Sterile Compounding:
Planning for the Future Landscape

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Learning Objectives

- Describe the overall intent of compounding compliance and the regulations that drive it
- Outline the key elements of a compliant cleanroom that have expected longevity.
- List the 4 main best practice elements of sterile compounding that are likely to become required
- Apply practice specific based analysis to designing a cleanroom

Disclaimer

- Speaker is not a representative of a regulatory body and as such content of this presentation does not constitute regulatory guidance.
- Speaker is not an attorney and therefore content of this presentation does not constitute legal advice.
- Regulations are constantly changing, always be sure to check current enforceable regulations before making licensed practice decisions.

Sterile Compounding Enforcement

The Primary function of a regulatory agency is to protect the ***public.***

See reference No. 5

A data table from THE PEW CHARITABLE TRUSTS | June 2017

U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-17

Update note: This chart was updated in February 2019 to include newly reported adverse events, remove previously listed events following additional investigation, and update information in citations.

Pew's drug safety project has identified 69 reported compounding errors or potential errors associated with more than 1,418 adverse events, including 114 deaths, from 2001 to 2017. However, a 2015 survey found that only 30 percent of states (13 of the 43 that responded) require sterile compounding pharmacies to report serious adverse events.[1] Of the states that require reporting, the type of information that is required to be reported may vary, further contributing to an incomplete picture of adverse events associated with compounded medications. Even in states with strong adverse event reporting requirements, illnesses and deaths caused by compounded drugs are not always linked to the compounding error.[2] Because many such events go unreported, this chart is an underestimation of the number of compounding errors since 2001. Contamination of sterile products was the most common error; others were the result of compounders' miscalculations and mistakes in filling prescriptions.

Drug compounding can be an interstate operation: compounders may prepare medicines in one state and ship them to another. States may encounter oversight challenges if an out-of-state compounder shipping into their jurisdiction is held to a different quality or regulatory standard than in-state compounders. As a result, for each row below, the state where the compounding error or potential error occurred and the state(s) where the adverse event(s) occurred are listed. Harmonized minimum quality standards for anyone who compounds drugs—in any setting—across states would help address challenges in regulating out-of-state compounders and ensure that all compounding meets strong baseline criteria for preparing safe drugs and protecting patients.

Year	Reported cases	Reported deaths	Adverse event(s)	Compounding error	Product	State where compounding error occurred	State(s) where adverse event(s) occurred	Notes

Sterile Compounding Enforcement: Critical Elements

Accuracy

- *5 Rights: the right patient, the right drug, the right dose, the right route, and the right time.*

Quality = Safe & Effective

- *Safety of the patient & public*
- *Quality of the product and quality of the process*

Regulations do not address business decisions

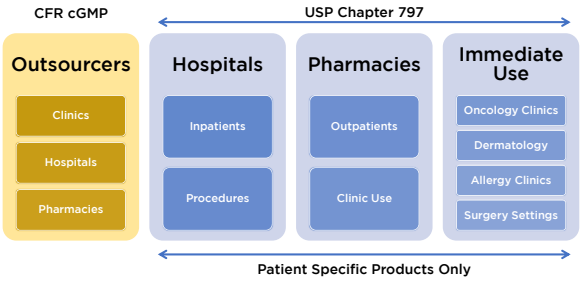
Who enforces sterile compounding?

- FDA
- CMS
- State Board of Pharmacy
- Dept of Public Health (CDPH)

Optional accrediting bodies:

- ACHC - PCAB
- NABP
- PCCA
- Joint Commission

Sterile Compounding Situations



503a versus 503b Pharmacies[1]

This presentation is intended for 503a pharmacy settings

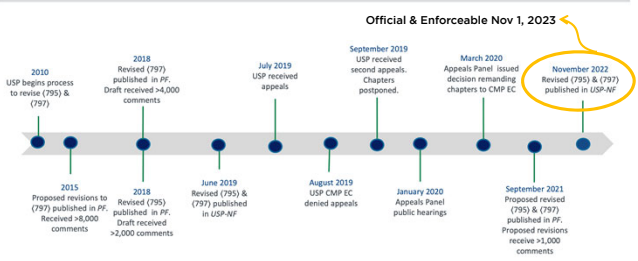
503a compounding pharmacies:

- Not required to register with FDA
- Allowed to produce compounded preparations upon receipt of a valid patient-specific prescription, or in limited quantities in anticipation of future prescriptions.
- Compounded preparations made by a licensed pharmacist or licensed physician
- Compounded in an FDA MOU state or within a licensed pharmacy
- Compounded preparations distributed out of state do not exceed 5 percent of total prescriptions dispensed
- May not use components of drugs removed from the market for being unsafe or ineffective

Federal Regulations & USP 797[2]

- The Food Drug & Cosmetic Act (FDCA) specifically references and mandates USP standards for compounding.
- USP standards are recognized in Section 503A of the 1997 Food Drug Administration Modernization Act, 21 U.S. Code § 353a
- Requires compliance with standards of the USP chapter on pharmacy compounding (<797>)
- USP <797> applies to ALL persons and places performing sterile compounding (doctors, nurses, pharmacists, hospitals, clinics, etc.)

History of Revisions



Regulation of Compounding

Where: Facilities

Who: Trained personnel

How: validated, aseptic processes following standardized procedures

Why: validated quality control

Most Common Regulatory Findings

- Unsupported BUDs
- Lack of sufficient training
- Lack of cleaning documentation
- Missing master formulas/compounding records
- Incomplete compounding records
- Inadequate action plans for out of specification events
- Missing quality control/quality review documentation
- Missing environmental control monitoring

Cleanroom Design

Designing a Cleanroom: Where to start?

What is required by law
- Requires analysis of applicable regulations
- *Minimum* standard

What is best business practice
- Requires analysis of the business needs, workflow, etc.

Designing a Cleanroom

For Compliance
- The What
- Certified Equipment
- Correct Air Supply
- Correct Cleaning process

Ex: Your ante room is certifiable to ISO-7

For Workflow
- The Why & How
- Where equipment is placed
- Where & how much air supply
- When to clean & agents to use

Ex: You place your work benches between the hoods nearest return air vents

Designing a Compliant Cleanroom: A Look at Regulatory Trends

- From less garbed to more garbed
- Increasing air quality requirements
- Increasing documentation of quality & faster access to it
- Shorter beyond use dates (BUDs)
- More frequent environmental monitoring
- Increasing specificity in training requirements
- Tighter cleaning controls

MORE LIKE CGMP

Areas of Compounding Compliance

- Physical/Environmental Design
- Quality Validation
  - Training
  - Environmental Monitoring
  - Process Validation
  - Quality Control Testing
- Data Integrity
- Error Investigation & Risk Mitigation

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Physical/Environmental Design

- Ceiling-based HEPA air supply
- Low-on-wall air return vents
- Clean & dirty sides of ante Room
- Hands-free access doors to ISO areas
- ISO-8 area ≥ 20 ACPH
- Only furniture, equipment, materials necessary for compounding allowed & must be low-shedding & cleanable

All of the above are required elements of USP <797> effective Nov 1, 2023[6]

Physical/Environmental Design

Best Practices

- Modular room build
- Dedicated air handler system*
- Separate ante rooms for hazardous (HD) & non-HD
- Perforated flat grates > louvered*
- Thermoplastic polyester surfaces (ex. Acrovyn)
- Medical grade stainless steel work surfaces
- Ergonomic considerations in the design

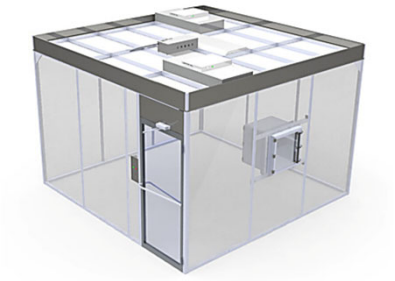
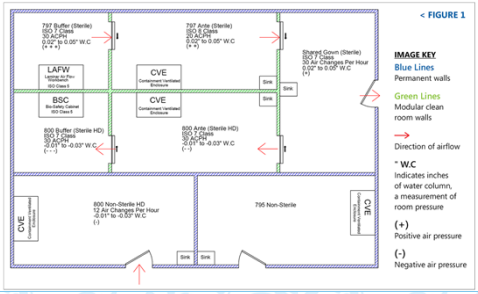


Image courtesy of Sapphire Cleanrooms

Example Floor Plan

Image courtesy of: https://pccarx.com/Blog/important-considerations-for-clean-room-design-rssid



Physical Design:
Primary Engineering Controls

- LAFW > RABS
- Horizontal flow LAFW are ideal for most settings
- Top pre-filter housing on PECs
- Class II A2 BSCs with thimble connection are the best fit for 503a IV compounding
- 4-ft LAFW is smallest practical size
- Consideration to outlets, cord holes, and inside mounted items

For description of BSC types:
https://www.ehs.washington.edu/biological/biological-safety-cabinets

Images courtesy of NuAire

Physical/**Environmental Design**

- Facility must develop procedures for environmental sampling
  - Diagram of sampling areas
  - Frequency & size of samples
  - Time of day to collect
- Sampling plan must be unique to the facility
  - Include highest risk areas
  - Include areas representative of general conditions

All of the above are required elements of USP <797> effective Nov 1, 2023[6]

Physical/**Environmental Design**

Best Practices

- Keep set # of high traffic sampling areas; rotate a selection of other sampling areas*
- For dynamic sampling, rotate the compounder (and document who)
- Built in air sampling tubing for non-viable
- Viable sampling in suspected turbulent or dead air zones
- Resample post OOS remediation*

All of the above are required elements of USP <797> effective Nov 1, 2023[6]

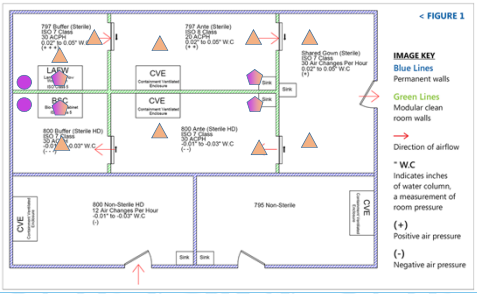
Example Sampling Plan

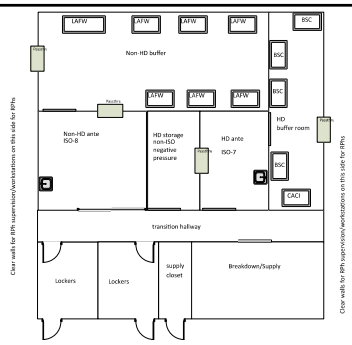
Image courtesy of: https://pccarx.com/Blog/important-considerations-for-clean-room-design-rssid

Air sample

Surface sample

Both





Cleanroom Processes

Areas of Compounding Compliance

- Physical/Environmental Design
- **Quality Validation**
  - Training
  - Environmental Monitoring
  - Process Validation
  - Quality Control Testing
- Data Integrity
- Error Investigation & Risk Mitigation

Quality Validation

- **Training**
  - Must cover USP listed topics & all tasks performed at the facility
  - Must be both didactic & practicum, and be validated (i.e. tested)
  - Trainers should be independently externally trained
- **Environmental Monitoring**
  - Viable air sampling at least every 6 months for Cat 1 & 2 CSP
  - Viable surface sampling at least monthly for Cat 1 & 2 CSP[6]
  - Clearly defined investigation & remediation plan

[6] USP required effective Nov 1, 2023

Quality Validation

- **Process Validation**
  - Media Fills every 6 months (Cat 1 & 2); every 3 months (Cat 3)[6]
  - Must have COA that media supports microbial growth
  - Gloved Fingertip Testing (GFT) must follow Media Fill
  - Must simulate most difficult and challenging procedures
- **Quality Control Testing**
  - No USP 797 requirement for random annual product testing
  - CA BOP has current requirement for at least annual sterility & potency testing[7]

[6] USP required effective Nov 1, 2023

Aren't Policies & Procedures Enough?

Would you….?

- Fly on a plane with a pilot that has only read a manual?
- Take your car to a mechanic that has never actually worked on a car but watched YouTube videos on how?
- Get surgery from a doctor that hasn't been passed their fellowship yet?
- How about get infused an IV made by someone whose proficiency was never validated by a highly trained qualifier?

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Data Integrity

- 21 CFR Part 11 applies to compounding records: requires digital records to be essentially un-editable
  - Ex. An Excel file would not be a compliant record keeping method
  - A dispensing software intended for sterile compounding is best choice
- Digital signatures/validation must also be un-editable
- Records should be traceable by data category: internal lot, manufacturer lot, ingredient, personnel involved, equipment serial number used, date prepared
- Any "correction" to a record must be accompanied by a clear and rationale reason for the needed correction, especially if the CSP is administered.

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Error Investigation & Risk Mitigation

- All testable outcomes have the potential for an "out of specification result."
- All "out of specification results" must be investigates and remediated.
- A facility must have their investigation and remediation processes well described in their policies & procedures including documentation process.
- Remediation categories:
  - Training
  - Processes, including cleaning
  - Physical Environment

Error Investigation & **Risk Mitigation**

- People are the #1 risk creators in compounding[9]
- Equipment can break, but humans make mistakes
- Human behavior is the most common cause of failed environmental monitoring
- Most reported adverse events from sterile compounding products can be traced back to a human behavior.[4]

ISMP Most Common Sterile Compounding Med Errors

- Incorrect dose or concentration (58%)
- Incorrect base solution (51%)
- Incorrect base solution volume (43%)
- Issue or error (including omission) with labeling of a CSP (41%)
- Incorrect reconstitution of a drug (volume or diluent) (36%)
- Incorrect drug (35%)
- Wrong preparation technique (e.g., improper filtering, wrong tubing) (26%)
- Expired drug, base solution, or CSP (16%)
- Wrong timing (e.g., preparing an antineoplastic on the wrong date) (12%)
- Omission of a drug (5%)
- Examples of other error types reported (7%) include coring of vials on robots, using the wrong port or container, and wrong patient errors.

Cleaning

- EPA-registered one-step germicidal disinfectant cleaner for general disinfecting
- At least monthly use of a Sporicidal Agent (also must be EPA registered for use in cleanroom)
- Sporicidal – destroys bacterial & fungal spores and kills all vegetative microorganisms
- Peroxide & Peracetic acid based-cleaners are the gold standard (added benefit of hazardous decontamination action)[10]

All of the above are required elements of USP <797> effective Nov 1, 2023[6]

Knowledge Assessment

Which of the following is NOT a considered a critical element in enforcement actions related to sterile compounding?

a) Patient safety
b) Public safety
c) CSP quality
d) Cost efficacy

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Knowledge Assessment

Failed environmental monitoring is most commonly traced back to:

a) Contaminated equipment
b) Human behavior
c) Air supply
d) Contaminated cleaning agents

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Knowledge Assessment

The cleanroom setup that is considered by current standards to be most ideal is:

a) a separate ante room for non-hazardous and hazardous compounding
b) a shared ISO-7 ante room for both hazardous and non-hazardous compounding buffer rooms
c) a cSCA for hazardous entered from the non-hazardous buffer room
d) a SCA and cSCA connected via a shared ISO-7 ante room

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Knowledge Assessment

Which type of PEC is considered the best standard for hazardous pharmacy sterile compounding?

a) Class I BSC
b) Class II A1
c) Class II A2
d) Class II B2

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Knowledge Assessment

Which cleaning agent provides the most versatility regarding both disinfection and decontamination?

a) one-step chloride-based germicidal detergents
b) two-step sporicidal gas cleaners
c) one-step peroxide-based sporicidal detergents
d) ammonia-based germicidal cleaners
e) any of the above

Knowledge Assessment

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References

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Thank you!

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