

Compounding Update: A Focus on USP <797>

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This Talk Will Cover...

- Review noncompliance and infractions that get pharmacies in trouble
- Review the differences between compounding and manufacturing
- Review USP Standards

History of Pharmacy Compounding in the U.S.

- In the past, Compounding was Pharmacy
- 1900s gave way to commercially prepared pharmaceuticals
- Many strengths/dosage forms available
- Economics changed all that
- Limited strengths/dosage forms
- “One Size Fits All” approach

Extent of Compounding in the U.S.

- More than 70% of pharmacies report they do some compounding (NCPA 2006)
- Virtually all hospitals do compounding
- Estimated 10% of all prescriptions and medication orders are compounded
- \$22-25 billion dollars per year

How Did We Get Here?

- Loss of manufactured drug products
- Growth of compounding
- Office use
- Drug shortages
- Other

NECC Infractions

- Non patient-specific
- No patient histories, DURs, as required by the Massachusetts BOP
- Distribution prior to receiving sterility testing lots
- Final sterilization did not follow proper standards
- Autoclaves not validated
- Powder hoods in clean rooms?
- Tacky mats visibly soiled
- Leaking boiler adjacent to the clean room

NECC Infractions

- Lack of Standard Operating Procedures
- Lack of training of pharmacists
- Lack of training of technicians
- Pharmacists oversight inadequate

NECC Infractions in Aseptic Compounding

- Deficient environmental monitoring in aseptic processing areas
- Equipment not maintained appropriately to prevent contamination
- Contamination prevention procedures for sterile preparations do not include adequate validation of the sterilization process
- Filtered air supply is deficient in aseptic processing areas

NECC Infractions in Aseptic Compounding

- No written standards or methods for sterilization or testing for pyrogenic properties
- Clothing is inappropriate for duties performed
- Preparation testing does not determine conformance to specifications and ingredient strength
- No written test to assess stability characteristics of drug preparations

NECC Infractions in Aseptic Compounding

- Routine calibration not performed on mechanical and electronic equipment
- Preparations not stored in recommended temperature or light
- QC personnel lack authority to fully investigate errors
- Building construction does not facilitate cleaning, maintenance and proper operations

The Fallout

- Congress
 - Representatives making noise
 - Introduction of proposed bills
- State Boards
 - Idaho Board of Pharmacy
- Agencies
 - PCAB

Congressional Activities

- **Markey Bill**
 - Introduced by Ed Markey (D-MA) on Nov. 2, 2012
 - Verifying Authority and Legality in Drug (VALID) Compounding Act of 2012
 - cites a “regulatory gap” and the need to “strengthen FDA’s oversight.”
- **Delauro and Lowery, H.R. 6638**
 - Introduced by U.S. Reps. Rosa DeLauro (D-Conn) and Nita Lowery (D-N.Y.)
 - Supporting Access to Formulated and Effectiveness (SAFE) Compounded Drugs Act
 - The proposed legislation would amend the Food, Drug, and Cosmetic Act to require notification to patients that a compounded drug has been prescribed, product labeling as a “non-FDA approved compounded drug product,” registration for drug compounders, training, the establishment of advisory committees, and reporting

Congressional Activities (cont'd)

- **Bill S.959: Pharmaceutical Quality, Security, and Accountability Act**
 - A bill to amend the Federal Food, Drug and Cosmetic Act with respect to compounding drugs
 - Subjects independent community pharmacists to broadly expanded FDA authority that could jeopardize patient access to medications
 - It would require community pharmacists to notify FDA every time they compound a medication that is in shortage
- **H.R. 3089, The Compounding Clarity Act**
 - Sponsored by U.S Reps. Morgan Griffith (R-Va.), Gene Green (D-Texas) & Diana DeGette (D-Colo.)
 - Preserves state board of pharmacy oversight of the majority of independent community pharmacies that compound
 - If a pharmacy prepares sterile medications for office use, ships those medications across state lines, and such medications account for >5% of drugs it produces, then the compounding provide would fall under the legislation's newly established category of "outsourcing facilities" subject to FDA regulation

What is Compounding?



USP Compounding Definition

- “The preparation, mixing, assembling, altering, packaging, and labeling of a drug or device or other article, as the result of a practitioner’s order or in anticipation of such an order based on routine, regularly observed prescribing patterns.”

Pharmaceutical Compounder

- A **pharmaceutical compounder** is involved in other activities concerned with the preparation of drugs as previously defined and is regulated by the individual state boards of pharmacy
- **FDA**-Compounding involves a physician-patient-pharmacist relationship for each prescription

USP Manufacturing Definition

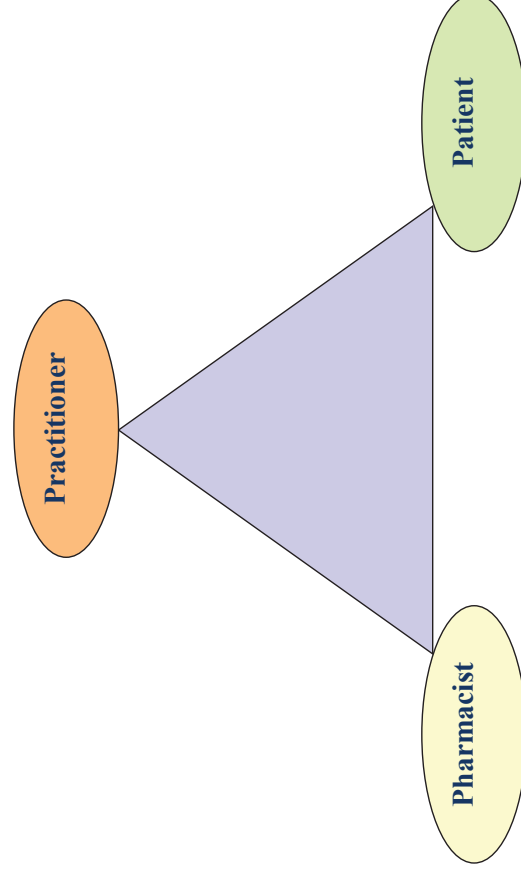
- “The production, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction of the drug from substances of natural origin or by means of chemical or biological synthesis.”

Pharmaceutical Manufacturer

- A **pharmaceutical manufacturer** is an entity that produces a drug or drug product for human or veterinary use that
 - Has been approved by the FDA through the NDA, ANDA or other appropriate regulatory channels, or
 - Is allowed by the FDA to produce a product that is not FDA approved, as in the case of pre-1938 drugs, veterinary, and over-the-counter drugs, etc.
- A pharmaceutical manufacturer is registered with and regulated by the FDA

How does compounding differ from manufacturing?

THE TRIAD



Compounding vs. Manufacturing

- Manufacturing
 - No specific patient in mind when drug is produced
 - Has prescribers matching patients to the product available
 - Economic considerations limit choices in drug dosages and dosage forms
- Compounding
 - Making the formula match the patient's needs
 - Administering the drug to the sight of action in the most effective dosage form available

GMPs, GCPs, Standards and Regulatory Issues

- Good Manufacturing Practices (GMPs)
- Good Compounding Practices (GCPs)
- USP Standards
- State Boards of Pharmacy
 - Laws
 - Regulations
- Congressional Activities



The United States Pharmacopeia and National Formulary (USP-NF)

- 3 volume collection
 - Drug information for the healthcare professional
 - Advice for the patient
 - Approved drug products and legal requirements
- USP's goal is to have monographs in USP-NF for all FDA-approved drugs
- USP also develops monographs for therapeutic products not approved by FDA
 - Pre-1938 drugs
 - Dietary supplements
 - Compounded preparations



COMPOUNDING

The USP on Compounding General Chapters

USP Chapters	Content
<797>	Pharmaceutical Compounding – Sterile Preparations
<795>	Pharmaceutical Compounding – Nonsterile Preparations
<1160>	Pharmaceutical Calculations in Prescription Compounding
<1163>	Quality Assurance in Pharmaceutical Compounding
<1176>	Prescription Balances and Volumetric Apparatus
<1191>	Stability Considerations in a Dispensing Practice
<1151>	Pharmaceutical Dosage Forms
<51>	Antimicrobial Effectiveness Testing
<71>	Sterility Tests
<85>	Bacterial Endotoxins Test

Good Compounding Practices

- <1075> Good Compounding Practices
 - Guidance for applying GCPs for compounded formulations
 - Now incorporated into
 - <795> and <797>
 - Input also provided by other chapters

USP-NF Chapters in Development

- Compounding with Hazardous Drugs
 - Reduce the potential harmful effects on healthcare workers
- Compounding for Clinical Drug Studies
 - Materials management, quality assurance program, assigning BUD, packaging, labeling

What is USP <797>?

- A chapter of the United States Pharmacopeia
 - National Formulary (USP-NF)
- Established best practices and regulations for the production of compounded sterile preparations
- USP <797> was designed specifically to be an **enforceable** set of standards

Who Wrote USP <797>

- United States Pharmacopeia Compounding Committee
- Center for Disease Control
- Food and Drug Administration
- Draft reviewed by members of the USP and industry



Where Does USP <797> Apply?

- Any facility producing CSPs and any personnel who perform compounding are subject to regulation by USP <797>
 - Hospitals, community pharmacies, home infusion services, ambulatory care services, nursing homes, practitioner's offices, etc.
- Many states have regulations
 - Each state varies

What is a Compounded Sterile Preparation (CSP)?

- “Compounded biologics, diagnostics, drugs, nutrients, and radio-pharmaceuticals...that must be sterile when they are administered to patients, “and “manufactured sterile products that are either prepared strictly according to the instructions appearing in the manufacturers’ approved labeling...or prepared differently than published in such labeling”



<797> Pharmaceutical Compounding – Sterile Environmental Quality and Control

- Facility design, environmental and engineering controls; environmental testing and cleaning procedures; and personnel garbing, training and testing requirements.

Area	ISO Class
Workbench	ISO Class 5
Buffer Area	ISO Class 7
Ante Room	ISO Class 8

<797> Pharmaceutical Compounding – Sterile Three Most Important Factors Guaranteeing Sterility

- **Proper hand hygiene and garbing**
 - Shoe covers, head/facial hair cover, facial mask/eye shields, perform hand cleansing procedures, gown, waterless alcohol-based surgical scrub, sterile powder free-gloves
- **Proper aseptic technique by compounding personnel**
- **Absence of surface contamination**
 - Cleaning hood at beginning of shift, before every new batch, every 30 min during compounding, spills, or obvious contamination

<797> Pharmaceutical Compounding – Sterile Microbial Contamination Risk Levels

Risk Level	Definition
Immediate-Use	ISO Class 5 environment is NOT required. Preparations are for emergency use or immediate patient administration. Must use within 1 hour.
Low-Risk	ISO Class 5 air quality environment or better, from sterile ingredients, products, components, and devices. No more than 3 packages of sterile product can be used, and not more than 2 entries into any one of the sterile containers.
Medium-Risk	Multiple individual or small doses of sterile products are combined, administered to multiple patients or to one patient on multiple occasions.
High-Risk	Non-sterile product is used, final prep has to be sterilized.

<797> Pharmaceutical Compounding – Sterile Verification of Compounding Accuracy and Sterility

- Quality of CSP is directly related to achieving the goal of purity, potency, and sterility
- USP Chapters <71>, <1035>, <731>, <1160> and <1211> are used for guidance on methods of sterilization and compounding accuracy and validation
- Filters used must undergo integrity testing per manufacturer
- Proof that the end-products are accurate and sterile is required

<797> Pharmaceutical Compounding – Sterile Beyond-Use Dates

Risk Level	Definition
Low-Risk	Room Temp: 48 hours Refrigerated: 14 days Frozen: 45 days
Medium-Risk	Room Temp: 30 hours Refrigerated: 9 days Frozen: 45 days
High-Risk	Room Temp: 24 hours Refrigerated: 3 days Frozen: 45 days

Multi-dose vials is 28 days after entering with a needle, or puncturing the stopper, unless specified by the manufacturer.
Single use containers is 6 hours after the first entry into the vial or 1 hour is not in an ISO Class 5 environment.

<797> Pharmaceutical Compounding – Sterile Environmental Sampling - Types

- Environmental Sampling
 - Non-viables
 - Viables
 - Air
 - Surface
 - Gloved finger tip
 - Media fill test

<797> Pharmaceutical Compounding – Sterile Non-Viable Particle Air Sampling

- Once every 6 months or when Primary Engineering Controls (PEC) are moved or altered
- In response to major servicing of the area around the PEC
- Each ISO 5 area, ISO 7 buffer area and ISO 8 ante area. All separate areas must be tested. ISO 14644
- Document location, collection method, frequency of sampling, volume, and time of day relative to compounding activities

<797> Pharmaceutical Compounding – Sterile Viable Particle Air Sampling

- Once every 6 months or when Primary Engineering Controls are moved or altered or serviced
- TSA or soybean casein digest agar for bacteria
- Malt Extract Agar (MEA) or Sabouraud Dextrose Agar for fungi; **only required for high risk compounding**

<797> Pharmaceutical Compounding – Sterile Viable Particle Surface Sampling

- No mandatory sampling period, once every six months is recommended
- Contact plates are the preferred method, swab sampling is permitted
- TSA (MEA for fungi) with lecithin or polysorbate 80
- **Fungi sampling only for high risk compounding**

<797> Pharmaceutical Compounding – Sterile Gloved Fingertip Sampling

- Used to evaluate worker garbing technique
- Once a year for low and medium risk compounding, every 6 months for high risk compounding
- All new workers must perform 3 successful glove tests prior to beginning compounding work
- Usually performed by the on site supervisor

<797> Pharmaceutical Compounding – Sterile Media Fill Test

- Designed to test ability of worker, procedure and equipment to produce sterile product
- Replicates entire compounding process using soybean casein digest media in place of drugs
- Annual testing for low and medium risk compounding, once every 6 months for high risk compounding
- New employees required to complete one test prior to beginning compounding

<797> Pharmaceutical Compounding – Sterile Action Levels

ISO Class	≥ 0.5 m particles/m ³	Viable Airborne (cfu*/m ³)	Viable Surface ** (cfu/contact plate)
5	3,520	>1	>3
7	352,000	>10	>5
8	3,520,000	>100	>100

- Any airborne cfu found in ISO 5, 7, or 8 must be identified to the genus level (species recommended)

* CFU – Colony Forming Units

** contact plate areas vary from 24-30 cm². when swabbing is used in sampling, the area covered should be at least 24 cm² but no larger than 30 cm²

<797> Pharmaceutical Compounding – Sterile Why Identify?

- Some organisms are pathogenic enough that they cannot be tolerated in a clinical environment at any concentration (MRSA, Acinetobacter)
- Genus identification is useful, but cannot distinguish between harmful and benign species within the same genus group
- Without knowing the species of an organism, all cfu from a genus that contains known pathogens have to be treated as if they are pathogens

<797> Pharmaceutical Compounding – Sterile Physical Factors

- Building Changes or Construction
- Primary Engineering Controls
 - Are they working properly?
 - Have they been properly maintained?
- Proper Cleaning
 - Check records
 - Cleaning agent types?
 - Rotation?
 - Proper cleaning tools?
 - Are materials in lab capable of being cleaned?

<797> Pharmaceutical Compounding – Sterile Physical Factors

- Environmental Conditions
 - Temperature, humidity, seasons, weather, etc.
- Building Changes or Construction
- Laboratory Workflow
 - Traffic areas
 - High risk areas (windows, doors, vents, equipment)
- Process and Materials
 - Are materials moved into and out aseptically?
 - Are supplies cleaned as they are brought into the

<797> Pharmaceutical Compounding – Sterile Remediation - Cleaning

- Is the proper cleaning agent being used for the task? Not all agents are effective against all viable particles.
- Is the cleaning agent being used properly?
- Is the cleaning agent being stored under proper temperature and light conditions?
- Has the cleaning agent expired?
- Are cleaning agents being rotated?

<797> Pharmaceutical Compounding – Sterile Remediation – Cleaning (cont'd)

- Are cleaning tools non-shedding and dedicated for the clean room only?
- Be aware that cleaning activities can impact the work environment
- Cleaning schedules
 - ISO 5: start of each shift, prior to compounding each batch or every 30 min, when obvious spills or contamination are suspected
 - ISO 7 and 8: floors and work surfaces daily
 - Areas around hoods and isolators daily
 - Storage shelves, walls and ceilings monthly
 - Storage sites as needed

<797> Pharmaceutical Compounding – Sterile Documentation

- Primary Engineering Controls
 - Calibration certificates
 - Maintenance records
- Investigation records (if involved)
 - Document investigation process
 - Results of investigation
 - Actions to correct issue
 - Results of corrective action
- Training/Testing records (fingertip and media fill)

<797> Pharmaceutical Compounding – Sterile First Steps Toward Compliance

- Determine risk level of the compounding
- Perform gap analysis
 - Compare current pharmacy compounding operations with USP 797
- Develop an action plan
- Evaluate the use of alternative products
- Reassess workload of compounding personnel
- Document performance and quality improvements

Surveying Pharmacies for Compliance with USP Chapters <795> and <797>

- Visit the bathroom
- Look in the refrigerator
- Look around the sink area and work area
- Is there functional linear work surfaces to adequately perform work?
- Waste and Sharp disposal
- Does any equipment have any expired certification stickers

Surveying Pharmacies for Compliance with USP Chapters <795> and <797>

- Surveying for Compliance
 - Who runs the pharmacy?
 - Who oversees the operations?
 - Who has final authority and approval power?
- Ask the pharmacist:
 - What do you do?
 - How do you do the work?
 - Show me how you do it.

Conclusion

- FDA is currently monitoring pharmacy's compliance with chapter 797
- Additional regulatory promulgations could be made to restrict the practice of compounding
- The restriction of compounding ultimately impacts patient care and our profession of pharmacy

Questions?

