

## **Summary of USP\* 797 – Pharmaceutical Compounding – Sterile Preparations**

Source of base information – Pharmacopeial Form – Vol 29 (4) July – Aug. 2003

Effective date – January 1, 2004

FDA enforceable

Scope – “ The content of this chapter applies to health care institutions, pharmacies, physicians practice facilities and other facilities in which compounded sterile preparations are prepared, stored and dispensed. ”

### **Facilities Impacted by USP 797**

1. Facilities in which sterile products are prepared according to the manufacturers’ labeling and where manipulations are performed during the compounding of sterile products which increase the potential for microbial contamination of the end product.
2. Facilities where products are compounded using devices or ingredients which are not sterile to prepare products which must be sterilized prior to use.
3. Products may be biologics, diagnostics, drugs, nutrients or radiopharmaceuticals which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, irrigations, metered sprays, ophthalmic and otic preparations.

### **Microbial Contamination Risk levels**

#### **Low Risk Conditions**

Compounding with aseptic manipulations entirely with ISO Class 5 or better air quality using only sterile ingredients, products, components and devices

Examples –

- A. Using sterile needles and syringes to transfer sterile drugs from the manufacturer’s original packaging (vials, ampoules)
- B. Manually measuring and mixing no more than three sterile products to compound drug admixtures and nutritional solutions.

#### **Medium Risk Conditions**

Multiple individual or small doses of sterile products are compounded or pooled to prepare a compounded sterile product that will be administered either to multiple patients or to one patient on multiple occasions.

The compounding process includes complex aseptic manipulations other than the single volume transfer.

The compounding process requires an unusually long duration, such as that required to complete dissolution or homogeneous mixing.

The compounded sterile products do not contain broad spectrum bacteriostatic substances and they are administered over several days

For a medium risk preparation in the absence of passing a sterility test, the storage period cannot exceed the following time periods; 30 hours at room temperature, 7 days at cold temperature and 45 days in a solid frozen state at  $-20\text{ C}$  or colder.

Examples –

- A. TPN fluids compounded using manual or automated devices requiring multiple injections, detachments and attachments of the nutrient source products to the device or machine to deliver all nutritional components to the final sterile container.
- B. Filling of reservoirs of injection and infusion devices with multiple sterile drug products and evacuations of air from these reservoirs before the filled device is dispensed.
- C. Filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25 and 40 degrees.
- D. Transfer of multiple ampoules or vials into a single final sterile container or product.

## High

Non-sterile ingredients including manufactured products for routes of administration other than those listed under c in the introduction are incorporated or a non-sterile device is employed before terminal sterilization.

Sterile ingredients, components, devices and mixtures are exposed to air quality inferior to ISO Class 5. This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives

Non-sterile products are exposed to air quality inferior to ISO Class 5 for at least 6 hours before before sterilization

For high risk preparations in the absence of passing a sterility test the storage periods cannot exceed the following; 24 hours at controlled room conditions, 3 days at cold temperatures and 45 days for solid frozen state at  $-20\text{ C}$  or colder.

Examples-

- A. Dissolving non-sterile bulk drug and nutrient powders to make solution, which will be terminally sterilized.
- B. Sterile ingredients, components, devices and mixtures are exposed to air quality inferior to ISO Class 5. This includes storage in environment inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives
- C. Measuring and mixing sterile ingredients in non-sterile devices before sterilization is preformed.

**Personnel Training and Evaluation in Aseptic Manipulations Skills**

Personnel who prepare compounded sterile products must be provided with appropriate training from expert personnel, audio-video instructional sources, or professional sources before beginning to prepare products.

Personnel shall perform didactic review, written testing, media fill testing of aseptic manipulative skills initially and at least annually for low and medium risk levels and semi annually for high risk level compounding.

Media fill challenge testing will be used to access the quality of aseptic skills.

**Clean Rooms**

Low and medium risk

Must have an ante area but need not be separated with a physical wall.

Air classification or quality must meet ISO class 8 standards

Class 100,000

Positive pressure to adjacent areas per ISO 14644-4

Physical characteristics of construction:

Walls, floors, fixtures and ceilings should be smooth, impervious and free of cracks, crevices and non-shedding.

Surfaces should be resistant to damage from sanitizing agents.

Junctures of ceilings to walls should be coved and caulked.

If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic and they should be caulked around each perimeter to seal them to the support frame.

Walls may be panels locked together and sealed or epoxy coated gypsum board.

Floors should be overlaid with wide sheet vinyl flooring with heat-sealed seams and coving at the sidewall.

The buffer or ante area should contain no sinks or floor drains.

### Gowning

Before entering the ante or buffer area personnel should remove outer lab coats, make-up, jewelry and thoroughly scrub hands and arms to the elbow.

After drying hands and arms they should don clean non-shedding uniforms consisting of:

- Hair covers

- Shoe covers

- Coveralls or knee length coats ( coats to fit snugly at the wrists and be zipped or snapped in the front)

- Appropriate gloves

- Facemasks should be put on after entering the clean room

### Leaving and reentry

Upon leaving the clean room the coveralls or coat should be carefully removed and hung outside the entry in the buffer area. Coveralls and coats can only be using for one shift. All other coverings are to be discarded and new ones donned prior to reentry.

Reentry follows original gowning procedure.

### High risk

All of low to medium risk procedures and facilities except the ante area must be a separate room

### **Barrier Isolator (MIC)**

A well-designed barrier isolator is an alternative to an ISO class 5 (class 100) LAFW device in an ISO class 8 clean room. The barrier isolator should be supported by adequate procedures for operation, maintenance, monitoring and control.

#### Physical facility

It is not necessary to locate the barrier isolator in a ISO class 8 area.

#### Gowning

- Hair covers
- Shoe covers
- Lab coats
- Facemasks ( for covering facial hair)

### **Quality Assurance Program**

Must have a formal audit program

Formalized in writing

Consider all aspects of preparation and dispensing

Description of specific monitoring and evaluation activities

Specifications on how results are to be reported and evaluated

Identifications of appropriate follow-up mechanisms when action limits or thresholds are exceeded

Delineation of the individual responsible for each aspect of the QA program.

### **Validation Minimum Requirements**

Low to Medium Risk

Personnel validation – Three consecutive media fill runs without contamination

Revalidation - One media fill run quarterly without contamination

Failure of revalidation – Three consecutive media fill runs without contamination

#### High Risk

Personnel validation – Three consecutive media fill runs without contamination

Revalidation - One media fill run quarterly without contamination

Failure of revalidation – Three consecutive media fill runs without contamination

Process validation – Three consecutive media fill runs without contamination

Revalidation - One media fill run annually without contamination

Failure of revalidation – Three consecutive media fill runs without contamination

#### **Cleaning and sanitizing the workspaces**

Written procedures

At the beginning of each shift

#### **Environmental Monitoring**

Verification of sterile compounding equipment

Written plan and schedule for monitoring airborne organisms

Verification of particulate

Verification of viable microorganisms

#### **Verification of automated compounding devices for nutrition compounding**

Sterility testing

All high risk compounded sterile products

Administered by injection into vascular and central nervous systems that are prepared in groups of 25 identical or single dose packages or in multi-dose vials for administration in multiple patients.

