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USP 797 AND ITS IMPLEMENTATION IN ASEPTIC COMPOUNDING ENVIRONMENTS

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Overview

The United States Pharmacopeia (USP) Chapter 797 provides a comprehensive framework for compounding sterile preparations (CSPs) to ensure patient safety and product quality. This paper aims to provide an in-depth understanding of USP 797, focusing on its relevance and implementation in aseptic manufacturing environments. By incorporating real-world examples and textual references, the paper aims to elevate the reader's understanding to a high level, particularly in the context of cleanroom applications and the susceptibility of aseptic products to contamination.

Fig 1.0 Compounding Pharmacists working in a bio safety cabinet

USP 797:2023

USP 797:2023 will be released in November 2023 is a critical standard that outlines the guidelines for the compounding of sterile pharmaceutical products. While it is primarily aimed at healthcare settings, the principles are highly relevant to aseptic manufacturing environments, especially those that require stringent control over particulate and microbial contamination. This paper will dissect the key components of USP 797 and discuss how they can be effectively implemented in aseptic manufacturing settings as well as highlighting the revisions to the 2023 Standard.

Types of Environments for Aseptic Compounding

Laminar Airflow (LAF) Workbenches

LAF workbenches provide a unidirectional flow of HEPA-filtered air over the work
surface and are commonly used for the preparation of low to moderate-risk compounds.

Fig 2.0 Two workers in side by side Laminar Airflow Benches

Biological Safety Cabinets (BSCs)

BSCs offer a higher level of protection and are used for the preparation of hazardous and high-risk compounds. They provide both the operator and the product with a HEPA-filtered environment.

Fig 3.0 Compounding Pharmacy worker working with compounds within a Biological Safety Cabinet.

Susceptibility of Aseptic Products to Contamination

Fig 4.0 Bacterial contamination growing on a petri dish.

The Nature of Aseptic Products

Aseptic products are pharmaceuticals that are free from contamination caused by harmful bacteria, viruses, or other microorganisms. These products often include injectables, ophthalmic solutions, and advanced biologics. Due to their nature, they are highly susceptible to contamination.

Impact on Patient Safety

Contaminated aseptic products can have severe consequences, ranging from localized infections to systemic conditions like sepsis. In worst-case scenarios, contamination can lead to fatalities. Therefore, the sterility of these products is not just a quality parameter but a critical safety concern.

Real-world Example

In 2012, a fungal meningitis outbreak was linked to contaminated steroid injections. The incident resulted in 64 deaths and hundreds of illnesses, highlighting the catastrophic impact of contamination in aseptic products.

Key Components of USP 797

Personnel Training and Evaluation

Insight: Proper training is the cornerstone of any aseptic operation. USP 797 mandates that personnel involved in the compounding process undergo rigorous training and regular competency evaluations.

Real-world Example: In aseptic manufacturing, operators are often required to pass a media fill test, which simulates the aseptic filling process using a microbial growth medium, to demonstrate their competency.

Facility Requirements

Insight: USP 797 specifies the types of engineering controls required, including primary (PECs) and secondary engineering controls (SECs).

Real-world Example: In aseptic filling lines for injectables, laminar airflow workbenches are commonly used as PECs to provide an ISO 5 environment, aligning with ISO 14644 standards.

Air Quality

Insight: The standard sets forth stringent air quality requirements, including specifications for High-Efficiency Particulate Air (HEPA) filtration.

Real-world Example: In semiconductor wafer manufacturing, ultra-low particulate air (ULPA) filters may be used to exceed the air quality standards set by USP 797.

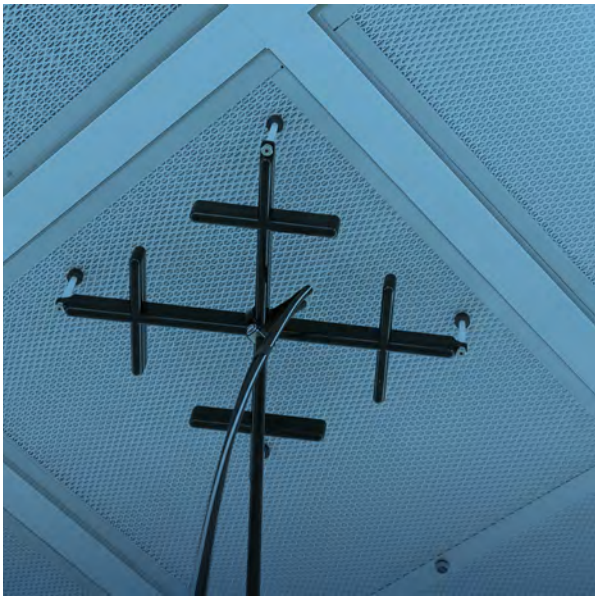

Fig 5.0 A HEPA filtered vent undergoing air velocity testing.

Cleaning and Disinfection

Insight: Regular cleaning and disinfection are crucial for maintaining a sterile environment.

Real-world Example: In aseptic manufacturing, rotational use of sporicidal and bactericidal disinfectants is common to prevent microbial resistance.

Procedures and Documentation

Insight: Detailed Standard Operating Procedures (SOPs) and record-keeping are mandatory under USP 797.

Real-world Example: Batch records in pharmaceutical manufacturing often include step-by-step documentation of the compounding process, including any deviations and corrective actions.

Quality Control and Assurance

Insight: USP 797 mandates quality control measures like sterility and endotoxin testing.

Real-world Example: In aseptic manufacturing of parenteral products, samples are often sent to Quality Control labs for testing before the batch is released.

Storage and Beyond-Use Dating

Insight: Proper storage conditions and beyond-use dates are essential for ensuring the sterility and efficacy of the end product.

Real-world Example: Vaccines are often stored in temperature-controlled environments, and their expiration dates are strictly monitored.

Handling of Hazardous Drugs

Insight: USP 797 provides guidelines for the safe handling of hazardous drugs.

Real-world Example: In the manufacturing of chemotherapy drugs, closed-system drug-transfer devices (CSTDs) are often used to minimize exposure.

Implementation Strategies

Fig 6.0 Worker goes over checklist in clean environment.

1. **Gap Analysis: Conduct a gap analysis to identify areas where your current practices deviate from USP 797 standards.**
2. **Training Programs: Develop and implement training programs tailored to the needs of your aseptic manufacturing environment.**
3. **Quality Audits: Regular internal and external audits can help ensure ongoing compliance.**
4. **Continuous Monitoring: Employ real-time particle counters and microbial air samplers to continuously monitor the environment.**

Summary of USP 797:2023 Revision Key Points

Key Points:

1. **Terminology Changes:** The Expert Committee made several changes to terminology, such as replacing "compounding space" with "compounding area" and "alcohol-based hand sanitizer" with "alcohol-based hand rub."
2. **Public Input:** The commentary addresses multiple comments from the public, including concerns about the necessity of the revisions, financial impact, and scientific evidence supporting the changes.
3. **Beyond-Use Dates (BUDs):** The committee emphasized that BUDs are based on stability and sterility data, the compounding environment, and the financial impact on compounders and patients.
4. **Scope and Exemptions:** The chapter was clarified to state that the administration of medication is outside its scope. Conditions for immediate use of Compounded Sterile Preparations (CSPs) were also detailed.
5. **Financial and Regulatory Concerns:** Several comments were made about the financial impact of the new requirements, especially in rural and underserved areas. The committee stated that the chapter aims to ensure quality compounded preparations regardless of location.
6. **Implementation Delay:** Due to public comments, the Expert Committee decided to delay the implementation of the new standards by one year to November 1, 2023.
7. **Veterinary Practices:** Some comments requested exemptions for veterinary practices. The committee clarified that the chapter's requirements are equally relevant to human and animal patients.
8. **Technology and Documentation:** Some commenters suggested that the chapter be more prescriptive about the use of technology for documentation. This was not incorporated, as the chapter describes minimum standards.
9. **Repackaging and Nonsterile Starting Ingredients:** Comments about including a section on repackaging and starting with nonsterile ingredients were not incorporated. The chapter provides a risk-based approach with shorter BUDs for Category 1 CSPs and longer BUDs for Category 2 CSPs.

Conclusion

USP 797 is not just a regulatory requirement but a comprehensive framework that ensures the highest level of patient safety and product quality. Its principles are highly applicable to aseptic manufacturing environments that require stringent control over contamination. The susceptibility of aseptic products to contamination and the severe impact on patient safety make the implementation of USP 797 not just advisable but imperative.

References

1. *United States Pharmacopeia, Chapter 797: "Pharmaceutical Compounding—Sterile Preparations."*

2. *ISO 14644-1:2015 "Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration."*

3. *Centers for Disease Control and Prevention (CDC), "Multistate Fungal Meningitis Outbreak Investigation," 2013.*