical device, and health care industries. A member of the USP's Compounding Expert Committee from 2005 to 2012, Eric now serves as an Expert Consultant on the USP Council of Experts and a member of the Compounding with Hazardous Drugs Expert Panel.

Kate Douglass, MS, RN, APN,C, CRNI, is vice president of CriticalPoint, a health care training and development company. She is one of the 2014 USP <797> Compliance Study co-directors. Kate has personally supervised the design, engineering, and build of several pharmacy compounding facilities that met or exceeded USP requirements and is on the faculty of CriticalPoint's Sterile Compounding Boot Camp.

Patricia C. Kienle, RPh, MPA, FASHP, an employee of Cardinal Health since 1999, currently serves as the director of accreditation and medication safety. She is the recipient of an MPA in health service administration from Marywood College in Scranton, Pennsylvania, a BSc in pharmacy from Philadelphia College of Pharmacy and Science, and has completed an executive fellowship in patient safety from Virginia Commonwealth University. She is a member of the USP Compounding Committee and chair of the Hazardous Drug Subcommittee and Expert Panel, though her comments here are her own and not official information from USP. Patti is also an adjunct associate professor at Wilkes University in Wilkes-Barre, Pennsylvania.

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Drugs

Compounding

Compounding Quality Act

Title I of the Drug Quality and Security Act of 2013

On November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA), legislation that contains important provisions relating to the oversight of compounding of human drugs[1].

Title I of this new law, the Compounding Quality Act, removes certain provisions from section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) that were found to be unconstitutional by the U.S. Supreme Court in 2002. Section 503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:

- Compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B));
- Labeling with adequate directions for use (section 502(f)(1)); and
- FDA approval prior to marketing (section 505).

By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide.

In addition, the new law creates a new section 503B in the FDCA. Under section 503B, a compounder can become an "outsourcing facility." An outsourcing facility will be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from CGMP requirements. Outsourcing facilities:

- Must comply with CGMP requirements,
- Will be inspected by FDA according to a risk-based schedule, and
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

If compounders register with the FDA as outsourcing facilities, hospitals and other health care providers can provide their patients with drugs that were compounded in outsourcing facilities that are subject to CGMP requirements and federal oversight.

If a compounder chooses not to register as an outsourcing facility and qualify for the exemptions under section 503B, the compounder could qualify for the exemptions under section 503A of the FDCA. Otherwise, it would be subject to all of the requirements in the FDCA applicable to conventional manufacturers. FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding. The Agency also intends to continue to cooperate with State authorities to address pharmacy compounding activities that may be violative of the FDCA.

FDA has initiated actions to implement the new law.

FDA Actions to Implement Compounding Quality Act[2]

- Outsourcing Facility Registration and Reporting[3]
- Traditional Compounding[4]
- Enhanced Communication with States[5]
- Creation of Advisory Committee[6]
- Nominations for Lists[7]
- Inspections and Enforcement[8]

Policy Documents

- Guidance for Industry on Fees for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug, and Cosmetic Act[9]
- Proposed Rule: Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness[10]
- Final Guidance: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and

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Cosmetic Act (PDF - 85KB)[11]
- Draft Guidance for Industry on Current Good Manufacturing Practice-Interim Guidance for Human Drug Compounding Outsourcing Facilities Under the Federal Food, Drug and Cosmetic Act (PDF - 223KB)[12]
- Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations[13]
- List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Request for Nominations[14]
- Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act Concerning Outsourcing Facilities; Request for Nominations[15]
- Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations[16]
- Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act (PDF - 185KB)[17]
- Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (PDF - 60KB)[18]
- Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (PDF - 107KB)[19]
- Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act[20]

For More Information

- Compounding: Information for Consumers and Health Care Providers[21]
- Historical Pharmacy Compounding Information[22]
- Letters to Stakeholders[23]

Related Information

- Medical Devices: Pharmacy Compounding Systems - Final Guidance for Industry and FDA[24]
- Animal Drugs: FDA Compliance Policy Guide: Compounding of Drugs for Use in Animals (CPG Sec. 608.400)[25]

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Drugs

Compounding and the FDA: Questions and Answers

On this page:

1. What is "compounding"?

In general, compounding is a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.

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2. Is combining two or more drugs considered compounding?

Yes, compounding includes the combining of two or more drugs.

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3. Why do some patients need compounded drugs?

Sometimes, the health needs of a patient cannot be met by an FDA-approved medication. For example:

- if a patient has an allergy and needs a medication to be made without a certain dye; or
- if an elderly patient or a child can't swallow a pill and needs a medicine in a liquid form that is not otherwise available.

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4. Are compounded drugs approved by the FDA?

Compounded drugs are not FDA-approved. This means that FDA does not verify the safety, or effectiveness of compounded drugs. Consumers and health professionals rely on the drug approval process to ensure that drugs are safe and effective and made in accordance with Federal quality standards. Compounded drugs also lack an FDA finding of manufacturing quality before such drugs are marketed.

Generally, state boards of pharmacy will continue to have primary responsibility for the day-to-day oversight of state-licensed pharmacies that compound drugs in accordance with the conditions of section 503A of the FDCA[9], although FDA retains some authority over their operations. However, outsourcing facilities that register under section 503B are regulated by FDA and must comply with CGMP requirements and will be inspected by FDA according to a risk-based schedule.

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5. What are the risks associated with compounded drugs?

There can be health risks associated with compounded drugs that do not meet federal quality standards. Compounded drugs made using poor quality practices may be sub- or super-potent, contaminated, or otherwise adulterated. Additional health risks include the possibility that patients will use ineffective compounded drugs instead of FDA-approved drugs that have been shown to be safe and effective.

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6. Who regulates and inspects facilities that compound drugs?

Generally, state boards of pharmacy will continue to have primary responsibility for the day-to-day oversight of state-licensed pharmacies that compound drugs in accordance with the conditions of section 503A of the FDCA[12], although FDA retains some authority over their operations. For example, the adulteration or misbranding of drugs compounded under section 503A, or false or misleading statements in the labeling or advertising of such drugs, may result in violations of Federal law. Firms that register with FDA as "outsourcing facilities" under section 503B will be regulated by FDA and inspected by FDA according to a risk-based schedule.

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7. What is FDA doing to implement the new law?

Please see FDA implementation of the Compounding Quality Act[14].

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8. **What is an outsourcing facility?**

The Drug Quality and Security Act, signed into law on November 27, 2013, creates a new section 503B in the FDCA. Under section 503B, a compounder can become an "outsourcing facility." The law defines an "outsourcing facility" as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B.

An outsourcing facility can qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from current good manufacturing practice (CGMP) requirements. Outsourcing facilities:

- must comply with CGMP requirements;
- will be inspected by FDA according to a risk-based schedule; and
- must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

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9. **How does an outsourcing facility register with FDA?**

FDA has issued draft guidance on registering and reporting for those entities that intend to register as outsourcing facilities.

They should register using FDA's electronic drug registration system or by sending an email to FDA's drug registration and listing staff with the required registration information. FDA will provide assistance to outsourcing facilities that need assistance with the electronic registration system. FDA is also providing an interim process that registered outsourcers may use to provide information about the products that they make under the reporting provisions of the new law.

In the future, FDA plans to makes necessary modifications to its electronic listing system to accommodate the information outsourcing facilities must provide. The interim provisions provide an Excel spreadsheet format that an outsourcing facility may use to provide the necessary information.

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10. **What happens to compounders who conduct outsourcing operations but do not register with FDA?**

If a compounder does not register with FDA as an outsourcing facility, it will not qualify for the section 503B exemption from the FDA approval requirements and the requirement to label products with adequate directions for use. If that compounder also fails to satisfy the conditions for the section 503A exemption, it will be subject to all of the requirements of the FDCA that are applicable to drugs made by conventional manufacturers, including the new drug approval, adequate directions for use, and CGMP requirements.

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11. **How will FDA deal with compounders that do not register as outsourcers but fail to comply with the requirements of section 503A of the FDCA?**

If a compounded drug does not qualify for the exemptions under either section 503A or 503B of the FDCA, it would be subject to all of the requirements of the FDCA that are applicable to drugs made by conventional manufacturers, including the new drug approval, adequate directions for use, and CGMP requirements.

FDA issued a draft guidance that describes FDA's intention with regard to the provisions of section 503A that require rulemaking or other action to implement. This draft guidance also describes the provisions of the law that are applicable to compounded drugs that do not qualify for the exemptions described above, and the other provisions of the FDCA applicable to compounded drugs regardless of whether they qualify for the exemptions under section 503A.

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12. **Does the Drug Quality and Security Act (DQSA) cover the compounding of animal drugs?**

No, the DQSA does not cover animal compounding. For questions about animal drug compounding, contact FDA's Center for Veterinary Medicine at CVM_ExecSec@cvm.fda.gov.

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Related Information

- Compounding[20]

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Drugs

FDA Implementation of the Compounding Quality Act

Outsourcing Facility Registration and Reporting

The new law allows an entity that compounds sterile drugs to register as an outsourcing facility. Once registered, an outsourcing facility must meet certain conditions in order to be exempt from the FDCA's approval requirements and the requirement to label products with adequate directions for use. Under the new law, the drugs must be compounded in compliance with CGMP by or under the direct supervision of a licensed pharmacist in a registered facility (section 503B(a)). The outsourcing facility must also report specific information about the products that it compounds, including a list of all of the products it compounded during the previous six months, and information about the compounded products, such as the source of the ingredients used to compound (section 503B(3)). In addition, the outsourcing facility must meet other conditions described in the new law, including reporting adverse events and labeling its compounded products with certain information (section 503B(b)(5) and section 503B(a)(10)).

Under the new law, an outsourcing facility[1] will not be considered registered until it has paid the applicable annual registration fee (see section 744K(g)(3)(A)). An outsourcing facility may register without paying a fee until September 30, 2014, however, because fees are not required until October 1, 2014. In addition, the new law requires that outsourcing facilities register and report their products to FDA electronically unless the Secretary grants a request for a waiver of such requirement because use of electronic means is not reasonable for the person requesting the waiver (section 503B(b)). FDA has issued draft guidances[2] on registering and reporting for those entities that intend to register as outsourcing facilities.

Traditional Compounding

Drugs produced by compounders that are not registered as outsourcing facilities must meet the conditions of section 503A to qualify for the exemptions specified in that section. Even if the conditions of section 503A are met, the compounded drugs are only exempt from those provisions of the FDCA listed above. All other applicable provisions of the FDCA remain in effect for compounded drugs, even if the conditions in section 503A are met. For example, a compounded drug cannot be contaminated or made under insanitary conditions (see sections 501(a)(1) and 501(a)(2)(A)). And if a compounded drug does not qualify for the exemptions under either section 503A or 503B of the FDCA, the compounded drug would be subject to all of the requirements of the FDCA that are applicable to drugs made by conventional manufacturers, including the new drug approval and adequate directions for use requirements.

FDA has issued for public comment a draft guidance[3] that describes FDA's intention with regard to the provisions of section 503A that require rulemaking or other action to implement. This draft guidance also describes the provisions of the law that are applicable to compounded drugs that do not qualify for the exemptions described above, and the other provisions of the FDCA applicable to compounded drugs regardless of whether they qualify for the exemptions under section 503A.

FDA also has announced the withdrawal of CPG 460.200, *Pharmacy Compounding*, issued in 2002, and the guidance "*Enforcement Policy During Implementation of Section 503A of the Federal Food, Drug, and Cosmetic Act,*" published in November 1998. Although we have withdrawn these guidance documents, under the DQSA, section 503A immediately applies nationwide. FDA plans to provide further information at a later date about how we intend to interpret certain provisions of section 503A.

Enhanced Communication with States

The new law requires the Secretary to establish a mechanism to receive submissions from state boards of pharmacy concerning certain actions taken against compounding pharmacies or expressing concerns that a compounding pharmacy may be acting contrary to section 503A. This section is to be implemented in consultation with the National Association of Boards of Pharmacy (NABP). In addition, state boards of pharmacy must be notified when the Secretary receives certain state submissions or makes a determination that a compounding pharmacy is acting contrary to section 503A.

Until further information regarding how this process will work can be provided, States that wish to provide this information to FDA should submit the information by email to the following mailbox: StateCompounding@fda.hhs.gov

The agency intends to follow up with states that provide this information and to notify other states about the receipt of the information in accordance with the new law.

Other Actions

Creation of Advisory Committee

Sections 503A and 503B require the creation of and consultation with a Pharmacy Compounding Advisory Committee before issuance of certain regulations required by the law. FDA has published in the *Federal Register* notices soliciting nominations for Committee members.

- Pharmacy Compounding Advisory Committee[4]
- Requests for Nominations: Pharmacy Compounding Advisory Committee[5]
- Requests for Nominations: Pharmacy Compounding Advisory Committee Voting Members[6]
- Requests for Nominations: Pharmacy Compounding Advisory Committee, Nonvoting Industry Representatives[7]
- Requests for Nominations; Pharmacy Compounding Advisory Committee, Nonvoting Industry Representatives; Reopening of Notification Period[8]

Nominations for Lists

Sections 503A and 503B contain various requirements for FDA to develop lists of drugs that may or may not be compounded and lists of bulk drug substances that may be used to compound. Specifically, section 503A specifies that to qualify for the exemptions under section 503A, a compounder may only use bulk drug substances to compound if:

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- The bulk drug substances comply with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph, if one exists;
- If such a monograph does not exist, the drug substance(s) is a component of an FDA-approved human drug product; or
- If such a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it appears on a list of bulk drug substances for use in compounding developed by FDA through regulation (section 503A(b)(1)(A)(i) of the FDCA).

Section 503B specifies that an outsourcing facility may only compound with a bulk drug substance which appears on an FDA-established list of bulk drug substances for which there is a clinical need or which are on FDA's drug shortage list.

Sections 503A and 503B also prohibit compounding drugs that are on a list of drugs that present demonstrable difficulties for compounding, as published by FDA.

FDA has published notices[9] requesting nominations for these three lists.

In addition, 21 CFR 216.24 contains a list of drugs that may not be compounded because they have been withdrawn or removed from the market because the drugs or components of the drugs have been found to be unsafe or not effective. Compounders may not compound any drugs that appear on this list. FDA intends to issue a proposed rule to update this list by amending section 216.24 and will apply the list to compounders seeking to qualify for the exemptions in either section 503A or section 503B. Nominations for this list can be submitted in comments on the proposed rule.

Inspections and Enforcement

FDA intends to continue proactive and for-cause inspections of compounding pharmacies, and FDA plans to take aggressive action, including enforcement actions, as appropriate to protect the public health.

For the past year, since the fungal meningitis outbreak began, FDA has been conducting inspections of compounding pharmacies for cause (in response to serious adverse event reports and reports of quality problems) and proactively to identify pharmacies with deficient sterile compounding practices. Using a risk-based model, we identified 29 firms for priority inspections focused on their sterile processing practices. FDA identified secondary firms associated with two of these inspections, for a total of 31 firms. Between October 1, 2012 and October 31, 2013, FDA completed 42 for-cause inspections in addition to the 31 proactive inspections.

When we identified problems during any of these inspections, we issued a Form FDA-483[10] listing our inspection observations. We have issued a Form FDA-483 at the majority of the inspections we have conducted since the fall of 2012. As these Form FDA-483s reflect, we observed serious quality problems, including contaminated products and sterile practices that create a risk of contamination. Numerous recalls[11] of sterile products have been conducted, and numerous pharmacies chose to stop sterile compounding after we identified problems with their sterile compounding processes. New problems continue to be identified at compounding pharmacies across the country, and FDA intends to continue its inspection and enforcement efforts to address these problems, using currently available resources. For oversight of outsourcing facilities registered under section 503B, FDA will use fees assessed and collected from those facilities in accordance with the law to supplement other agency resources.

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USP U.S. Pharmacopeial Convention

Compounding

1. Is USP considering revisions to General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations?*
   Yes, the Compounding Expert Committee began the revision process for General Chapter <797> in July 2010. Additionally, the Expert Committee formed an Expert Panel in April 2013. When the revisions are completed, the proposed changes will be posted in the Pharmacopeial Form (PF) for public comment. PF is a free on-line resource published every two months and is a forum for stakeholders to submit their comments on the proposed changes. The PF comment period is 90 days.

2. Can the table of "Beyond-Use Date (BUD) by Type of Formulation" under the section General Guidelines for Assigning Beyond-Use Dates in <795> *Pharmaceutical Compounding – Nonsterile Preparations* be applied to sterile preparations?
   No, General Chapter <795> is specific for nonsterile preparations. Footnote (a) under the table indicates that the table represents the maximum Beyond-Use Date (BUD) for compounded nonsterile preparations in the absence of stability information. A Revision Bulletin for <795> was posted on November 22, 2013 (official January 1, 2014) to further clarify this.

3. What are the considerations for assigning a BUD for a compounded sterile preparation?
   When assigning a BUD for a compounded sterile preparation, the compounder must consider both the *sterility* and *stability* of the preparation.

4. Is there a difference between testing stability with a strength (potency) or a stability-indicating method?
   Yes, a strength (potency over time) test determines the amount of active ingredient in a preparation, however, it may not be able to separate the inactive ingredient from its degradation products and impurities for quantitation depending on the analytical methods used for the test. A stability-indicating method will be able to quantitate the active ingredient and its degradation products or related impurities in the preparation by separating the inactive ingredient from its degradation products and impurities, and to show a change in the concentration of the active ingredient with increasing storage time. A stability-indicating method is used to determine stability of a drug and used to establish the BUD. (See article, "Strength and Stability Testing for Compounded Preparations.")

5. Does General Chapter <797> require me to test according to <51> *Antimicrobial Effectiveness Testing* when compounding a multiple-dose container that contains a preservative?
   Currently, General Chapter <797> provides minimum practice and quality standards for compounding sterile preparations, but it does not contain specific requirements for compounding multiple-dose containers, such as the need for a preservative, nor requirements for testing, labeling, and container closures for compounded multiple-dose containers. Future revisions of <797> may contain more specific standards for compounding multiple dose containers.

6. Why is General Chapter <51> *Antimicrobial Effectiveness Testing* mentioned in <797>?
   The reference to General Chapter <51> under the section Single-Dose and Multiple-Dose Containers in <797> is provided for informational purposes to refer to commercially manufactured sterile multiple-dose containers. The reference to <51> serves to indicate the source of the 28-day BUD after initially entering or opening (e.g., needle-punctured) a multiple-dose container, unless otherwise specified by the manufacturer.

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U.S. Pharmacopeial Convention

General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings

The Compounding Expert Committee is proposing new General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings. The purpose of the new proposed General Chapter is to provide standards to protect personnel and the environment when handling hazardous drugs (HDs). Each year, approximately 8 million U.S. healthcare workers are potentially exposed to HDs. The new proposed General Chapter defines processes intended to provide containment of HDs to as low as a limit as reasonably achievable.

The new proposed General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings addresses:

- Standards that apply to all personnel who compound HDs preparations and all places where HDs are prepared, stored, transported, and administered
- Receiving, storing, compounding, dispensing, administering, and disposing of both nonsterile and sterile products and preparations
- Altering, counting, crushing, and pouring HDs.

General Chapter <800> will be published in Pharmacopeial Forum (PF) 40(3) [May–Jun. 2014]. The General Chapter is being presented in advance of publication of PF 40(3) to allow additional time for public review and comment. To ensure that all comments are addressed, please indicate the line number(s) corresponding to your comments and submit to CompoundingSL@usp.org. The General Chapter is available with line number at the link below. Comments will be accepted until July 31, 2014, the end of the comment period for PF 40(3).

- <800> Hazardous Drugs—Handling in Healthcare Settings

Proposed General Chapter <800> applies to all personnel who are involved in handling HDs including but not limited to, healthcare practitioners and staff, occupational health and safety specialists, and human resources. An overview of the proposed General Chapter is available below:

- Proposed Chapter 800 Webinar Recording*
- Slides for proposed Chapter 800 Webinar

Should you have any questions, please contact the Healthcare Quality Standards staff at CompoundingSL@usp.org.

*WebEx ARF Player is required to listen to this recording. The program can be downloaded at: https://uspmeetings.webex.com/client/T29L/nbr2player.msi

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