The Inspection Process for Pharmacies Compounding Sterile Preparations (CSPs)

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Learning Objectives

At the completion of this presentation, the participant will be able to:

- Review the timeline of the regulations in Texas regarding compounded sterile preparations (CSPs)
- Understand the purpose of TSBP rules for pharmacies preparing CSPs
- Explain TSBP procedures for inspecting pharmacies preparing CSPs
- Discuss the laws that allow TSBP to inspect pharmacies and to collect samples of CSPs during the inspection
- Describe the process of collecting samples by TSBP staff
- Identify violations that have occurred in pharmacies compounding sterile preparations



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Timeline of the Regulation of CSPs in Texas

1981 – The passage of House Bill 1628, established The Texas Pharmacy Act, effective January 1, 1982. Among the multitude of amendments, was the establishment of four classes of pharmacy, including the Class C Institutional Pharmacy.

1982 – The Texas State Board of Pharmacy (TSBP) adopts new sections for Class C Institutional Pharmacy, which include brief sections pertaining to the preparation of "IV Admixtures."

1987 – TSBP establishes an Advisory Committed on Sterile Products to study trends and advancements in the field and to make recommendations to the Board.



Timeline of the Regulation of CSPs in Texas

1980s – TSBP adopts a new section entitled "Class A Pharmacies Dispensing Compounded Sterile Parenteral and/or Enteral Products". Revisions also made to the "IV Admixtures" section of rules for Institutional Pharmacies.

1991 – TSBP extensively revises and replaces existing rules regarding sterile compounding. Class A section re-titled "Class A Pharmacies Compounding Sterile Pharmaceuticals."



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Timeline of the Regulation of CSPs in Texas

1995 – TSBP adopts new amendments to both Community and Institutional Pharmacy Rules, making the requirements for the preparation of sterile pharmaceuticals the same for both classes of pharmacy, including specific requirements for training.

2002 – TSBP establishes the first of three Task Forces on Sterile Compounding to study trends and advancements in the field, and to make recommendations to the Board regarding sterile compounding.

2004 – TSBP adopts Section 291.26 entitled "Pharmacies Compounding Sterile Pharmaceuticals", which includes definitions and abundant language found in the United States Pharmacopeia's General Chapter <797>.



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Timeline of the Regulation of CSPs in Texas

2005 – TSBP establishes a second Task Force on Sterile Compounding to provide new recommendations to the Board largely based on the recently <u>revised</u> USP General Chapter <787>.

2007 – TSBP adopts new Section 291.133, entitled "Pharmacies Compounding Sterile Preparations", which includes many of the recommendations presented by the Task Force on Sterile Compounding.

2013 – TSBP amends Section 291.133 to implement recommendations of a third TSBP appointed Task Force on Compounding, incorporate additional provisions included in the USP General Chapter <797>, and implement Senate Bill 1100 passed during the 83rd Session of the Texas Legislature.



Three New Classes of Pharmacy Established 12/10/13

 Classes of Pharmacy 	 New "S" Classes
 A – Community 	• A-S
 B – Nuclear 	• C-S
 C – Institutional 	• E-S
• D – Clinic	
 E – Non-Resident 	
 F – FEMCC 	
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- G Call Center
- H Limited Prescription

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Key Points of SB 1100 (2013) & TSBP Adopted Rules Rank Changes

- Gave TSBP authority to inspect Class E pharmacies and requires the pharmacy to pay all costs associated with the inspection
- Requires an inspection prior to opening a pharmacy that compounds sterile preparations
- Requires an inspection before the license can be renewed
- New "-S" designation allows TSBP to know which pharmacies compound sterile preparations and maintain a database of both in-state and out-of-state pharmacies compounding CSPs



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Timeline of the Regulation of CSPs in Texas

2014 – TSBP amends Section 291.133 to clarify the training requirements for pharmacy technicians in American Society of Health-System Pharmacists accredited programs, and to clarify the placement of primary engineering control devices.

2015 – TSBP amends Section 291.133 to clarify in-process and final checks for CSPs; the evaluation of aseptic technique procedures; requirements for media-fill tests for the most challenging or streesful conditions; and to update requirements to be consistent with USP 797 requirements, including the use of sterile gloves and sterile alcohol, and other quality assurance requirements. The Board also added a definition for "compounding personnel."

2016 – TSBP continues to amend Section 291.133 to clarify the rules to be consistent with USP 797 requirements.



TSBP Rule §291.133 Pharmacies Compounding Sterile Preparations



Connection between Texas Pharmacy Rules & USP Chapter 797

Texas is one of at least 22 states that either:

- codifies language from USP Chapter 797 into its regulations regarding CSPs; or
- harmonizes statements found in USP Chapter 797 within its regulations regarding CSPs

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Purpose of §291.133

The purpose of this section is to provide standards for the:

- compounding of sterile preparations pursuant to a prescription or medication order for a patient from a practitioner in Class A-S, Class B, Class C-S, and Class E-S pharmacies;
- <u>compounding, dispensing, and delivery of a reasonable quantity of a</u> compounded sterile preparation in Class A-S, Class B, Class C-S, and Class E-S pharmacies <u>to a practitioner's office for office use</u> by the practitioner;
- <u>compounding and distribution</u> of compounded sterile preparations by a Class A-S pharmacy for a Class C-S pharmacy; and
- <u>compounding</u> of sterile preparations by a Class C-S pharmacy and the distribution of the compounded preparations to other Class C or Class C-S pharmacies under common ownership.



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The Inspection Process

- Environment
- Primary Engineering Control Devices
- Equipment and Supplies
- Library
- Personnel Cleansing and Garbing
- Cleaning and Disinfection Procedures
- Environmental Sampling
- Records of Compounded Sterile Preparations
- General Operational Requirements
- Quality Control and Verification of Compounding Accuracy
- Label
- Training and Competency

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The Inspection Process

If applicable,

- High-risk Sterile Preparations
- Hazardous Sterile Preparations
- Compounding for Office Use



Environment

Cleanroom includes:

- Buffer Area
- Ante-Area
- Primary Engineering Control Device(s)



ISO Classification

ISO Class	Particle Count (per m3)
3	35.2
4	352
5	3520
6	35,200
7	352,000
8	3,520,000



Environment – Clean Room Layout



Environment

Is the cleanroom . . .

- · free of objects that shed particles?
- · contain only appropriate supplies?
- · used only for sterile preparations?



Environment

Does the ante-area . . .

- · provide at least ISO Class 8 conditions?
- · contain a hands-free sink?

Does the buffer area . . .

- · provide at least ISO Class 7 conditions?
- · free from sources of water?
- have hands-free access?

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Environment

- Are floors, walls, ceilings, and fixtures smooth, impervious, and free from cracks and crevices?
- · Does the floor enable regular disinfection?
- · Are supplies stored above the floor?



Environment

Does the cleanroom have a pressure gauge to monitor pressure differential

- · between the buffer area and ante-area?
- between the ante-area and the general environment?

Is the pressure differential monitored and documented (at least daily)?



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Primary Engineering Control (PEC) Devices

Types of PECs

- Laminar air flow hood (LAFH)
- Biological safety cabinet (BSC)
- Containment aseptic isolator (CAI)
- Compounding aseptic containment isolator (CACI)

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Primary Engineering Control (PEC) Devices

LAFH

- Located in buffer area with a positive pressure differential of at least 0.02 inches water column
- Maintains at least ISO Class 5 conditions



Primary Engineering Control (PEC) Devices

CAI/CACI

- Provide unidirectional flow
- Located in an ISO class 7
 buffer area OR maintain
 documentation from
 manufacturer
- If used for high risk compounding, placed in at least an ISO Class 8 area



Primary Engineering Control (PEC) Devices

BSC/CACI

- For hazardous drugs
- Located in an ISO Class 7 area that is physically separated (except for low volume preparation)
- Maintain a negative pressure of not less than 0.01 inches water column from adjacent positive pressure area



Primary Engineering Control Devices

- Are certified by an independent contractor every 6 months and when relocated?
- Have pre-filters that are inspected and replaced as needed periodically?



Equipment and Supplies

Does the pharmacy have . . .

- Disposable needles, syringes and other applicable supplies?
- Lint-free towels/wipes or electronic hand dryer appropriately located?
- Handwashing agents with bactericidal action including a nail cleaner?
- Appropriate garb masks, caps, gowns with tight cuffs, shoe covers, beard covers?



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Equipment and Supplies

Does the pharmacy have . . .

- Disinfectant cleaning solution(s)?
- Dedicated cleaning supplies?
- Sterile alcohol, sterile gloves and waterless alcohol-based surgical scrub with persistent activity?



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Equipment and Supplies

- · Does the pharmacy have . . .
 - · Filters and filtration equipment?
 - · Hazardous spill kit, if applicable?
- If using automated compounding devices (i.e., repeater pumps), does pharmacy staff calibrate, verify accuracy, and document calibration on a daily basis?





Cleaning and Disinfecting Procedures

Does the pharmacy . . .

- Have written procedures regarding cleaning/disinfecting of the direct compounding area by trained personnel using an approved agent?
- Perform appropriate daily and monthly cleaning?
- Document cleaning?
- Are supplies wiped with a disinfecting agent prior to being brought into the clean room?





Is surface sampling performed . . . - on a periodic basis?

- in all ISO classified areas?
- Is air sampling performed . . .

- by trained individuals at least every six months?

Is there an appropriate response to sampling based on action levels?



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Compounding Records

- · Are records maintained for 2 years?
- Does the record include all required information?
- If batch compounding, are the master worksheets . . .
 - complete?
 - developed and approved by a pharmacist?

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General Operational Requirements

- · Is a pharmacist available 24/7?
- Are there written SOPs on the required topics (including recalls)?
- Are requirements met if compounding commercially available products?
- Are CSPs being dispensed to other states without proper licensure?



Quality Control

- Does the pharmacist review all compounding records for accuracy and perform a final check of the CSP?
- Are periodic in-process checks performed as defined in the pharmacy's written procedures?
- Are drug components manufactured in an FDA-registered facility?
- Is a Certificate of Analysis available, if applicable?

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Label

- Is the CSP properly labeled including . . .
 - generic name?
 - BUD?
 - · "compounded by pharmacy," if applicable?
 - unique facility lot number, if compounded as a batch?
- Are CSPs assigned a BUD based on labeling for the drug, literature sources, and/or direct testing?



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Training and Competency

Have all compounding personnel (pharmacist and pharmacy technician) completed the required education and training?

- ACPE-accredited course or ASHP-approved program
- · On-the-job training

Is there documentation of an initial competency evaluation that includes . . .

- Observation?
- Media-fill testing?
- Gloved fingertip testing?

Is there documentation of ongoing training and testing?



	Initial (prior to preparing CSPs for patients)	Ongoing
Education	20/40 hours of ACPE- accredited training	2 or 4 hours of continuing education per renewal period
Observation	By a trained compounder	By a trained compounder
Media-fill Test	Representing the most challenging or complex preparation	Representing the most challenging or complex preparation
Gloved Fingertip Test	Thumb and all fingers of both hands on 3 occasions to demonstrate competence at donning garb and sterile gloves	Thumb and all fingers of both hands after preparing a compound or completing media fill test to demonstrate aseptic technique competency

High-risk Sterile Preparations

- Does the buffer area provide physical separation?
- Are non-sterile measuring, mixing, and purifying devices rinsed with sterile, pyrogen-free water prior to use?
- Is sterility testing performed if . . .
 - CSPs are prepared in groups > 25?
 - MDVs are prepared for multiple patients or when exposed to > 12 hrs at 2-8 degrees C?
 - Exposed > 6 hrs at > 8 degrees C?



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High-risk Sterile Preparations

- Are CSPs ...
 - Pre-filtered using no larger than a 1.2 micron filter?
 - Filtered using a sterile 0.2 to 0.22 micrometer pore size filter in at least an ISO Class 5 environment?
- Are filter integrity tests performed and documented?
- Are pre-sterilization procedures (weighing and mixing) completed in an ISO 8 or better environment?



Hazardous Sterile Preparations

Does the pharmacy have . . .

- protective apparel?
- · safety and containment techniques?
- · appropriate waste disposal?
- · appropriate labeling?
- pressure indicator to readily monitor room pressurization?

Are hazardous drugs stored separately?



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Compounding for Office Use

- Does the pharmacy have a written agreement with the prescriber that meets all requirements?
- If the pharmacy is distributing to another pharmacy, are the specified requirements met?

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Examples of Commonly Seen Violations

Environment

- Objects that shed particles in the cleanroom cardboard, exposed particle board, chipped paint
- Cracks and crevices outlets not sealed, linoleum separating from wall, cracks in linoleum
- Sink is not hands-free
- Access to buffer area is not hands-free
- Certification of ISO classified areas are > 6 months
- Environmental Sampling
- Air sampling was not done
- Surface sampling was not done, or not done in all ISO classified areas
- · No response to reported growth on air sampling



Examples of Commonly Seen Violations



Violations Resulting in a Referral to the Legal Division

Pharmacies compounding sterile preparations without proper licensure (e.g., Class C who should have a Class C-S pharmacy license)

Pharmacies posing a continuing threat, such as

 Sterile compounding pharmacies who have extensive non-compliance with TSBP Rule 291.133 and will not voluntarily agree to "cease and desist" sterile compounding until conditions have been corrected.



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Sampling and Testing of CSPs



Texas Pharmacy Act Section 556.01 Gives TSBP authority to enter and inspect a licensed pharmacy including: - Drug storage and security - Equipment - Components used in compounding, finished and unfinished products, containers and labeling of any item - Sanitary conditions - Records, reports, or other required documents

Classes of Pharmacies Licensed by TSBP

Class A and A-S (Community) Class B (Nuclear) Class C and C-S (Institutional) Class D (Clinic) Class E and E-S (Non-resident) Class F (Freestanding Emergency Medical Care Facility) Class G (Central Prescription Drug or Medication Order Processing) Class H (Limited Prescription Delivery)



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Licensed Pharmacies that do not Compound Sterile Preparations

	Number of Pharmacies licensed by TSBP
Class A (Community)	4,935
Class C (Institutional)	732
Class D (Clinic)	375
Class E (Non-resident)	658
Class F (Free Standing Emergency Medical Facilities)	222
Class G (Central Processing)	26
Class H	01
TOTAL	6,949 pharmacies that do not compound sterile preparations

Licensed Pharmacies that Compound Sterile Preparations

Active Pharmacies FY2015	Number of Pharmacies licensed by TSBP
Class A-S	321
Class B	37
Class C-S	459
Class E-S	148
TOTAL	965 pharmacies compound sterile preparations
*as of 08/31/2	2015
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Sample Collection

- · Samples are collected during inspections
- Sent to Analytical Research Laboratories(ARL)
- Analysis/Testing of the sample is paid by TSBP
- TSBP does not pay the pharmacy for the cost of the drug

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Testing of Samples

Samples of compounded preparations are analyzed for:

- Potency (began in 2008)
- Sterility (began in 2008)
- Endotoxin (began in 2008)
- Fungal (began Sept 1, 2012)

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Sample Collection Form



Chain of Custody Form



Sampling Process

- · Lab Results submitted directly to TSBP
- If sample passes testing TSBP notifies pharmacy by letter
- If sample fails potency testing TSBP sends letter requiring written response by pharmacist-in-charge



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Process relating to Potency Failures

Written response to address:

- Initiate recall if part of a batch
- Discuss potential cause(s) of error
- Changes implemented at the pharmacy
- Submit passing sample potency results of second sample (preferably same drug) from independent lab of choice
- Imposes 60 day due date of written response to TSBP



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Process relating to Potency Failures

- TSBP re-inspects in-state pharmacy to collect a second sample.
- If second sample fails potency, pharmacy is referred to TSBP Legal Division for consideration of disciplinary action



Failure of Sterility/Fungal testing

- TSBP requests microbiology identification of specific bacteria/fungi by ARL
- TSBP requests the pharmacy to discontinue sterile compounding
- If the pharmacy does not agree, TSBP would consider an emergency suspension hearing



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Summary of Texas Compounded Sample Testing Program

	FY2012	FY2013	FY2014	FY2015	FY2016	5-YR AVG
Number of Samples Tested	28	58	124	193	197	120
Number of Non- Sterile Samples	20	9	7	24	14	15
Number of Potency Failures	2	1	2	5	4	3
Number of Sterile Samples	8	49	117	169	120	93
Number of Potency Failures	1	2	9	24	14	10
Number of Sterility Failures	1*	0	0	0	1	<1
Number of Fungal Failures**	N/A	0	0	0	0	0
Number of Endotoxin Failures	0	0	0	0	0	0
	*Nasal p ** Funga	reparation I Testing began in	FY2013			
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Classes and Types of Compounded Samples Collected on Inspection FY2016

Class of Pharmacy	Non-sterile sample collected	Sterile sample collected	Total collected
Class A	14	0	14
Class A-S	0	52	52
Class B	0	0	0
Class C	0	0	0
Class C-S	0	68	68
Class E	0	0	0
Class E-S	0	63	63
Class D, F, G, H	0	0	0
TOTAL	14	183	197
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Results of Samples Collected during Inspections in FY2016

197 samples collected in FY2016 by TSBP inspectors/vendor contract inspectors

- 134 samples TX pharmacies (13% failure rate)
 - 18 Potency failures
 - 0 Sterility/Fungal failures
- 63 samples non-resident pharmacies (11% failure rate)
 - 6 potency failures
 - 1 Sterility failure
 - 0 Fungal failures



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TSBP Website www.pharmacy.texas.gov



Question & Answer Session



Thanks for your attendance!

