Sterile Compounding: USP<797> Revisions and the Compounding Quality Act

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Disclosure:

I have no financial interests to disclose.

Objectives:

- Compare and contrast <797> changes
- Describe the history leading up to <797>
- Share best practices
- Review the Compounding Quality Act (CQA)
- Describe the implications on pharmacy of the CQA

Sterile Products: A Brief History

Sterile Products: A Brief History

In the 1930's and 40's, 60% of <u>all</u> medications were compounded.

Sterile Products:
A Brief History

There were 5000 compounding pharmacies in 2009 according to the IACP

Sterile Products:
A Brief History

In 2012, there were 7500 compounding pharmacies

Sterile Products:
A Brief History

Sterile compounding started in hospitals with some custom injections and ophthalmics.

What a hospital pharmacy probably looked like in the 1930's

Compared to something more up-to-date:

Sterile Products:
A Brief History

The 1926 edition of the USP only listed two injections and there was no <797>.

Sterile Products: A Brief History

In 2013, the UPS lists 566 injections

Sterile Products: A Brief History

Up to 1933 hospitals compounded their own CSPs

Sterile Products: A Brief History

1933 saw the first commercially available parenteral product. That company is still in business.

Sterile Products: A Brief History

In 1964, ASHP reported on major deficiencies in sterile compounding.

Sterile Products: A Brief History

At that time, most sterile products were being produced by nurses in patient care areas.

Sterile Products: A Brief History

In the mid-60's LAFW and HEPA filtration were introduced as was the first TPN and in-line filtration.

Sterile Products: A Brief History

In the 70's we had the addition of filters attached to syringes, lipid emulsion, and Medicare started paying for home infusion.

Sterile Products: A Brief History

In the 80's-2000's we see the introduction of compounded cardioplegia, ACDs, and increased drug shortages.

Sterile Products: Patient Safety

Pharmacy has been slow to recognize and mitigate contamination issues related to CSPs.

Sterile Products: Patient Safety

1971: 100 patients die from septicemia from LVPs manufactured by Abbott Labs due to faulty glass closures.

http://www.sciencedirect.com/science/article/pii/0002934376907130

Sterile Products: Patient Safety

1977: Drug related hospital deaths were 1.2 per 1000 patients, mostly due to LVPs

Sterile Products: Patient Safety

1988: 1 death due to hospital compounded cardioplegia using an ACD.

Sterile Products: Patient Safety

2012: NECC compounded steroids and cardio tested positive for fungi.

Sterile Products: Patient Safety

2012: NECC Over 750 patients harmed with meningitis, strokes, para-spinal infections. 64 deaths over 20 states.

Objective Question

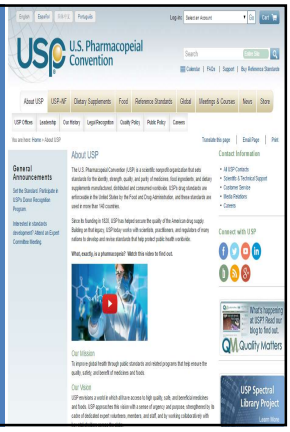
Based on the brief history, which of the following are true?

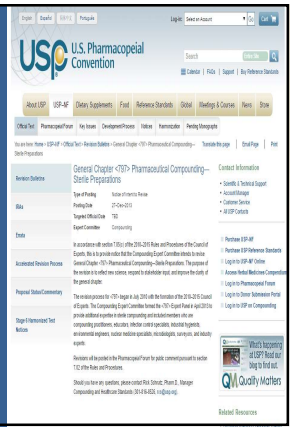
A. The profession of pharmacy has known about potential CS contamination for a relatively long time.
B. Patient care has become more complex over time.
C. HEPA filtration and LAFW came into use in the 1960's.
D. Prior to 1933, hospitals compounded all CSPs.
E. All of the above.

Where can I find the USP<797> revisions?

The USP Website

www.usp.org



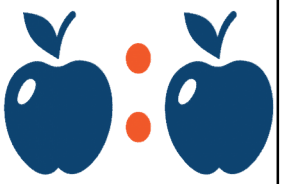
Chapter <797>	
2004 Original Review Venues	Any place where sterile products are compounded. Excludes manufacturers.
Environment	Air quality, particulate counts, ISO classification, risk levels.
Personnel	Responsibilities, training, monitoring, and mitigation.
Types of CSPs	Immediate-use, SDVs, MDVs, nuclear, hazardous, allergen extracts
Quality	Verification of accuracy, environmental QC, suggested SOPs, ACD verification, finish prep checks and release

Storage	Assignment of BUD, maintaining integrity from pharmacy to patient

Patient Care	Training, ADR monitoring and reporting, QA

Enforcement	USP defers to state regulatory bodies but warns that the FDA can get involved.

Enforcement	The State of Florida doesn't codify USP<797> until 2014. (64B16-27.797)

2014 Revisions: Compare and Contrast	

Three Original Risk Levels Collapsed into two	Table 1. USP <797> BUD Limitations for CSPs Compounded in a Cleanroom Risk Level / BUD for Controlled Room Temp Storage / BUD for Cold Storage / BUD for Frozen Storage Low / 48 hours / 14 days / 45 days Medium / 30 hours / 9 days / 45 days High / 24 hours / 3 days / 45 days ↓ Category I Category II

Three Original Risk Levels Collapsed into two

Table 1. USP <797> BUD Limitations for CSPs Compounded in a Cleanroom

Risk Level	BUD for Controlled Room Temp Storage	BUD for Cold Storage	BUD for Frozen Storage
Low	48 hours	14 days	45 days
Medium	30 hours	9 days	45 days
High	24 hours	3 days	45 days

Based on number or complexity of manipulations

Category I BUD Assignment

Storage Conditions	
Controlled RT (20-25C)	Refrigerate (2-8C)
</= 12 hours	</= 24 hours

BUD Assignment for Category II CSPs

	Preparation Characteristics			Storage Conditions		
	Method of Sterility	Sterility Test Performed?	Preservatives Added?	Controlled RT (20-25C)	Refrigerator (2-8C)	Freezer (-25 to -10C)
BUD	Aseptically Prepared	No	No	Prepped from non-sterile components 4 days	7 days	45 days
				Prepped from sterile components 6 days	9 days	45 days
			Yes	28 days	42 days	45 days
		Yes	No	28 days	42 days	45 days
			Yes	42 days	42 days	45 days
	Terminally Sterilized	No	No	14 days	28 days	45 days
			Yes	28 days	42 days	45 days
		Yes	No	28 days	42 days	45 days
			Yes	42 days	42 days	45 days

Three Original Risk Levels Collapsed into two

Essentially this is the former Low Risk and Low Risk 12hr levels

	Category I	Category II
Hygiene/Garbing	Quarterly	Quarterly
GFS	Quarterly	Quarterly
Media Fill	Quarterly	Quarterly
PEC	ISO classified space not required	ISO classified space required
Recert	Q 6 months	Q 6 months
VAS	Monthly	Monthly
Surface Samp	Monthly	Monthly
Physical Inspection	Required	Required
Sterility Testing	Not required	Required based on BUD
Endotox Test	Not Required	Required if prepared from non-sterile ingredients
BUD	<12hr RT; </=24hr fridge	>12hr RT; >24hr fridge

Defines In-use time

"The time before which a conventionally manufactured product or CSP must be used after it has been opened or needle-punctured."

In-Use Time in ISO5 or better air

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use immediately after opening and filtering
Pharmacy Bulk Package	As specified by manufacturer (4-6 hours)
Single-dose container (vial, bag, syringe, etc)	6 hours
Multi-dose container	28 days
CSP	
Compounded single-dose container	6 hours
Compounded stock solutions	6 hours (peds??)
Compounded multi-dose container*	28 days, unless otherwise specified by the original compounder.
*Must pass antimicrobial effectiveness testing in accordance with <51>	

In-Use Time in worse than ISO5 air

Components	In-Use Time
Conventionally Manufactured Sterile Product	
Ampuls	Use immediately after opening and filtering
Pharmacy Bulk Package	Not applicable
Single-dose container (vial, bag, syringe, etc)	Use within the time specified by manufacturer or by then end of procedure
Multi-dose container	28 days unless manufacturer states other
CSP	
Compounded single-dose container	Use immediately. Discard remainder
Compounded multi-dose container*	28 days, unless otherwise specified by the original compounder.
*Must pass antimicrobial effectiveness testing in accordance with <51>	

Garb and Gloving Requirements

CSP Category	PEC Type	Minimum Requirement
Category I	Any	-Non-cotton, low-lint gown or coveralls -Low-lint disposable shoe covers -Low-lint head covers that covers ears and forehead -Sterile gloves and sleeves
Category II	LAFS and BSC	In addition to above: - Mask - Eye shield
Category II	RABS (CAI or CACI) or isolator	- Gowns/coverall - Shoe and head cover - Sterile gloves

General organization of the chapter

Layout of the chapter is more user friendly in that it is now sectioned and numbered for ease of use.

Sampling and QA

More stringent as we have seen with the CSP Categories. More labor intensive for leadership to monitor.

Personnel

Describes specific training and mitigation strategies and when those strategies should be used.

Hazardous Drugs

Completely removed and placed into USP<800>

Based on the previous section, which of the following is true?

A. Personnel surveillance would now be a quarterly task.
B. BUD for Category II CSPs is a function of the method of sterility, whether sterility tests were performed, and the presence or addition of preservatives.
C. Category I CSPs are the same as immediate or emergency use products and can be produced outside of an ISO5 PEC.
D. All of the above.
E. Only A and B

Best Practices and Q&A
(5-10 min)

Is there any non-proprietary practices you are willing to share? Were they well received by staff and leadership? What were the outcomes?

The Drug Quality and Security Act: FDA Guidance

http://www.natlawreview.com/article/new-compounding-policies-fda-may-affect-hospital-and-health-system-pharmacy

Draft Guidance: Facilities

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496288.pdf

Section 503(b) added to the DQSA of 2013 defines "outsourcing facility"

Draft Guidance: Facilities

If a facility registers as an outsourcing facility, ALL products produced there whether upon receipt of a prescription or not, must meet CGMP standards.

Draft Guidance: Facilities

An outsourcing facility is "at one geographic location or address."

Draft Guidance: Facilities	Outsourcing facilities cannot avoid the CGMP requirements by subdividing the facility.

Draft Guidance: Facilities	An outsourcing facility may produce compounds and manufacture approved drugs however, compounds must bear the phrase, “This is a compounded drug”.

Draft Guidance: Facilities	Facilities are subject to FDA inspection on a risk-based schedule.

Draft Guidance: Hospitals and Health-System Compounding http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM496287.pdf	Section 503(a) of the FDCA describes the conditions under which compounded drugs meet certain exemptions from the FDCA.

Draft Guidance: Hospitals and Health-System Compounding	Compounded drugs which meet all of the above criteria are exempt from CGMP.

Draft Guidance: Hospitals and Health-System Compounding	Enforcement of Section 503(a)

Draft Guidance: Hospitals and Health-System Compounding

The FDA position on compounding…

Draft Guidance: Hospitals and Health-System Compounding

The Prescription Requirement

Draft Guidance: Hospitals and Health-System Compounding

The One Mile Provision

Questions for previous section:

A. True or False: Outsourcing facilities must be a licensed pharmacy in order to compound.
B. True or False: Health-system pharmacies are exempt from CGMP provided they meet the 10 conditions for compounding.
C. True or False: Compounds may be made in anticipation of a prescription order.
D. True or False: Hospitals may distribute compounds to commonly owned facilities greater than 1 mile from the compounding facility.

Questions or Comments?