

**Put Your Trust in Baker for Compliance with USP <797>  
Pharmaceutical Compounding – Sterile Preparations**  
[Executive Summary]

The Baker Company is committed to helping pharmacists ensure the sterility of drugs, the safety of patients, and the health of pharmacy personnel. In light of the new USP Chapter 797, which became effective on January 1<sup>st</sup>, The Baker Company has released a whitepaper to provide an overview and interpretation of the new requirements.

- **Scope:** Chapter 797 is considered a standard requirement for a broad range of health care settings and sterile products. Many state boards of pharmacy are setting timelines for compliance, and healthcare facilities have recently been cited during JCAHO inspections for not having a compliance plan in place.
- **Classification:** Different types of compounding activities are classified into Low, Medium, and High risk levels. Each risk level has associated provisions for the compounding environment, storage conditions, and beyond use dating.
- **Compounding Environment:** Chapter 797 requires that compounding be performed in a “controlled area” (a clean room) providing ISO Class 8 (FS209E Class 100,000) air quality conditions. A “primary engineering control” (a clean bench or BSC) must also be used within the clean room to provide ISO Class 5 (FS209E Class 100) air quality.
- **Clean Room Requirements:** Clean rooms require special materials and techniques for construction, with initial cost estimates starting at \$150/sq. ft. (and likely to be higher). Clean room procedures, such as use of special garments and restrictions on movement of people and materials, may also increase operating costs.
- **The Glovebox Alternative:** USP 797 indicates that *“a well-designed positive pressure barrier isolator [glovebox] may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing.”*
- **Advantages of Gloveboxes:** Barrier isolators (such as The Baker Company’s SterilSHIELD® Glovebox) offer the same or better air quality as a clean room, however their design offers some significant advantages:
  - Less floor space required from the pharmacy
  - Lower startup and construction costs
  - Lower operating costs
  - Better working conditions for pharmacy personnel
  - Greater sterility assurance provided by physical barrier
- **Chemotherapy Preparation:** USP 797 does not cover in detail the risks to pharmacy personnel associated with handling cytotoxic or other hazardous drugs. A recent NIOSH alert on Hazardous Drugs recommends that BSCs or gloveboxes used for such preparations be vented to the outdoors. The Baker Company’s ChemoSHIELD® Glovebox is a negative pressure barrier isolator which provides Class 5 conditions while also protecting personnel from exposure.
- **Solutions from The Baker Company:** We offer a full range of products to help your pharmacy become USP 797 compliant, while protecting your patients and employees. Visit us today at [www.bakerco.com/pharmacy](http://www.bakerco.com/pharmacy) to learn more, or call The Baker Company at 800.992.2537 to request additional information.

## **Put Your Trust in Baker for Compliance with USP <797> *Pharmaceutical Compounding – Sterile Preparations***

Beginning with the introduction of the EdgeGARD laminar flow clean bench to the pharmacy setting over 30 years ago, The Baker Company has been a trusted partner in helping pharmacists to keep their patients and employees safe. Recent adverse events traced to contaminated parenteral products have sparked new concerns, and a great deal of lively discussion has ensued around equipment and best practices for sterile compounding. As a result, pharmacy professional organizations and governing bodies have recently revised, or are now considering revisions to, standards and guidelines for the preparation and handling of compounded sterile products (CSPs).

The Baker Company is committed to helping pharmacists ensure the sterility of drugs, the safety of patients, and the health of pharmacy personnel. This paper provides an overview of key points in the recently adopted chapter from United States Pharmacopeia, <797> *Pharmaceutical Compounding – Sterile Preparations*, and describes the solutions offered by The Baker Company to help pharmacies meet the requirements therein.

### **USP Chapter 797**

United States Pharmacopeia has issued a new chapter on sterile compounding, which became effective on January 1, 2004. This replaces the previous chapter, <1206> *Sterile Drug Products for Home Use*, and has been re-numbered to reflect that Chapter 797 is now considered a standard requirement that may be enforced and cited by JCAHO, the FDA and state boards of pharmacy. Many states are already setting timelines for compliance, and healthcare facilities have recently been cited during JCAHO inspections for not having a compliance plan in place.

The contents of Chapter 797 are applicable to a wide range of settings, including “*health care institutions, pharmacies, physician practice facilities, and other facilities in which CSPs [Compounded Sterile Preparations] are prepared, stored, and dispensed.*” The provisions of the chapter touch on many aspects of pharmacy operations, including: risk assessment, facilities design, equipment, materials storage, beyond-use dating, training, aseptic technique, quality assurance, end product testing, and environmental monitoring & control.

According to USP Chapter 797, the definition of a CSP is quite broad, including:

- *Preparations prepared according to the manufacturer’s labeled instructions and other manipulations when manufacturing sterile products that expose the original contents to potential contamination.*
- *Preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration.*
- *Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powders for injection, irrigations, metered sprays, and ophthalmic and otic preparations.*

### **Risk Levels for CSPs**

Within Chapter 797, CSPs are classified into various risk levels (low-, medium-, and high-risk) based on the potential for introducing microbial, chemical, or physical contamination during compounding activities. These risk levels then help to determine the required compounding conditions, storage conditions, beyond-use dates, and verification procedures. The following table provides a summary of these risk levels.

Risk Level	Description	Examples
<b>Low</b>	<ul style="list-style-type: none"> <li>• Involves only transfer, measuring, and mixing with closed or sealed packaging systems.</li> <li>• Limited to aseptically opening ampuls, penetrating sterile stoppers on vials with sterile needles or syringes, transferring sterile liquids in sterile syringes to sterile administration devices.</li> <li>• Prepared entirely in an ISO Class 5 (see below) or better air quality environment.</li> <li>• Storage for a maximum of 48 hours at room temperature, 14 days refrigerated, or 45 days in solid frozen state.</li> </ul>	<ul style="list-style-type: none"> <li>• Single transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles.</li> <li>• Manually measuring and mixing no more than three manufactured products to compound drug admixtures and nutritional solutions.</li> </ul>
<b>Medium</b>	<ul style="list-style-type: none"> <li>• Multiple individual or small doses are combined or pooled to prepare a CSP for administration to multiple patients or to one patient on multiple occasions.</li> <li>• Involves complex aseptic manipulations or requires a long duration.</li> <li>• Does not contain broad spectrum bacteriostatic substances, and is administered over several days (e.g. worn or implanted infusion device).</li> <li>• Prepared entirely in an ISO Class 5 (see below) or better air quality environment.</li> <li>• Storage for a maximum of 30 hours at room temperature, 14 days refrigerated, or 45 days in solid frozen state.</li> </ul>	<ul style="list-style-type: none"> <li>• TPN fluids using manual or automated devices, involving multiple injections, detachments, and attachments of nutrient source products to deliver components to a final sterile container.</li> <li>• Filling reservoirs of injection and infusion devices with multiple sterile drug products and evacuation of air from those reservoirs before dispensing.</li> <li>• Filling reservoirs of injection and infusion devices with sterile drug solutions that will be administered over several days at ambient temperatures between 25 and 40 degrees C.</li> <li>• Transfer from multiple ampuls or vials into a single, final sterile container or product.</li> </ul>
<b>High</b>	<ul style="list-style-type: none"> <li>• Nonsterile ingredients are incorporated, or a nonsterile device is employed before terminal sterilization.</li> <li>• Nonsterile components are exposed for at least 6 hours before being sterilized.</li> <li>• Exposed to air quality inferior to ISO Class 5 (see below).</li> <li>• Storage for a maximum of 24 hours at room temperature, 3 days refrigerated, or 45 days in solid frozen state.</li> </ul>	<ul style="list-style-type: none"> <li>• Dissolving nonsterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized.</li> <li>• Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.</li> </ul>

*Adapted from Fourth Interim Revision Announcement, Pharmacopeial Forum, Vol. 29(4), July-Aug. 2003*

### The Compounding Environment

Compliance with USP Chapter 797 will likely require changes to the facilities and engineering controls used to limit the potential for airborne contamination within the compounding area, as well as a program for regular monitoring and testing of air quality in these areas. USP references accepted standards for contamination control, which are based on the number of particles detected in a defined air volume (with a lower class meaning “cleaner” air). For example, ISO Class 5 calls for a maximum of 3,520 particles of 0.5 μm and larger per cubic meter (or 100 particles per cubic foot based on US Federal Standard 209E). See the table below for a summary of air cleanliness classifications:

ISO Class	Particles/m <sup>3</sup> (≥0.5 μm)	FS209E Class	Particles/f <sup>3</sup> (≥0.5 μm)
Class 1	n/a	n/a	n/a
Class 2	4	n/a	n/a
Class 3	35	Class 1	1
Class 4	352	Class 10	10
Class 5	3,520	Class 100	100
Class 6	35,200	Class 1,000	1,000
Class 7	352,000	Class 10,000	10,000
Class 8	3,520,000	Class 100,000	100,000
Class 9	35,200,000	n/a	n/a

*Adapted from EN/ISO 14644-1, Classification of Air Cleanliness*

Applying this to the pharmacy setting, USP 797 states that compounding should take place within an ISO Class 8 or better clean room (called a "controlled area"). The clean room must also include an attached anteroom at the same air quality level (ISO Class 8) for movement of personnel and materials in and out of the clean room. Additionally, USP 797 indicates that a "primary engineering control" providing ISO Class 5 or better air quality must be used to perform compounding activities. Primary engineering controls include traditional equipment such as clean benches and Class II Biological Safety Cabinets (BSCs), which the USP chapter refers to collectively as LAFWs (laminar airflow workstations). The chapter also discusses a technology that is relatively new to the pharmacy setting called a glovebox (or barrier isolator), which is discussed in more detail below.

## How Gloveboxes Work

A glovebox (also called a "barrier isolator" or simply "isolator") provides a physical barrier between pharmacy personnel and the compounding activity. Traditional clean benches and BSCs have an open front access area, which allows the possibility that disruptions in the room airflow or poor aseptic technique by the operator will introduce contaminants to the work area. A glovebox provides an additional level of protection, as the sterile product is never exposed to the room environment or to compounding personnel directly.

When using a glovebox, materials are passed into the main working chamber through an enclosed pass-thru chamber, and accessed through glove ports to perform aseptic manipulations. Clean air is supplied to the work area through a HEPA filter, providing better than ISO Class 5 conditions under positive pressure within the glovebox. The Baker Company's SterilSHIELD® Glovebox operates with a top-to-bottom laminar (or "unidirectional") mass airflow to ensure that contaminants and generated particles are immediately swept away from the sterile product. This contrasts with other design approaches that rely on dilution of turbulent air to achieve the desired air cleanliness.



Figure 1: The SterilSHIELD® Glovebox

## Clean Room Requirements

A clean room requires a large dedicated space, and calls for specialized construction materials and methods to enable proper operation and maintenance. Estimates of startup costs for a clean room installation begin at \$150 per square foot, and actual costs may be much higher. Notable clean room construction requirements include:

- Separate anteroom for hand sanitizing, gowning, and unpacking materials
- Ceilings, walls, floors, fixtures, shelving, counters and cabinets must be smooth, impervious, free from cracks & crevices, and non-shedding
- Surfaces should be resistant to damage from sanitizing agents
- Junctures of ceilings to walls should be covered or caulked
- Ceiling panels are inlaid
- Floors overlaid with vinyl having heat-welded seams and coving to the sidewall
- Penetrations and light fixtures should be sealed

Clean rooms also require modifications to work processes in order to reduce the possibility of introducing contaminants to the controlled area. Implementing these procedures will

increase the cost of operating a pharmacy, though the extent of the cost increase will vary for each facility. Highlights of these operating procedures include:

- Remove outer lab jackets, make-up, and jewelry before entering clean room
- Scrub hands and arms to the elbow
- Use of non-shedding clothing (hair covers, shoe covers, coats, gloves, face masks)
- Restrict the use of shedding materials (includes pencils, cardboard cartons, paper towels, all cotton items)
- Use only non-shedding cleaning tools, including wipers, sponges, and mops
- Discard hair covers, masks, shoe covers, and gloves upon leaving the clean room, and don new ones prior to re-entry

## The Glovebox Alternative

Building and operating a clean room can be an expensive and time-consuming proposition. However, pharmacies do have another option to comply that requires a much lower investment in floor space, construction costs, and operating costs. USP 797 indicates that :  
*"a well-designed positive pressure barrier isolator [glovebox]...may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing."*

Gloveboxes offer the same or better air quality as a clean bench or BSC located within a clean room; however their design offers some significant advantages in both initial investment and ongoing operating expenses. Notably:

- **Less space:** clean rooms require both a main work area and an anteroom at ISO Class 8 air quality
- **Lower startup costs:** clean rooms call for specialized materials and construction methods as described above
- **Lower operating costs:** clean rooms require specialized clothing that is disposed of frequently, as well as specialized maintenance products and procedures
- **Better working conditions:** personnel must "gown up" on entering and "un-gown" when leaving the clean room, and may not wear make-up or jewelry
- **Greater Sterility Assurance:** a physical barrier between the worker and the sterile product reduces the risk of introducing contaminants

Pharmacists may be concerned that working through gloves will reduce the dexterity and efficiency of their staff. However, gloves are available for different size hands and are not appreciably thicker than the gloves currently used for aseptic manipulations. Pharmacies already using gloveboxes report that after an adjustment period of approximately one month, their productivity returns to nearly 100% of the level prior to adoption.

Gloveboxes must be maintained in much the same way as a clean bench or BSC. The work area should be cleaned before and after each procedure. Additionally, the USP chapter calls for periodic monitoring of air quality and microbial contamination. Regular service should be performed by the same accredited certifiers who currently maintain clean benches and BSCs to ensure that the glovebox functions as designed. Certification should be performed on a regular basis (usually every 6 months or 1 year), as well as any time the isolator is serviced or re-located.

## Chemotherapy and Other Hazardous Drugs

USP Chapter 797 speaks to aseptic conditions for compounded sterile preparations; however the chapter does not cover in detail the risks to pharmacy personnel associated with handling cytotoxic or other hazardous drugs. For these special cases of CSPs, a negative pressure glovebox should be used to provide ISO Class 5 conditions while also protecting personnel from exposure.

Negative pressure operations ensure that any leaks, which may develop over time around gasketing and gloves, will be entrained within the glovebox and passed through HEPA exhaust filters. The Baker Company's ChemoSHIELD® Glovebox is designed to provide top-to-bottom laminar mass airflow to sweep away aerosols or particulates generated by compounding activity. This not only keeps the product clean and safe, but also reduces the possibility of cross contamination from residues of previous activities that may exist in gloveboxes utilizing non-laminar (or "turbulent") airflow design.

Measures should also be taken to prevent pharmacy personnel to exposure to hazardous agents that may be exhausted from the glovebox. Some research has shown that hazardous compounds may vaporize, thereby passing through HEPA filters. The National Institute for Occupational Safety and Health (NIOSH) has recently issued an alert regarding preparation of hazardous drugs, which recommends that any cabinet (glovebox or BSC) used for preparation of chemotherapy or other hazardous drugs be exhausted to the outdoors through a properly functioning facility HVAC system. This is available online at: <http://www.cdc.gov/niosh/docs/2004-HazDrugAlert/pdfs/2004-HazDrugAlert.pdf>

### **Solutions From The Baker Company**

There is a great deal of concern in the pharmacy profession about the impact of USP 797. Continuing our long tradition of providing solutions to the pharmacy, The Baker Company is committed to helping you protect your patients and employees. We offer a full range of products for use in the pharmacy to help your facility become USP 797 compliant, including:

Gloveboxes (ISO Class 5 barrier isolators, stand alone alternative to a clean room)

#### **SterilSHIELD® Positive Pressure Glovebox**

For sterile compounding of non-hazardous pharmaceutical compounds and related clinical, pharmacy and process applications.

#### **ChemoSHIELD® Negative Pressure Glovebox**

For sterile compounding of hazardous or potent pharmaceutical compounds, chemotherapy agents and IV admixtures that can be harmful to pharmacy personnel.

Biological Safety Cabinets (ISO Class 5 LAFWs, for use in ISO Class 8 clean room)

#### **SterilGARD®III Advance®, Class II, Type A2 Biological Safety Cabinet**

This BSC is designed for sterile product preparation and biological experimentation involving agents of low to moderate risk. Also available is the compact model SG-303, a 3-foot Biological Safety Cabinet with a smaller footprint for low-volume facilities.

#### **SterilchemGARD®III, Class II, Type B2 Total Exhaust Biological Safety Cabinet**

This BSC is designed for biological testing and product preparation involving low to moderate risk agents where chemical effluent is present and clean air is essential.

Clean Benches (ISO Class 5 LAFWs, for use in ISO Class 8 clean room)

#### **EdgeGARD® Horizontal Clean Bench**

This horizontal laminar-flow clean bench provides HEPA-filtered airflow across the work area and hence, a particulate-free work surface.

### **For More Information**

Copies of USP Chapter 797 may be ordered directly from USP ([www.usp.org](http://www.usp.org)). The Baker Company has also created an online library of links to articles and studies relevant to current trends and standards in pharmacy compounding. Visit us today at [www.bakerco.com/pharmacy](http://www.bakerco.com/pharmacy) to learn more, or call The Baker Company at 800.992.2537 to request a quotation or receive more information.