How to Design Your Compounding Cleanroom to Meet the Standards of the FDA and State Boards of Pharmacy

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Today's Regulatory Environment

Compounders today face a confusing regulatory environment in which compliance requirements seem to shift from month to month.

The U.S. Pharmacopeia (USP), the American Society of Health-System Pharmacists (ASHP) and the FDA have introduced diverse and occasionally conflicting regulations, recommendations and enforcement practices for safe compounding of hazardous and non-hazardous drugs. This paper clarifies these guidelines, including the provisions of the newly enacted Drug Quality and Security Act (DQSA): where to find the relevant regulatory prescriptions, where (and to whom) they apply, and how to navigate your way to a compounding cleanroom solution that ensures you meet state and federal certification requirements.

In order to determine which federal regulations apply, a compounding operation must be identified as either a 503(a) traditional compounding pharmacy or a 503(b) outsourcing facility as defined in the DQSA (simplified definition provided below).

<table>
<thead>
<tr>
<th>503(a)</th>
<th>503(b)</th>
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<tbody>
<tr>
<td>Traditional pharmacies that compound sterile medications pursuant to a physician’s order for an identified patient</td>
<td>Outsourcing facilities that compound larger quantities of sterile medications without a prescription or beyond the prescribed amount</td>
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</table>
A 503(a) compounding pharmacy must meet all of the criteria in the Section 503(a) FDA guidance document and adhere to the standards outlined in the FD&C Act (link below); otherwise, registration as a 503(b) outsourcing facility will be required. Primarily subject to state-level oversight, these entities must also comply with all applicable USP standards and State Board of Pharmacy regulations.

- USP <795> applies to all non-sterile compounding
- USP <797> applies to all sterile compounding
- USP <800> applies to all compounding that uses hazardous drugs

(Refer to NIOSH Publication 2014-138 for the complete list of hazardous drugs)

The FDA has published final guidance for compliance with 503(a), along with an explanation of the exemption criteria: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469119.pdf

A 503(b)-registered outsourcing facility must comply with the Current Good Manufacturing Practices (cGMP) mandated by the FDA, which is a system of strict quality control standards modeled after the cGMP of the pharmaceutical manufacturing industry. 503(b) entities must also comply with all applicable USP standards and State Board of Pharmacy regulations.

The FDA has released the following guidance document for determining whether or not to register as a 503(b) entity: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434171.pdf

For the cleanroom design requirements related to 503(a) and 503(b), please refer to the Condensed Compounding Cleanroom Requirements Infographic.

The Gray Area of Enforcement

The DQSA, which contains sections 503(a) and 503(b), became law in November 2013. The Act requires outsourcing facilities to register as 503(b) entities with the FDA if they wish to qualify for certain exemptions and avoid being classified as conventional pharmaceutical manufacturers. The DQSA also gives the FDA the authority to inspect both 503(a) and 503(b) facilities to ensure compliance with the Act’s provisions, especially the implementation of cGMP at registered 503(b) outsourcing facilities.

All 503(b) entities will be inspected by the FDA. 503(a) entities are primarily regulated by the State Boards of Pharmacy, but the FDA can inspect any traditional compounding pharmacy, particularly in response to reported adverse events.
FDA Pressing to Expand Enforcement

Because 503(b) registration is voluntary, Margaret Hamburg, Commissioner of the FDA, sent a Dear Hospital/Purchaser letter in January 2014 encouraging purchasers of compounded medications to require their outsourcing facilities to register with the FDA as a 503(b) entity. Essentially, the FDA has given healthcare purchasers and the State Boards of Pharmacy the responsibility of identifying the unregistered outsourcing facilities and forcing them to comply with the DQSA in order to remain in business.

Although the FDA’s guidance for cGMP compliance has only been published in draft form, outsourcing facilities have already begun registering as 503(b) entities, triggering FDA inspections. Many outsourcing facilities were served with FDA Form 483, a Letter of Warning, that lists all of the federal violations discovered during the inspection. Often these inspections resulted in a compounding pharmacy’s products being classified as adulterated, which had the potential to develop into a complete product recall or a cease-and-desist order.

To clarify the impact of DQSA 503(a) and 503(b), ASHP has published guidelines that explain the expanded regulation of compounding services, with a particular focus on hospital accreditation: http://www.ashp.org/Outsourcing-Compounding-Services

The Timeline for Updating USP Standards Remains a Mystery

To further complicate the regulatory environment, USP is currently in the process of revising their sterile compounding standards (known as USP <797>) to better match the standards at the federal level. Despite a complete reorganization of the chapter and new classifications for CSPs, the most significant change is the development of the stand-alone chapter on hazardous drug compounding called USP <800>, which will clarify some of the ambiguity of USP <797> and incorporate enforceable language. A working draft of USP <800> Hazardous Drugs – Handling in Healthcare Settings was open to public commentary up until May 31 and was posted online available to the public: http://www.usp.org/sites/default/files/usp_pdf/EN/m7808_pre-post.pdf

On November 20, 2015, USP announced that a newly revised General Chapter <800> has been approved and will be published on February 1, 2016, with a delayed implementation date of July 1, 2018, to allow entities more than two years to implement the chapter. The chapter has been revised from the 2014 draft version, and it is important to note that USP has changed some mandatory requirements to recommendations. This implies that the standards suggested in the draft version are unlikely to have become more stringent, but instead may have been relaxed. This document will be updated as new information is made available.

Furthermore, the latest draft revision of USP <797> was only just posted online in October for public commentary, which means the overall revision process is still far from complete. Without a clear timeline for widespread enforcement of these standards, many compounding pharmacies are seriously concerned by the compliance issues they may face down the road if they design a substandard facility.
According to *Specialty Pharmacy Times*, “[s]ome states, notably Washington, Maryland, and North Carolina, have already adopted more stringent standards regarding the storage, handling, and transport of hazardous medications.”

The full article from *Specialty Pharmacy Times*:  

Due to the growing number of cases where health issues surface after years of exposure to hazardous drugs, more and more states will be forced to adopt USP <800> standards sooner rather than later.

**Enforcement Discrepancies**

As an example (or a warning?) of what to expect in the future, the FDA has posted online the results from inspections of both traditional compounding pharmacies and outsourcing facilities, including official Warning Letters and FDA Form 483s:  
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339771.htm#South_Coast

As we can see in the Form 483 for each inspection, even 503(a) entities have been found to be in violation of federal law for failing to maintain and monitor strict sterile conditions in their ISO-rated hoods or cleanrooms, even though cGMP does not apply to them. The implication is that the FDA is strengthening its enforcement practices across the board, not just for outsourcing facilities. But if the violations are readily correctable, the FDA has the option to report the observed violations to the State Board of Pharmacy, who would be charged with following up on the correction of the FDA’s perceived deficiencies.

The State Boards of Pharmacy all typically base their inspections on USP standards, but USP <797> has been slated for revision since 2010, long before the tragic events involving the New England Compounding Center. With the FDA moving aggressively towards stricter standards and enforcement, USP is still far behind and trying to catch up with today’s regulatory expectations.

In the meantime, some State Boards have taken equally aggressive steps to ramp up enforcement of stricter compounding standards. For example, the California State Board of Pharmacy has emphasized in recent public notices that California pharmaceutical compounding law will be revised to reflect the new national standards and will be more restrictive than the federal law in several areas.

**Because the FDA, USP, and State Boards of Pharmacy have not completely harmonized their standards and enforcement procedures, compliance with the current USP standards may fall short in the event of an FDA and State Board of Pharmacy inspection.**
Recommendations

In order to navigate the tangled regulatory framework, pharmaceutical compounders must choose between two approaches when designing a cleanroom: the **safe, fully compliant approach** or the **risky, cost-cutting approach**.

Cutting short-term costs at long-term risk

Cost-sensitive pharmacies may want to take the less-expensive approach of building a cleanroom to meet the bare minimum, current USP requirements. Although this approach may be attractive for pharmacies operating on a tight budget and may be sufficient for many State Boards of Pharmacy, it would be significantly risky given the aggressive moves by the FDA to strengthen enforcement.

All compounding pharmacies need to pay particular attention to the new requirements in USP <800>, which clarify and expand upon the hazardous drug guidelines in USP <797>. Notable changes may include the elimination of the low-volume compounding exception, the requirement for a dedicated space for any hazardous drug compounding, and the stipulation that all HDs must be stored in negative pressure environments.


Full FDA conformance at nominal additional cost

Given the relatively low cost of meeting more stringent requirements, Terra recommends compliance with the higher standards of the FDA, which are likely to be closely mirrored in the upcoming USP <797> revisions.

The Key Requirement of Title 21 USC (FD&C Act):

“The drug product must not consist in whole or in part of any filthy, putrid, or decomposed substance, or be prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or whereby it may have been rendered injurious to health. (Sections 501(a)(1) and (a)(2)(A) of the FD&C Act)”

All compounding pharmacies should take note of the broad discretion granted to the FDA inspectors by this language. This requirement, which applies to both 503(a) and 503(b) entities, can be interpreted as a catch-all that allows the FDA to enforce much higher standards of sterility based on their determination of what constitutes “insanitary conditions.” In reality, this directly reflects the original intent of the DQSA and cGMP: to protect the public from the potentially deadly contamination of compounded sterile pharmaceuticals.
For 503(b) outsourcing facilities, the FDA will especially scrutinize the quality assurance procedures that cGMP requires. The FDA will verify the implementation of a strict quality control system by the compounding facility, which includes proper sterilization procedures and environmental monitoring procedures. In order to pass the FDA’s inspection, a pharmaceutical compounder will have to meet and to some extent exceed USP <797> standards for sterile compounding by passing a battery of viable sampling tests and inspector observation periods.


In addition, FDA inspectors will thoroughly investigate any sterility failures and the subsequent corrective actions, so compounding facilities must strive to create the most sterile environment possible in order to limit the presence of any Colony Forming Units (CFU).

For the reasons stated above, Terra Universal recommends an ISO class 5 compounding cleanroom rather than the minimum ISO 7 required by USP standards.

An ISO 5 cleanroom would drastically reduce the risk of microbial contamination by significantly lowering the bioburden of the cleanroom with the simple addition of one or two Fan Filter Units to the typical compounding cleanroom. This strategy minimizes the risk of failing FDA or State Board of Pharmacy inspections by providing a large margin of safety in terms of sterility.

The Bottom Line

Compliance with cGMP is the safest approach to ensure that your cleanroom meets all applicable federal and state regulations, now and in the future!
Condensed Compounding Cleanroom Requirements

**Recommended Cleanroom Configurations for Implementing cGMP (Federal Level)**

- **Class I or II BSC, HEPA**
  - **ISO 5**, **ISO 7** or better
  - **Positive pressure between 0.02 and 0.05 WC**
  - **USP 797-compliant finishes**
  - **Can contain water sources or floor drains**
  - **Hand-free hardware**

- **Containment Ventilated Enclosure (CVE)**
  - **ISO 5** or better
  - **Minimum 30 ACPH**
  - **Positive pressure between 0.02 and 0.05 WC**
  - **USP 797-compliant finishes**
  - **Can contain water sources or floor drains**
  - **Hand-free hardware**

**USP Minimum Requirements (State Level)**

- **Class I or II BSC, HEPA**
  - **ISO 5**, **ISO 7** or better
  - **Positive pressure between 0.02 and 0.05 WC**
  - **USP 797-compliant finishes**
  - **Can contain water sources or floor drains**
  - **Hand-free hardware**

- **Contamination Cleanroom (negative pressure)**
  - **ISO 5** or better
  - **Minimum 30 ACPH**
  - **Positive pressure between 0.02 and 0.05 WC**
  - **USP 797-compliant finishes**
  - **Can contain water sources or floor drains**
  - **Hand-free hardware**

**Infographic Legend**

- **ACPH**: Air Changes Per Hour
- **ESC**: Bio Safety Cabinet
- **CAI**: Compounding Aseptic Isolator
- **CAE**: Compounding Aseptic Containment Enclosure
- **CACI**: Laminar Air Flow Workbench
- **ISO (R)**: Particle Count Rating
- **WC**: Inches of Water Column (pressure)
- **PEC**: Aseptic manipulation zone (hood)
- **SEC**: Containment hood (negative pressure)
- **C-PEC**: Containment cleanroom (negative pressure)
- **C-SEC**: External ventilation through HEPA filter
- **CSCI**: Class II BSC (Types A2, B1, B2)
- **CAI or LAFW**: Class I or II BSC, HEPA filtered, hands-free hardware
- **PEC**: Containment hood (negative pressure)
- **PEC**: Containment cleanroom (negative pressure)
- **ISO 5 or better**: Minimum 30 ACPH
- **ISO 7 or better**: Minimum 30 ACPH
- **ISO 7**: Minimum 30 ACPH
- **ISO 7**: Minimum 30 ACPH

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**Notes**

- **Does Not Apply to Non-Sterile Compounding**
USP <797> Exceptions (Based on 2015 Draft Version)

Exceptions for Sterile Compounding

The Primary Engineering Control (the device or zone where sterile compounding takes place) may be located in an unclassified segregated compounding area if:

- Only Category 1 CSPs are prepared;
- The beyond-use-date (BUD) of the CSP is less than 12 hours; and
- The PEC is located away from unsealed windows, doors to the outside, high traffic areas, and other sources of contamination

*Source: USP 797 Draft*

A PEC, which meets the requirements listed below, can be considered an isolator according to USP <797> and may be used to prepare Category 2 CSPs within an ISO Class 8 area if:

- The manufacturer has provided documentation that the isolator will continuously meet ISO Class 5 conditions, including during material transfer;
- The isolator maintains constant overpressure of at least 0.05-inch water column;
- The isolator is decontaminated using a generator that distributes a sporicidal chemical agent throughout the isolator chamber; and
- High-integrity transfer ports are used to move supplies, ingredients, components, and devices into and out of the isolator

*Source: USP 797 Draft*
USP <800> Exceptions (Based on 2014 Draft Version)

Exceptions for Non-Sterile Hazardous Compounding

A C-PEC and C-SEC are not required if:

- Manipulations are limited to handling of final dosage forms (e.g. tablets, capsules); and
- Do not produce particles, aerosols, or gasses

*Source: USP 800 Draft*

Exceptions for Sterile Hazardous Compounding

The Containment Primary Engineering Control (C-PEC) can be located in an unclassified (i.e. non-ISO 7) Containment Segregated Compounding Area (C-SCA) if:

- Only Category 1 CSPs are prepared in the C-SCA;
- BUDs are less than 12 hours;
- Maintains negative pressure between 0.01 and 0.03 "WC
- Minimum 12 ACPH of HEPA-filtered supply air; and
- A hand-washing sink is placed at least 1 meter from C-PEC

*Source: USP 800 Draft*

The C-PEC used for hazardous drugs may be used for non-HD compounding if:

- The non-HD preparation is placed in a protective outer wrapper during removal from C-PEC; and
- The CSP is labeled to require PPE handling precautions

*Source: USP 800 Draft*

Sterile and non-sterile hazardous compounding can occur in the same room if:

- The C-PECs can continuously maintain ISO 7 in the room throughout non-sterile compounding;
- The C-PECS are placed at least 1 meter apart; and
- Particle-generating activity is not performed while sterile compounding is in process

*Source: USP 800 Draft*

A sterile C-PEC may be used for occasional non-sterile HD compounding if:

- The C-PEC is decontaminated, cleaned, and disinfected before it is used for sterile compounding again

*Source: USP 800 Draft*
USP Guidelines Walkthrough

Non-Sterile Compounding (USP <795>)

For the purposes of facility design, USP <795> does not specify any special requirements for non-sterile compounding. The compounding area must be kept segregated from sterile preparation areas and must be climate-controlled. The area and all equipment must be kept reasonably sanitary and orderly.

Sterile Compounding (USP <797>)

USP <797> specifies a high-level of contamination control that incorporates three separate cleanroom areas to maintain sterility. These areas are referred to as the Primary Engineering Control (PEC), the Buffer Area, and the Anteroom.

**Note:** Cleanrooms are rated according to the ISO Classes, a standardized system of “cleanliness” measured by the maximum number of particles allowed within a sample volume of air. A lower class number indicates exponentially lower particle counts, and vice versa.

The **Primary Engineering Control** refers to the enclosure that makes up the compounding zone or critical area where the aseptic compounding manipulations will take place. For all sterile compounding, the PEC must have HEPA-filtered, unidirectional airflow and maintain at least ISO Class 5 conditions. The PEC can take the form of a compound aseptic isolator (CAI) or a laminar air flow workbench (LAFW).

The PEC is placed within a cleanroom called the **Buffer Area**, which acts as a buffer zone between the PEC and the “less-clean” Anteroom. The buffer area for sterile compounding must be at least ISO Class 7 and have a minimum of 30 ACPH (air changes per hour). The buffer area must also maintain positive pressure (between 0.02” and 0.05”WC) to the adjacent spaces. All surfaces within a USP <797>-compliant cleanroom must be smooth, impervious, free from cracks and crevices, non-shedding, and all junctures between walls and horizontal surfaces must be coved. The buffer area cannot have any water sources (such as sinks) or floor drains. Furniture and equipment should follow the same principles and be limited to only that which is necessary for compounding procedures. Hands-free hardware is preferred.

The **Anteroom** is the outermost cleanroom area and serves as the first line of defense against contaminating particles. For sterile compounding, the anteroom must be rated as ISO 8 or better, with a minimum of 30 ACPH and positive pressure between 0.02" and 0.05"WC. The anteroom generally contains the sink and serves as a cleanroom garb/de-garb station.
Hazardous Compounding (Based on 2014 USP <800> Draft)

When a compounding operation involves hazardous drugs, additional requirements outlined in USP <800> must be addressed (the complete list of hazardous drugs can be found on the CDC’s website, called the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2014, Publication Number 2014-138). The key difference is prioritizing the safety of workers rather than the end-users.

The terminology for HD compounding operations reflects the emphasis on minimizing operator exposure to the hazardous ingredients. “PEC” becomes Containment Primary Engineering Control (C-PEC) and “Buffer Area” becomes Containment Secondary Engineering Control (C-SEC).

There are four provisions of USP <800> that are common to both non-sterile and sterile compounding operations:

- The C-PEC and C-SEC must both be externally vented through a HEPA filter
- HD compounding requires a dedicated room separate from non-HD compounding
- The C-SEC must maintain a negative pressure differential between 0.01” and 0.03”WC
- An emergency hand/eye washing sink must be available

Non-sterile HD compounding does not require an ISO classification in the C-PEC or C-SEC. The C-PEC may be a Class I or II Bio Safety Cabinet (BSC), a Compound Aseptic Containment Isolator (CAI), or a Containment Ventilated Enclosure (CVE). The C-SEC does require at least 12 ACPH and USP <797>-compliant smooth finishes in order to minimize any hazardous particle build-up and ease decontamination. Anterooms are only required for sterile compounding.

Sterile HD compounding must fulfill the requirements of both USP <797> and USP <800>. This type of operation would require an ISO 5 or better C-PEC, an ISO 7 or better C-SEC, as well as an ISO 7 or better Anteroom.

USP <800> accepts the following C-PECs for use in sterile HD compounding:

- Class II Bio Safety Cabinets that are Type A2, B1, or B2;
- Class III Bio Safety Cabinets; or
- Compound Aseptic Containment Isolators.

The C-SEC and Anteroom both must have a minimum of 30 ACPH, but the Anteroom is required to have a positive pressure differential between 0.02” and 0.05”WC to protect the negative pressure C-SEC from contamination. No water sources or floor drains are allowed in the C-SEC and the finishes must be smooth, seamless, and coved.
Containment Supplemental Engineering Controls (CSTDs) provide additional protection for workers and are encouraged in USP <800> but are not required. A CSTD is not to be used as a substitute for a C-PEC in the appropriate C-SEC.

Storage Requirements for Hazardous Drugs (USP <800>)

Antineoplastic HDs and any HD API must be stored in a negative-pressure area with at least 12 ACPH, unless they meet one of the following criteria for exception:

- Non-antineoplastic;
- Reproductive risk only; or
- Final dosage forms of an antineoplastic hazardous drug

These exceptions may be stored with other inventory.

Refrigerated antineoplastic HDs must be stored in a dedicated refrigerator, within a negative-pressure area, with at least 12 ACPH.

The negative-pressure area may be a storage room or a containment-segregated compounding area (C-SCA), but only sterile HDs may be stored in a negative-pressure Buffer Area. Otherwise, sterile and non-sterile HDs may be stored together.