

USP <797>



A Road to Compliance **The New Mexico Board of Pharmacy**

What is the USP?

- The United States Pharmacopeia and The National Formulary (USP-NF) is a compilation of drug monographs, biologics, medical devices, dietary supplements, reference tests and standards, and standards for compounding of sterile and nonsterile drug preparations.
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Who uses the USP?

- *USP–NF* is recognized by law and custom in many countries throughout the world. In the United States, the federal Food, Drug, and Cosmetic Act (FD&C Act) defines the term “official compendium” as the official *USP*, the official *NF*, or any supplement to them. FDA may enforce compliance with official standards in *USP–NF* under the adulteration and misbranding provisions of the FD&C Act.
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Who uses the USP?

- In New Mexico's Drug, Device and Cosmetic Act is stated (26-1-16 B):
 - “ All official compendium requirements for the preservation, packaging, labeling and storage of dangerous drugs are applicable where drugs are held for dispensing to the public, whether by a pharmacy, clinic, hospital or practitioner. “
 - The official compendium for New Mexico is the USP-NF.
 - The New Mexico Board of Pharmacy is charged with enforcement of this law.
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What is the **PURPOSE** of <797>?

“THE INTENT OF <797> IS TO PREVENT HARM AND FATALITY TO PATIENTS THAT COULD RESULT FROM MICROBIAL CONTAMINATION (NONSTERILITY), EXCESSIVE BACTERIAL ENDOTOXINS, LARGE CONTENT ERRORS IN THE STRENGTH OF CORRECT INGREDIENTS, AND INCORRECT INGREDIENTS IN COMPOUNDED STERILE PRODUCTS (CSPs).”

Who does <797> apply to?

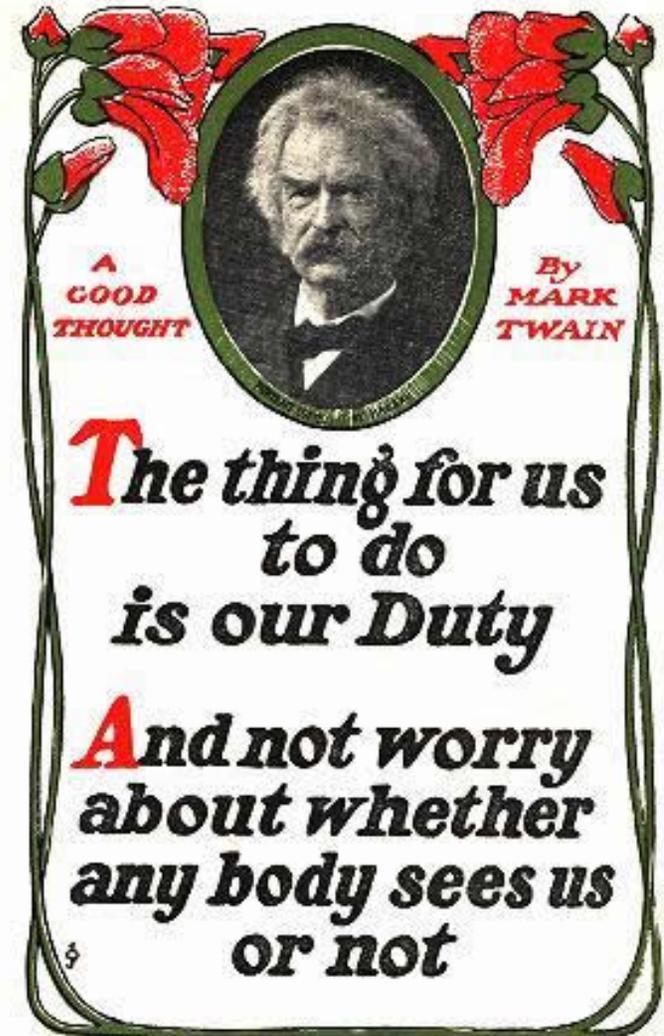
- The standards in this chapter are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared (e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, physicians' practice facilities, and other locations and facilities in which CSPs are prepared, stored, and transported). Persons who perform sterile compounding include pharmacists, nurses, pharmacy technicians, and physicians.
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USP 797

- “Diligence is a good thing, but taking things easy is much more--restful.”

- Mark Twain

Speech, 3/30/1901



USP 797

- Compliance with USP 797 is our *DUTY* because:

1. It improves the health and well-being of our patients

AND

- 2. In New Mexico, it is the law (NMSA 26-1-16. and NMAC 16.19.6.11).

A healthy patient is a happy patient!



USP 797 Also...

Is recognized by Joint Commission as a “valuable set of guidelines—contemporary consensus-based safe practices—that describes a best practice for establishing safe processes in compounding sterile medications”

Is included in the National Association of Board’s of Pharmacies’ MODEL STATE PHARMACY ACT and Model Rules

Is recognized by the New Mexico Board of Pharmacy in rule 16.19.6 as the standard for preparation of sterile products including drugs for injection or infusion.

Who is effected by 797?

Type of Facility Operations

- Hospital Pharmacy
- Home Infusion
- Retail Pharmacy
- Clinic
- Specialty
 - Nuclear pharmacy
- Compounding

Health Practitioner Facilities- for example

Ophthalmologist

Oncologist

Dermatologist



How does <797> *EFFECT* compounding practices in our daily routine?



How well maintained is the work space?

- Are things organized and free of “clutter”?
- Does everything work?
- Is there enough work space?



Work Environment

Look in the Refrigerator:

- Look for opened, undated and non-initialed Single Dose Vials (SDV) and Multiple Dose Vials (MDV)
- Look for food or other prohibited items
- Look for Temperature log
- Look around the sink and work area:
- Is there hand washing supplies (e.g. soap, nail brushes, lint-free wipes)?
- Hot and cold running water?
 - Organized or messy?
 - Properly maintained?



Work Environment



- Is there a lot of cardboard and other “unclean” material around?
 - Proper cooling capabilities:
Where is it located relative to the hood?
 - Waste and Sharp disposal:
Is it safe?
When does it get picked-up?
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Work Environment

“Busted Stuff or Expired Certificates”

- Gauges
- Temp recording “wheels”
- Hood certification stickers



Are policies and procedures in place and guidelines up to date and documented?

Do you like a clean area when you cook?

It's the same idea for compounding sterile products!!



Compounding Sterile Products

Type of CSPs:

- PCA
- Cardioplegia
- Inhalation
- TPN
- Eye Drops
- Large and small volume drugs for infusion
- Hazardous drugs for infusion (e.g.. Chemotherapy)



Sterility

- Definitions
- **Sterile:** When something is sterile it is free of any viable organisms.
- **Sterilization:** Any physical or chemical process which destroys all life forms, with special regard to microorganisms (including bacteria and sporogenous forms), and inactivates viruses.

Three methods used:

- 1. Physical: Moist heat, dry heat and irradiation
 - 2. Filtration (0.22 micron filter) is another method that **removes** but does not inactivate microorganisms
 - 3. Chemical: Gaseous or liquid sterilants (e.g. ethylene oxide) (EtO)
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Personnel Training and Garbing

- Personnel must receive appropriate training
- Since personnel are the largest particle generators, all personnel entering controlled areas must perform hand hygiene and garbing procedures
- *This includes any personnel performing cleaning- No exceptions!*
- *Only possible exception for garbing is for Isolators*



Personnel Garbing for Sterility

- Hair net
- Beard cover and face mask
- Gown
- Gloves
- Shoe covers

Sorry ladies-

- Make-up must be removed or not present and
- No jewelry

Wow! Is she serious?
Where is that hair net?



Sterility



- Hand hygiene is often described as the single most important way to reduce the risks of transmitting germs, and yet it remains the *most* violated of all infection control procedures
- Even after using anti-microbial soap, there is still about 20,000 microbes per sq. mm
- At least a 30-second hand and arm wash is required with a hands free sink
- **Rings/jewelry must be removed**

How Do We Meet Sterility Requirements?



Sterile product production

- The **ante-area or room** is where personnel hand hygiene and garbing procedures, staging, order entry, CSP labeling, and other high particulate generating activities are preformed.
- This room leads into the sterile IV and compounding room. This transition room needs to be an ISO 8 or better approved room that is pressurized to move particulate filled air through HEPA filters.
- The sterile IV products should be mixed in a **positive pressure room**
AND
in a ISO 5 or better approved hood

FOR CHEMOTHERAPY:

A **negative pressure hood** that is vented to the outside is needed that is ISO 5 or better *IN* a **negative pressure room**

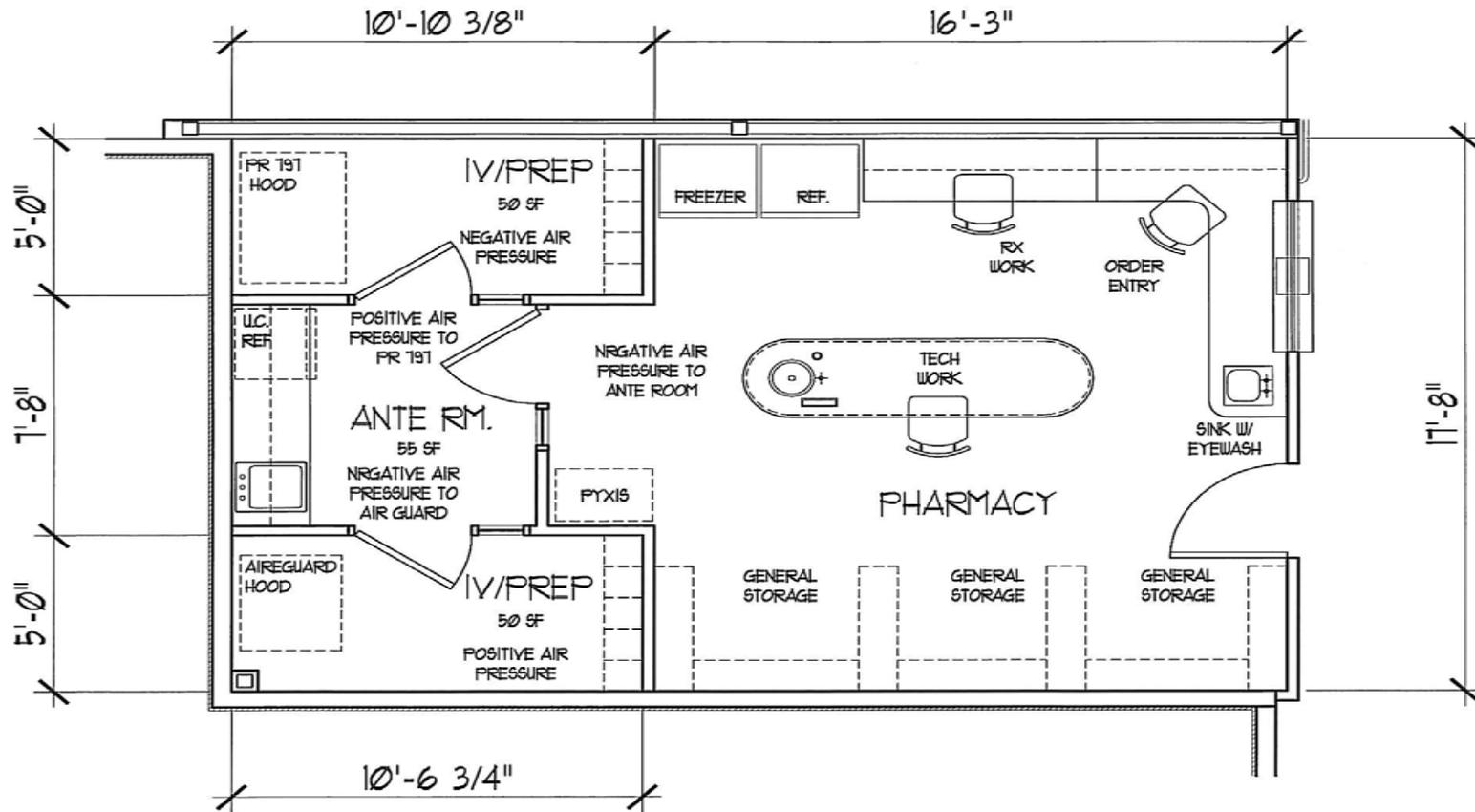
(SEE TABLE 1 for ISO specifications)

Table 1. International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air [Limits are in particles 0.5 μm and larger per cubic meter (current ISO) and cubic feet (former Federal Standard No. 209E, FS209E).]*

ISO CLASS	U.S. FS 209E	ISO, m ³	FS 209E, ft. ³
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3,520	100
6	Class 1000	35,200	1,000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

Class Name Particle Size ISO Class U.S. FS 209E ISO, m³ FS 209E, ft.³ Class 1 35.2 1 Class 10 352 10 Class 100 3,520 100 Class 1000 35,200 1,000 Class 10,000 352,000 10,000 Class 100,000 3,520,000 100,000* Adapted from the Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO [4644-1:1999 Clean rooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 μm per m³ or larger (ISO Class 5) is equivalent to 100 particles per ft³ (Class 100) (1 m³ = 34.314 ft.³).

An example...



- Sterile product facility

How are the CSP's stratified?



Compounding Conditions

- **CSP MICROBIAL CONTAMINATION RISK LEVELS**

- **IMMEDIATE USE CSP:**

- —Simple transfer of not more than 3 commercially manufactured packages of sterile **nonhazardous** products. The compounding procedure is a continuous process not to exceed 1 hour. If administration has not begun within that hour the CSP is to be discarded
- —CSP shall bear a label with patient identification information, and the names and amounts of all ingredients

- **ALLERGEN EXTRACTS**

- Allergen extracts as CSPs are single and multiple-dose intradermal or subcutaneous injections that are prepared by specially trained physicians and personnel under their direct supervision. Allergen extracts as CSPs are NOT subject to the personnel, environmental, and storage requirements for all CSP *Microbial Contamination Risk Levels* in this chapter. But certain requirements **DO NEED** to be met. See USP <797> for complete specifications.
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Compounding Conditions

LOW-RISK LEVEL

- **Compounded entirely under ISO Class 5 (Class 100) conditions**
 - **Compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems**
 - **Manipulations are limited to aseptically opening ampule, penetrating sterile stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile administration devices and packages of other sterile products**
 - **In the absence of passing a sterility test, periods cannot exceed the following time periods: Before administration, the CSP's are properly stored and are exposed for not more than 48 hours at a controlled room temperature, for not more than 14 days at a cold temperature, and for 45 days in solid frozen state at – 20 degrees or colder.**
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Compounding Conditions

MEDIUM-RISK LEVEL

- All conditions apply as listed under low-risk level
 - Compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems that are performed promptly and attentively
 - Manipulations are limited to aseptically opening ampuls, penetrating sterile stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile administration devices and packages of other sterile products
 - Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple conditions
 - Compounding process includes complex aseptic manipulations other than the single-volume transfer
 - Compounding process requires unusually long duration
 - The sterile CSPs do not contain broad-spectrum bacteriostatic agents, and are administered over several days. In the absence of passing a sterility test, periods cannot exceed the following time periods: Before administration, the CSP's are properly stored and are exposed for not more than 30 hours at a controlled room temperature, for not more than 7 days at a cold temperature, and for 45 days in solid frozen state at – 20 degrees or colder
-

Compounding Conditions

HIGH-RISK LEVEL

- **Non-sterile ingredients 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 (Class 100)**
 - **Non-sterile preparations are exposed for not more than 6 hours before being sterilized**
 - **Non-sterile preparations are terminally sterilized but are not tested for bacterial endotoxins**
 - **It is assumed that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients**
 - **The sterile CSPs do not contain broad-spectrum bacteriostatic agents, and are administered over several days. In the absence of passing a sterility test, periods cannot exceed the following time periods: Before administration, the CSP's are properly stored and are exposed for not more than 24 hours at a controlled room temperature, for not more than 3 days at a cold temperature, and for 45 days in solid frozen state at – 20 degrees or colder**
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USP <797> Cabinets/Hoods

- How do we work aseptically in the hood?



Utilizing unidirectional airflow

- **First Air Zone**

Nothing to be placed between the HEPA filter and the critical compounding zone

- **Zone of Confusion**

Turbulent area downstream of an obstruction
possible source of cross contamination

- The advantages of unidirectional airflow should be exploited when considering placement of materials within the DCCA.
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Improper hand placement disrupts first air



Facility design and environment control

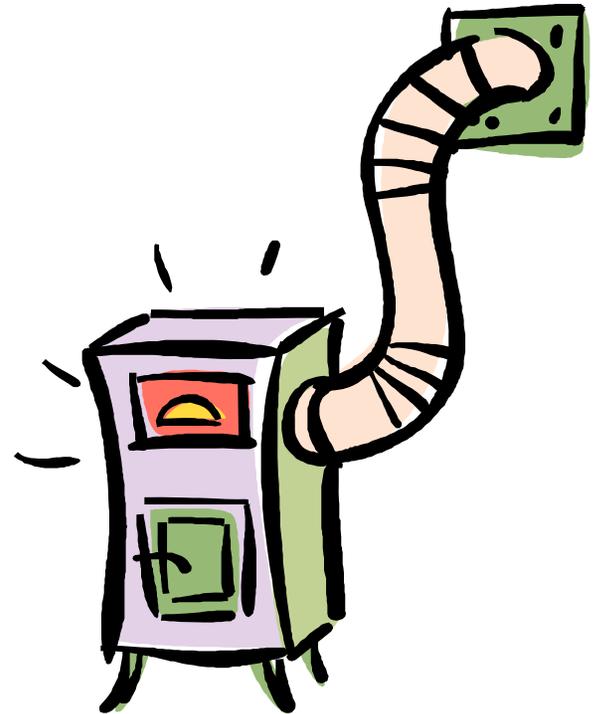
- Good aseptic technique in sterile compounding requires the understanding and proper use of “First-Air”.
 - “First-Air” is the air exiting the HEPA filter in a unidirectional air-stream and is virtually free of particulate contaminants.
 - All critical manipulations must be carried out in the unobstructed “first air” zone in the direct path of the HEPA filter discharge.
 - Proper product and process:
placement with respect to the supply and discharge will provide a contamination free compounding area.
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Proper hand placement permits first air



SO... How clean *IS*... it?

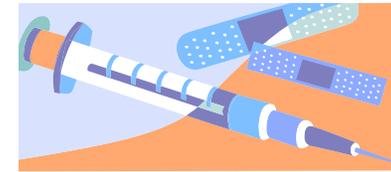
- De-activating microorganisms thru
 - Heat
 - Moisture
 - Autoclaving



Quality Assurance of Sterility thru Filtration

- **Size and configuration of filtration devices should accommodate the volume being filtered to permit complete filtration without clogging.**
 - **Filter and housing should be physically and chemically compatible with the product to be filtered and capable of withstanding the temperature, pressures and hydrostatic stress imposed on the system.**
 - **Filter manufacturers can provide information on the compatibility of their filter material and solutions being filtered**
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Filtration continued...



- Filtration removes microorganisms (bacteria, yeasts, molds and viruses) and particles larger than 0.22 microns
 - Filtration is the method of choice for heat-sensitive liquids such as antibiotic solutions, toxic chemicals, radioisotopes, vaccines, carbohydrates, and EtOH
 - Sterilizer filters should be validated by the manufacturer and documented in the filter's Certificate of Performance for filter
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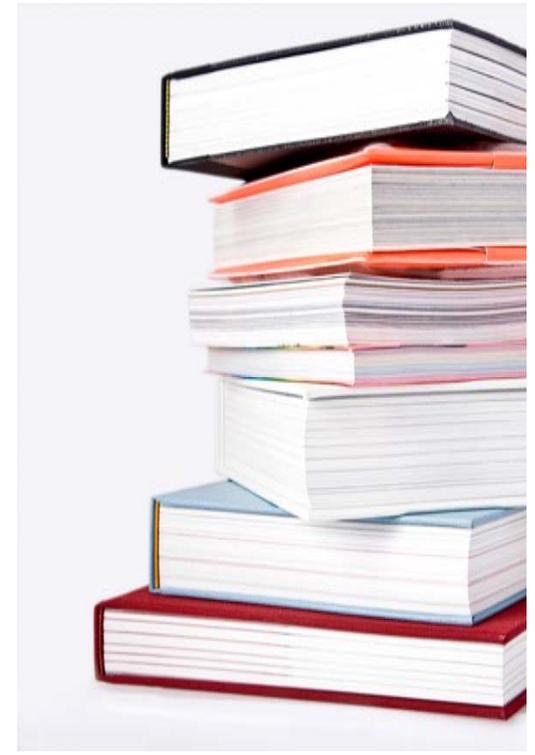
How do we remember everything that we need to do to be compliant?



Policies and procedures

USP <797> requires policies and procedures for all aspects of sterile compounding from personnel to product that:

- Communicates information
- Facilitates continuity
- Aids in audit and peer review activities
- Improves likelihood that Standard Operating procedures are followed
- Provides data for benchmarking
- Documents regulatory compliance
- Provides data valuable in cost evaluations
- Acts as the *best* witness in a court of law



Documentation

- 1. If it isn't written down, it didn't happen.
- 2. If it isn't written down *correctly*, it still didn't happen.
- 3. Don't forget rules 1 and 2.

- **Documentation should be simple, unambiguous, easy to read**

- **Documents should be kept up-to-date**

Do you have:

- 1. Correct form
- 2. Correct information on form
- 3. Form is complete
- 4. Information is legible and readily accessible
- 5. Demonstrates conformity: ZERO GAP between actual performance and established policy



How will everyone learn these rules?



Compounding Area: Personnel Training & Evaluation

■ Janitorial Staff

- 1. Proper cleaning procedures
- 2. Isolated cleaning equipment
- 3. Documentation

■ Facility Staff

Regularly Scheduled Training

Training is critical on:

1. Daily calibration
2. Proper use
3. Documentation

- Competency Evaluation of Garbing
- Competency Evaluation of Cleaning/Disinfecting Procedure
- Competency Evaluation of Aseptic Work Practices
- Environmental Monitoring



In Conclusion

■ YES!!!!!!



Activities Needed for Compliance

How to Identify key activities in the facility

- **These may be observed during a compliance visit that can be used to quickly determine if a pharmacy has a strong quality management system.**
- **Ask “Can you show me. . . .the following process?”**

Identify acceptable methods of compliance for the following activities:

- **Documentation of lot numbers, expiration dates and manufacturer’s name**
-

Activities Needed for Compliance

Please show me. . .

Proper use of pharmacy equipment thru certification/demonstration of:

- **Calibration of electronic scales, balances or compounding pumps**
 - **ISO Class 5 primary engineering controls (e.g. LAFWs)**
 - **The use of biological indicators**
 - **0.22 micron filters**
 - **Proper employee hand hygiene and garbing procedures**
 - **Remember... Document, Document, Document. EVERYTHING!!!**
-

Activities needed for compliance

Please show me. . . .

- **Proper aseptic technique**
- **Principles of “First-Air”**
- **Identify three critical metrics necessary to ensure that quality is being monitored**
- **Documentation**
- **Temperature logs**
- **Cleaning logs**
- **Calibration records**
- **Expiration date checks**
- **Environmental Monitoring**
- **Air sampling**
- **Employee training records**
- **Didactic training records and written tests**
- **Psychomotor skill assessments**
- **Aseptic media fill**



In Summary. . .

- **USP <797> HAS SPECIFIC GUIDELINES FOR:**
 - **Design of the Facility**
 - **Environmental and Engineering Controls**
 - **Environmental Testing**
 - **Personnel Training and Competency Testing**
 - **Standard Operating Procedures and Documentation**
 - **Quality Assurance**
 - **Patient Monitoring and Adverse Events Reporting**
 - **Storage and Dating**



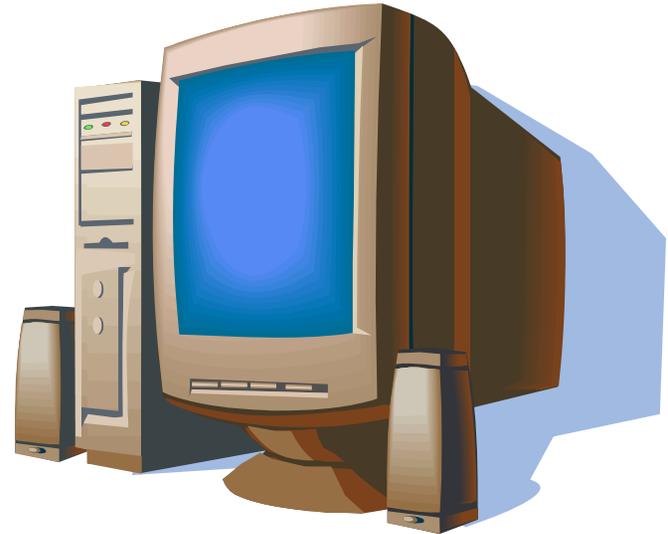
Finally....

- Each chapter of the USP/NF is assigned a number. The general chapters that are numbered <1> thru <999> are enforceable by the FDA. The FDA defers to the states to enforce the practice of pharmacy . In New Mexico the law/rules pertaining to CSPs are NMAC 16.19.6.10 -11 and 16.19.7.9. and NMSA 26-1-16.
- Please refer to the USP/NF online or hard-copy for the most current and complete edition/revisions of <797>. This is a comprehensive guide to the compounding of sterile products. As new technology develops and new information is discovered, these chapters will evolve, so remember these are the *minimum standards* for safe compounding of Sterile Products at this time.



Resources

- CLASSES/TRAINING
- ORGANIZATIONS WEBSITES:
- www.cetainternational.org
- WWW.CRITICALPOINT.INFO
- WWW.NMSHP.COM
- WWW.MCNHEALTHCARE.COM
- WWW.USP.ORG
- WWW.SAFEHOPITAL.ORG
- WWW.CMICENTERS.COM
- WWW.PHARMACYEDUCATION.CC
- WWW.ASHP.COM
- WWW.BAXA/COM/STARCENTER.COM
- www.USP797.org.org/Vendors.htm
- www.rxinsider.com/laminar_flow_pharmacy_hoods_cleanrooms.htm



Resources

- AND OF COURSE.....

THE NEW MEXICO BOARD OF PHARMACY IS HERE TO HELP YOU!!

www.rld.state.nm.us/pharmacy

Or 505-222-9830

THANK YOU !!

