NAVIGATING USP <797>

GREG STANLEY RPH

MAY 21ST, 2020

DISCLOSURE

- My presentation represents my views and opinions on achieving compliance with USP <797>. It does not represent the views of any organization, membership or affiliation.
- All participants are encouraged to obtain official interpretations or explanations directly through USP and your State Board of Pharmacy.
- USP FAQ / Public Comment Periods

LEARNING OBJECTIVES

- Understand the evolution of USP <797> and how it has changed pharmacy practice.
- Identify regulatory agencies who may enforce the chapter.
- Be able to differentiate the requirements for Category 1 and Category 2 compounding.
- Will summarize training and competency requirements for compounding staff.

LEARNING OBJECTIVES CONTINUED

- Better understand engineering controls and requirements.
- Summarize environmental monitoring requirements and discuss the role of technician support to perform these tasks.
- Be familiar with beyond use date restrictions of compounded sterile products (CSPs) made in various environments.

THE TRAJECTORY OF USP <797>

- 1993: ASHP Technical Assistance Bulletin
- 2002: USP changed from <1206> to <797>
  - Paves the way for enforceability
- 2004: Version 1 made official
  - Makes the standards applicable to ALL healthcare organizations
- 2005: Formation of Sterile Compounding Committee
  - Public comment periods

THE TRAJECTORY OF USP <797>

- 2008: Version 2 becomes official
- 2016: USP <800> is published
  - Creates the framework for environmental and healthcare worker protections related to HDs
- 2018: Proposed USP revisions and extensive public comment
- June 1st, 2019: USP <795> (non-sterile) and <797> published
- December 1st, 2019: OFFICAL DATE FOR ALL THREE CHAPTERS !!! (or so we thought)

NOTICE OF INTENT TO REVISE <795>, <797>, AND <825>

- 09/23/2019: Various stakeholders submitted formal appeals on these compounding chapters.
- USP appeal hearings 1/21 + 1/22/2020.
- Previous versions of USP <795> (2014) and USP <797> (2008) will remain official.
- Appeals were granted to USP <795> and <797> (BUDs). USP <825> appeal denied.

EARLY ADOPTION

- In USPs formal announcement, early adoption of the revised standards in advance of the official date is permitted. However, speak with appropriate regulators in your state to determine what is required.
- The appeals center around the following:
  - BUD provisions that were described in USP <795> and USP <797>
  - Removal of Alternative Technology provisions
  - Applicability to veterinary practitioners

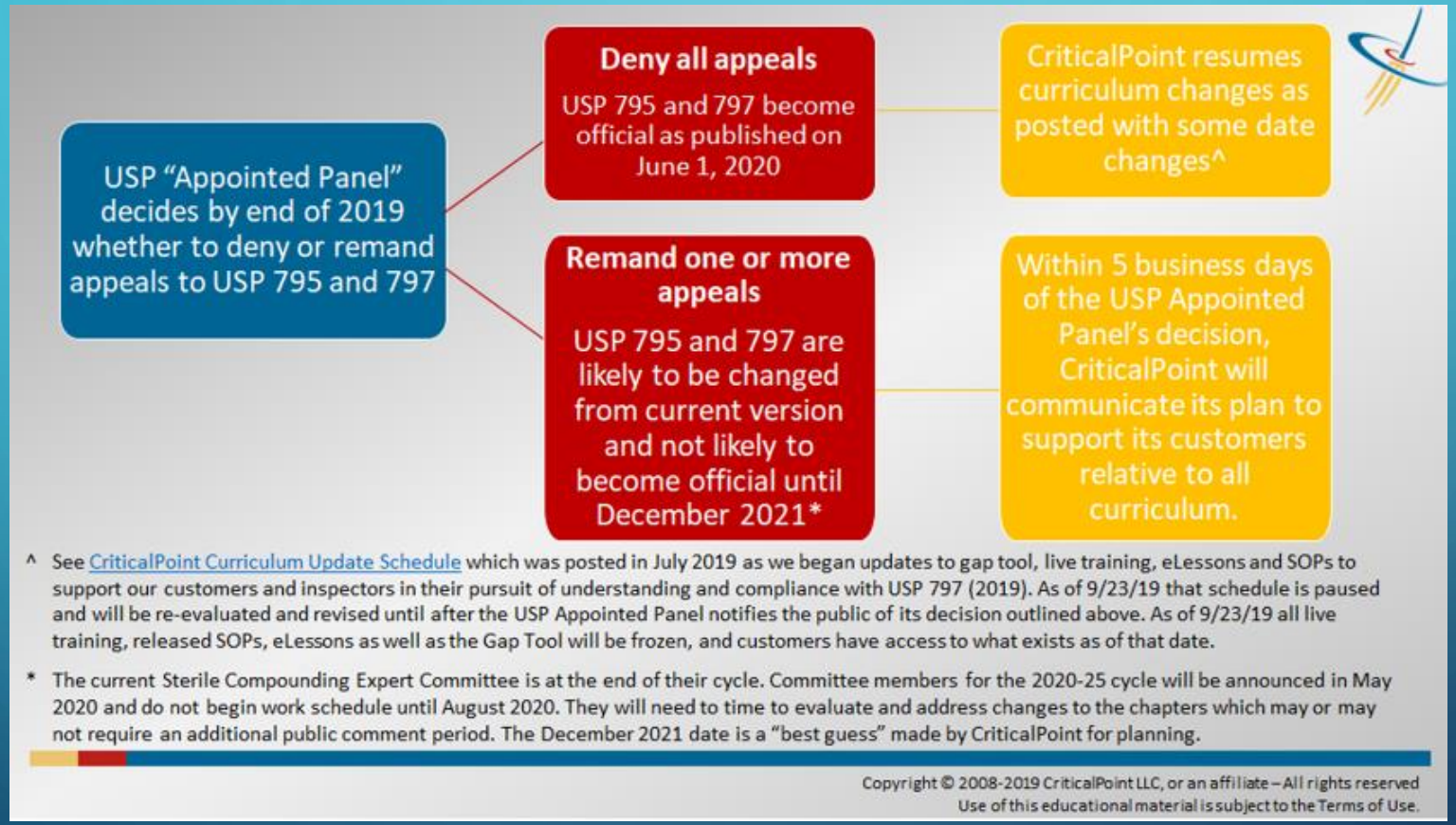
WHERE DOES LEAVE US WITH USP <800>?

- <800> is not subject to any pending appeals and will become enforceable on 12/1/19 as scheduled.
- However, even though it is assigned a numerical value <1000, USP <800> is informational and not compendially applicable. Not listed in the General Notices standards that apply to compounding
- State and federal regulators, however, can adopt enforceability of USP <800> and it is strongly encouraged to adopt the standards in the interest of employee/patient health.

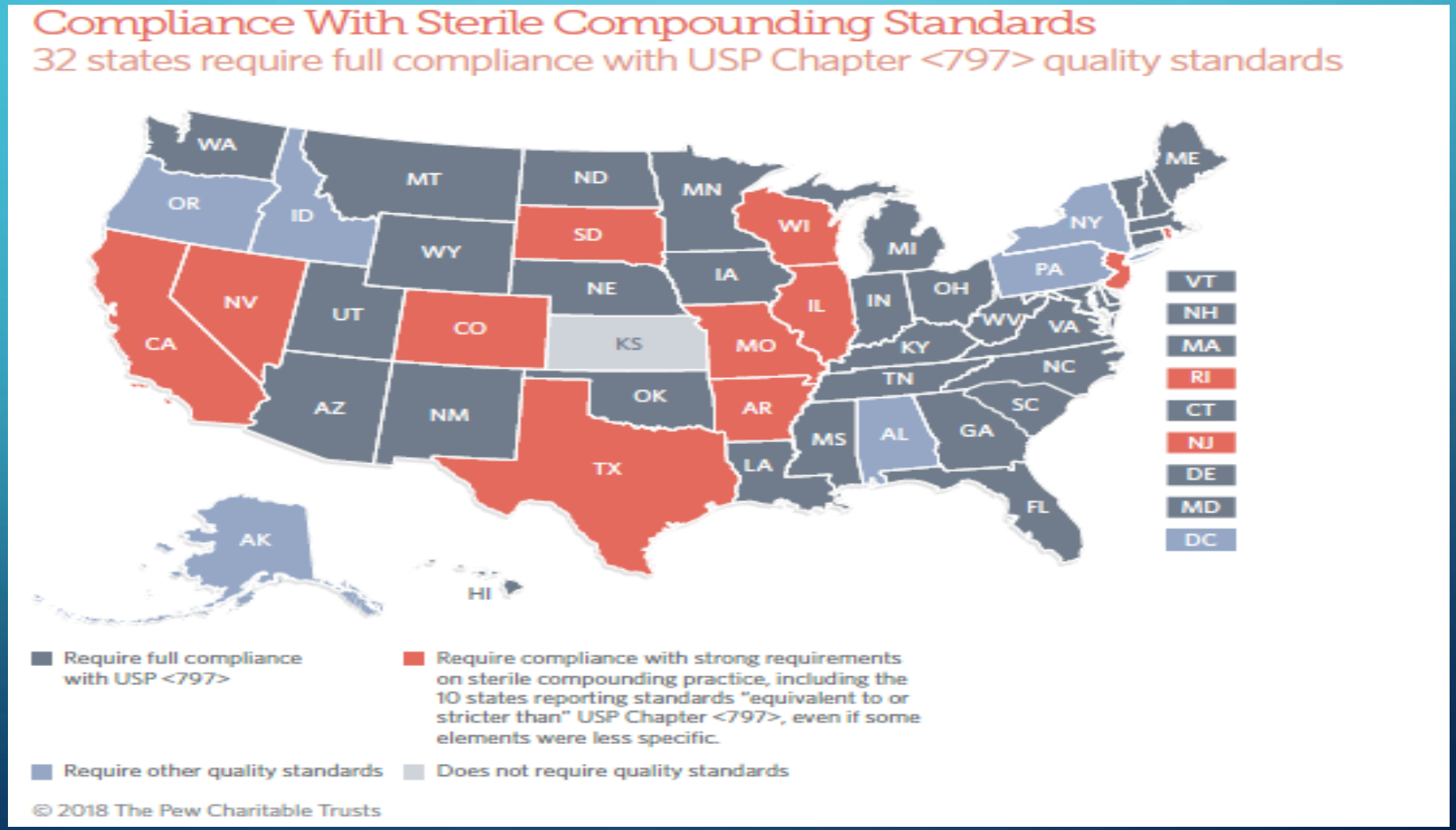
WHAT SECTIONS ARE NOT HARMONIZED

- There are two conflicts that exist between the current <797> 2008 and <800>
  - Segregated Compounding Area (SCA)
    - USP 797 only allows low risk, NONHAZARDOUS CSPs with 12 hour BUD
    - USP 800 allows for HD compounding in a Containment-Segregated Compounding Area
  - Low Volume HD Compounding
    - USP 797 allows “low volume” HD compounding with two tiers of containment
    - USP 800 requires a Containment Secondary Engineering Control (C-SEC)

WHAT CAN WE NOW EXPECT



WILL NYS BOP MAKE A FORMAL ANNOUNCEMENT



BEFORE WE PROCEED

- It is important to consider that these new standards represent the MINIMUM REQUIREMENTS to ensure proper sterile compounding and patient safety.
- What will the next version require?
- Do we evaluate cGMP guidance to steer our planning?
- What additional changes should you made that reflect BEST PRACTICE RECOMMENDATIONS?
- What are the views of the various regulatory agencies?

SECUNDUM ARTEM MY ARRSSS !

- Historically, there was an elegance and art associated with pharmacy compounding.
- The consequence was a variability in processes leading to tragic results.
- USP recognized it needed to “bridge the gap” between traditional pharmacy compounding and Current Good Manufacturing Practices (cGMP).
- Quality is built into the process.

REGULATORY ALPHABET SOUP

- USP has NO role in enforcement.
- State Board of Pharmacy.
- CMS: Required under its Conditions for Participation.
- TJC / DNV / URAC (specialty) / ACHC (home care).
- FDA ???

DRUG QUALITY AND SECURITY ACT (DQSA)

- Title 1 created a “safe harbor” under section 503A.
  - Holy trinity of Drug, Order, Practitioner
  - Limited activities were permissible to satisfy anticipatory needs
- 503B Outsourcing
  - FDA registration and oversight, meeting cGMP requirements
- “Insanitary Conditions” and others allowed for FDA inspection of 503A
  - In 2016-2017 there were 185 form 483s issued by the FDA

NECC UPDATE

- New England Compounding Center
  - Fungal meningitis outbreak statistics as of May, 2019:
    - 793 patients across 20 states
    - 100 deaths (up from 64 reported in January 2018
    - SP Glenn Chin sentenced to 8 years in prison
    - Owner Barry Cadden sentenced to 9 years in prison
    - 13 Total defendants associated with NECC have been convicted of a total of 178 charges

DESIGNATED PERSON

- Like USP <800> The compounding facility MUST designate one or more individuals to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs.
- Does not indicate the minimum experience requirements or licensure.
- Someone at your facility needs to LIVE IT, BREATH IT and be granted the proper RESOURCES to achieve success.
- Lots of training and programs are available.

SCOPE AND SETTINGS AFFECTED

- Chapter clearly specifies what products MUST be sterile:
  - Injections
  - Irrigation for INTERNAL body cavities
  - Ophthalmic dosage forms
  - Pulmonary inhalations
  - Tissue and organ soaks
  - Implants

USP <797> IS NOT JUST A PHARMACY ISSUE

- Applies to ALL PERSONS who prepare CSPs and ALL PLACES where CSPs are prepared.
- Pharmacists, technicians, nurses, physicians, dentists, veterinarians, etc..
- All practice locations: hospitals, surgical treatments sites, infusion suites, and physician practice sites.
- Please note that administration of medication is out of the scope of this chapter.

THIS COUNTER-TOP WILL DO

- Exemptions for direct and immediate administration to a patient are granted under the IMMEDIATE USE CRITERIA.
  - 1. Aseptic processes and procedures followed (demonstrate nurse proficiency)
  - 2. Evidence based compatibility information is used
  - 3. No more then 3 sterile products (drug, diluent, bag).. Multiple vials ok
  - 4. Single dose containers used for only 1 patient (no communal bags or products)
  - 5. Administration BEGINS within 4 hours from the time that preparation started
  - 6. Labelling requirements if not given or witnessed by the preparer

PREPARATION VERSES COMPOUNDING

- It is not considered compounding when performing preparation of a sterile product in accordance with approved labelling directions (FDA approved PI).
- USP <797> or <800> is not applicable or compendially required in these contexts.
- We still must do the right thing for a patients and our personnel.
  - This should not be an excuse to off load activities to nursing departments
  - Will employee protections considering ALARA work practices trump this for HDs?

NEW CATEGORIZATIONS FOR CSPS

- OLD methodology considered the COMPLEXITY of making a CSP
  - Low, Medium and High Risk
- NEW methodology considers the CONDITIONS under which they are made, microbial growth concerns, and time periods.
  - Category 1 and Category 2
  - All CSPs have the potential to cause harm, training requirements should be universal
  - What about Category 1.5 ??? Is 90% compliant really compliant ???

IN THE WORDS OF ARISTOTLE

We are what we repeatedly do. Excellence, then, is NOT an act, but a habit.

TRAINING

- Proficiency in Core Competencies EVERY 12 months
  - Demonstrated via written or electronic testing
  - Subscription based services available
  - Compounding staff verses “Checking Staff”
    - BOPs and regulators have varied opinions on this
    - What about staff accessing the compounding area?
      - ENVIRONMENTAL SERVICES

TRAINING

- Garbing and Hang Hygiene EVERY 6 months.
  - VISUAL observation
  - Gloved finger tip AND thumb
    - Plates verses Paddles
    - Initial testing is used to assess ones ability to perform proper handwashing and garbing
      - 3 times after SEPARATE and distinct hand washing/garbing activities
    - Ongoing testing is used to assess ones ability to maintain sterile technique
      - Conducted AFTER media fill testing inside a PEC (ISO-5) environment

TRAINING

- Aseptic Technique evaluations EVERY 6 months.
  - Simulate the MOST difficult and challenging compounding procedures
  - Aseptic technique KITS should be evaluated
- Use of commercial sterile growth media
- Purchase 2 Incubators
  - MAYBE 4 if conducting sterility assurance testing

CLEANLINESS IS NEXT TO GODLINESS

- People are the dirtiest thing in our controlled environments
  - Nail Picks
  - Eyeglass stations
  - Closed system of soap
  - Low-lint towels
- Note: SOPs will need to be individualized to your lab based on sink location, movement of materials, etc..

GARBING

- Evaluate each piece of Personal Protective Equipment (PPE)
- Gowns may be used for an entire shift
- Hospital scrubs verses street clothes
- ASTM-6978 compliant gloves for all activities?

ENGINEERING TO THE DECK

DO YOU HAVE A “SCOTTY”?

PRIMARY ENGINEERING CONTROLS (PEC)

- Laminar AirFlow Systems (LAFS): ISO5, unidirectional airflow
  - Laminar AirFlow Workbench (LAFW): Horizontal or vertical
  - Integrated Vertical Laminar Flow Zone (IVLFZ): Challenges with flow
  - Biological Safety Cabinet (BSC): Class 2 A2 or B2, HD compounding
- Restricted Access Barrier Systems (RABS): Glove boxes
  - Compounding Aseptic Isolator (CAI)
  - Compounding Aseptic Containment Isolator (CACI): HD compounding

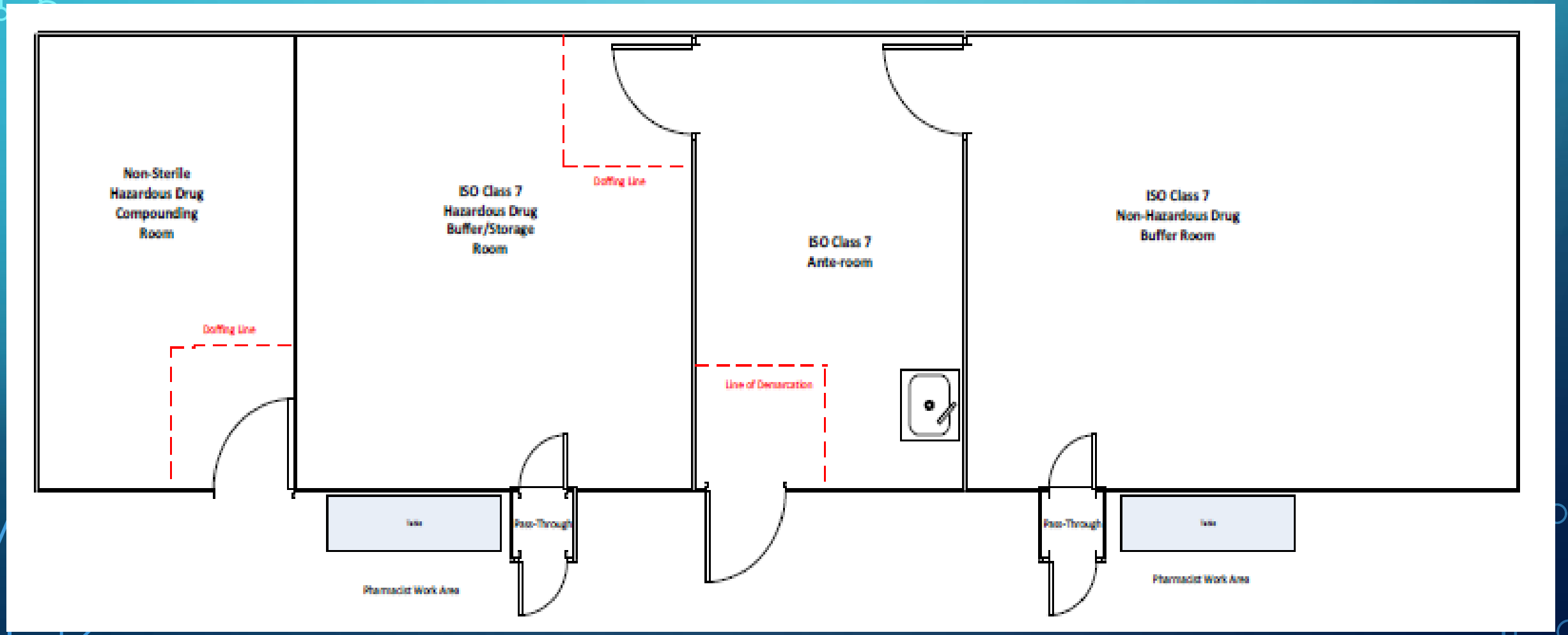
SECONDARY ENGINEERING CONTROLS (SEC)

- Cleanroom Suite
  - ISO-8 Ante-Room (ISO-7 if communicating to HD buffer room)
    - Line of Demarcation (LOD) required: dirty-side vs clean side (sink location?)
    - Should not be considered a stock location
  - ISO-7 Buffer Room
    - Positively pressurized for sterile compounding
    - Negatively pressurized for HD sterile compounding

HEPA SUPPLIED ROOM AIR

- Air supplied to the cleanroom MUST be introduced through HEPA filters located in the CEILING of the buffer AND ante-rooms.
  - Remote air handlers are no longer compliant
- With redesign or new construction consider:
  - HEPA accessibility (room accessibility is preferred)
  - Although ISO-8 must have 20 ACPH, buffer room 30 ACPH ; you may want 60 ACPH in ante-room and 45 ACPH in buffer room

SAMPLE CLEANROOM



TOUR YOUR CLEANROOM

- Surfaces MUST be smooth, impervious, free from cracks/crevices, and non-shedding (SCAs are SHOULDS, C-SCAs still should have these fit and finishes)
  - Ceilings
    - Gypsum board with 2 component epoxy paint
    - Heavy gauge polymer panel
    - Inlaid ceiling panels which are cleanroom rated and caulked to support grid
  - Walls
    - Gypsum board or polymer panel

FIT, FINISHES AND FIXTURES

- Floors
  - Sheet vinyl or rubber (no tiles)
  - Consider colored vinyl line of demarcation verses tape
  - Epoxy poured floor
  - Coving to walls OR baseboard caulked to floor and wall
- Windows and Doors
  - Flush with no ledges

FIT, FINISHES AND FIXTURES

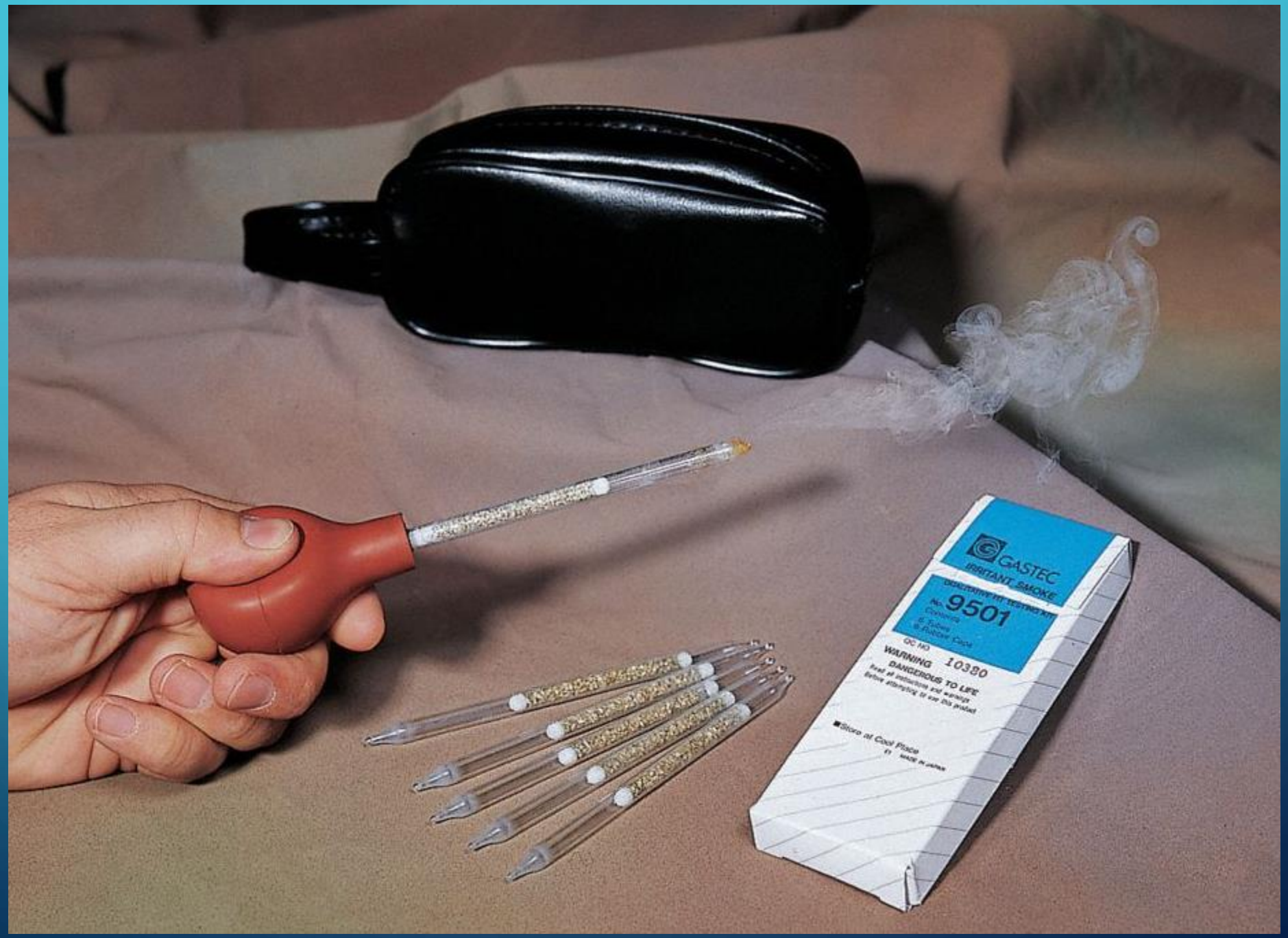
- Doors
  - Anodized aluminum or Epoxy painted metal/reinforced polymer
  - No wood
- Light fixtures
  - Sealed and flush
- Stainless steel work counters, shelving, carts (avoid bleach)
- Evaluate pass-through for porous materials
- Place all shelving and work stations on casters

MONITORING

- Temperature and Humidity
  - SHOULD be 20C or cooler, and Rh < 60%
  - MUST be monitored in EACH room EACH day
  - Documented DAILY or stored in recording device
- Pressure Differentials
  - Minimum Positive Diff of 0.02wc between EACH classified area (HD: neg 0.01-0.03)
  - CONTINUOUSLY MONITORED
    - Review, Documentation, Record Retention (Pharmacy verses Physical Plant?)

CERTIFICATION COMPANY

- DYNAMIC conditions
- Smoke studies in PECs: teaching tool to visualize DCA, first air
  - Smoke studies if you do not have low wall returns, assess HD refrigerators
  - DO you consider conducting yourself?
- ACPH and particle counts for ISO classification
  - Report must differentiate air exchange rate from PECs and SECs separately
- HEPA filter integrity testing


GASTEC
IRRITANT SMOKE
9501
WARNING
DANGEROUS TO LIFE

DO NOT ASSUME CERTIFICATION IS DONE CORRECTLY

- It is the responsibility of the DP to ensure and prove compliance with applicable standards.
- Ask for certification from your vendor
  - CETA CNBT (Controlled Environment Testing Association – CETA National Board of Testing)
  - NSF accreditation for certified of Class 2 BSCs
- Read and understand CAG-003
- Documentation of testing conducted, referenced SOPs, calibration certificates, etc.

PROPER VETTING OF CERTIFICATION COMPANIES

- CAG-000 Application Guide Creation Flowchart (Revised 2019)
- CAG-001-2005 Applications Guide For The Use Of Compounding Isolators In Compounding Sterile Preparations In Healthcare Facilities (Revised December 2008)
- CAG-002-2006 Compounding Isolator Testing Guide (Revised December 2008)
- CAG-003-2006 Sterile Compounding Facilities (Revised May 2015)
- CAG-004 Biological Decontamination and Disinfection of Accessible Surfaces in Biosafety Cabinets (Revised 2019)
- CAG-005-2007 Servicing Hazardous Drug Compounding Primary Engineering Controls
- CAG-006-2010 CETA High Efficiency Filter Application Guide
- CAG-007 Exhaust System Requirements of Class II Biosafety Cabinets (Revised 2019)
- CAG-008-2010 CETA Certification Matrix for Sterile Compounding Facilities (Updated January 2012)
- CAG-009-2011v3 CETA Certification Application Guide USP <797> Viable Environmental Sampling & Gowning Evaluation
- CAG-010-2011 Application Guide for Informational Notes to Meeting the NSF/ANSI 49:2010a Standard Requirements

AM I A MICROBIOLOGIST NOW TOO?

Microbiological Air and Surface Monitoring

** Technician Career **

ENVIRONMENTAL MONITORING

- Volumetric active air sampling in ALL classified areas during DYNAMIC conditions EVERY 6 MONTHS (Monthly for trending)
- Surface Sampling EVERY MONTH
  - Purchase own equipment
  - DO you continue to use certification company? What about remediations?
  - Research Credentialed Environmental Testing Labs (ISO 17025)
  - Genus Level ID required when action levels EXCEEDED
  - Data Review with infection control departments, physical plant, ES, HVAC

ACT ON THE DATA

- Compounding facility MUST investigate findings and develop a remediation plan.
  - Skin flora (hand hygiene and garbing)
  - Mold spores (packaging materials, disinfecting supplies)
  - Gram negative rods (water sources)
- If you are demonstrating that you are maintaining an environmental state of control, does this satisfy an inspector when there is non-compliance with engineering controls (construction delays, limited vendors)?

CLEANING AND SPORICIDAL AGENTS

- No such thing as an odorless sporicidal agent.
  - Respiratory protection
- Use EPA registered one-step disinfectant cleaners.
- Some sporicidal agents all can be suitable for decontaminating surfaces exposed to HD residues.
- 70% IPA must be STERILE (EPA agents do not have to be sterile)
- Research dwell times and interactions with surfaces (bleach)

PAPRS

Work with EHS and infection control departments and establish a team of individuals who are trained and medically cleared to wear appropriate PPE needed for monthly sporicidal cleaning activities.

STERILIZATION

- Highly specialized area of pharmacy compounding
  - Depyrogenation (dry heat)
  - Steam (autoclave)
  - Irradiation
- Sterilization by filtration is NOT terminal sterilization
  - Research “sterilization” grade filters (pore size, bacteria challenge testing)
  - Bubble point testing

MASTER FORMULATION AND COMPOUNDING RECORDS

- MFs: Must be created when batching or compounding from non-sterile starting components.
  - Make sure your documentation system has all the required elements
  - List a reference source to support the stability (USP monograph or a properly designed stability indicating study)
    - Evaluate your reference data in regards to drug, vehicle, bracketed concentrations, container
    - What will be process for regular review of reference sources

COMPOUNDING RECORDS

- CRs: Make sure your Rx label, order or workflow management system contains all the required information (date AND time of preparation)
- As you integrate technologies into your organization, evaluate the terminology used.
  - Struggles with BUD verses expiration date
  - “Hang by”
- Lot and Expiration dates for components ONLY required when making for more than 1 patient or from non-sterile ingredients (what happens in 2022/3)

BUDS

OLD DATING

Beyond-use dating for CSPs according to Risk-Level			
Risk Level	BUD at Room Temperature (20 to 25° C)	BUD under Refrigeration (2° to 8° C)	BUD with Frozen Storage (-25 to -10° C)
Immediate Use	1 hour	N/A	N/A
Low Risk with 12h BUD	12 hours	12 hours	N/A
Low Risk	48 hours	14 days	45 days
Medium Risk	30 hours	9 days	45 days
High Risk	24 hours	3 days	45 days

CATEGORY 1 DATING RESTRICTIONS

- For an SCA

Table 10. BUDs for Category 1 CSPs

	Storage Conditions	
	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)
BUD	≤12 hours	≤24 hours

- No Category 1.5 or guidance on reduced dating for CATEGORY 2
- All dating considers the shortest of STERILITY and STABILITY dates

CATEGORY 2 DATING RESTRICTIONS

PEC placement	Must be placed in ISO 7 Buffer Room served by ISO 7/8 ante-room				
Sterility Testing (ST)	See "ST" BUD assignment below				
Endotoxin Testing	Required if nonsterile ingredients used and if assigned a BUD that requires ST				
Storage	Greater than 12 hours room or 24 hours refrigerated				
Specific BUD Assignment	**Method**	**Sterility Testing**	**Controlled Room**	**Refrigerated**	**Frozen**
	Aseptically prepared CSPs	NO	**Made from 1 or more *nonsterile* components**		
			1 day	4 days	45 days
			Made with all *sterile* components		
			4 days	10 days	45 days
		YES	30 days	45 days	60 days
	Terminally Sterilized CSPs	NO	14 days	28 days	45 days
		YES	45 days	60 days	90 days

WHAT ARE YOUR OPTIONS

- Category 1 dating for SCAs or non-compliant labs
- Outsourcing by use of registered 503B pharmacies
  - Responsibilities for properly vetting external vendors
- Category 2 dating without sterility assurance testing
  - Can you live in a 4 day / 10 day world
  - Consider your distribution model (Automated dispensing cabinets)
- Category 2 dating WITH sterility assurance testing

STERILITY ASSURANCE TESTING PROGRAM

- Can you fully comply with USP <71>
  - Minimum quantities to test USP <71> table 2 and 3
  - Dual testing media required TSB (fungal/aerobic) and FTM (anerobic)
  - Use of commercially available testing media (COA) verses “home brews”
  - Method Suitability testing
  - 14 day quarantine and hold
  - Early release of product and requirements of a recall
- What about alternative testing technologies USP <1223>

Number Items in Batch	Minimum Number Items to be Tested for Each Medium (unless otherwise justified and authorized)*
Parenteral Preparations	
• Not more than 100 containers	10% or 4 containers, whichever is the greater
• More than 100 but not more than 500	10 containers
• More than 500 containers	2% or 20 containers, whichever is less
For large-volume parenterals	2% or 10 containers, whichever is less

Quantity Per Container	Minimum Quantity to be Used (unless otherwise justified and authorized)*
Liquids (other than antibiotics)	
• Less than 1 mL	The whole contents of each container
• 1 – 40 mL	Half the contents of each container, but not less than 1 mL
• Greater than 40 mL and not greater than 100 mL	20 mL
• Greater than 100 mL	10% of the contents of the container, but not less than 20 mL

TEMPERATURE HOPPING

- If several of your institution's products will be ultimately stored under room temperature conditions, initial holding or quarantine can occur under freezing or refrigeration provided the total BUD does not exceed the original storage BUD.
- Frozen product and requirements for container integrity.
- Proper inventory control
  - Planning, central verses peripheral storage models (Candy Jars Everywhere!!)

OTHER BUD CONSIDERATIONS

- Single Dose Containers: Opened in ISO5 (not stored) 12 HOURS
- Multi Dose Containers: 28 Days unless specified
- Bulk Packages: Per Manufacturer
- Stock Solutions/Peds Bags: 12 HOURS once patient specific doses drawn
- Compounded components used for CSPs permitted
- Proper dating required for components placed on ACDs (TPN machines)

WHAT'S MISSING?

- "The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein."

▸ Reinstate the Alternative Technology Provision from the 2008 Version of <797>

- The CMP EC recognized that <797> may not capture all modalities used in pharmacy compounding. However, the CMP EC also intends to publish a Frequently-Asked-Question (FAQ) to clarify that the reinstatement of the Alternative Technology provision is not intended to permit BUD extension or to extend the time during which single-dose containers may be used.

IMPACT

- Robotic Technologies
- Drug Vial Optimization
  - CSTDs
  - Status of Performance Test Protocol
- Establishing “statistical significance”
  - 3000 Samples, ask your friendly, local statistician.

PAPERWORK AND MORE PAPERWORK

- Record retention: USP <797> requires 3 year
  - Training records
  - Competencies
  - Certification Reports
  - Environmental Monitoring
  - Equipment
  - COAs
  - Sterility testing results
  - Investigations and Remediations

POLICY DEVELOPMENT

- Several Policies and Procedures will be individualized based on the facilities engineering controls (Cleanroom suite verses SCA, sink location), methods for monitoring (manual verses electronic systems), use of other departments (pharmacy staff cleaning verses Environmental Services), and activities conducted (non-sterile compounding, HD compounding, etc.).
- Review by DP EVERY 12 MONTHS

POSSIBLE TECHNICIAN ROLES

- Master Trainers
- Environmental Monitoring
- Documentation Logistics
- Sterility Assurance Programs
- Status of legislation regarding technician compounding
  - NY is very late to this party!

PHARMACY TECHNICIAN LEGISLATION

- “Assist pharmacist, as directed, in compounding … where such tasks require no professional judgement”.
- National certification (PTCB) – compounding certification also offered.
- How will “UNDER DIRECT SUPERVISION” be interpreted regarding compounding activities performed by technician support
- Technicians could be listed as the Designated Person to oversee compliance with USP <797> and/or USP <800>

SUMMARY

- Compliance is achieved by:
  - Leadership
  - Complete buy-in !!!
  - Resource allocation
  - Tackle tasks that you can control first
  - Make some tough decisions
- Questions ???