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Knoxville Infectious Disease Consultants

HEALIX

Infection Control Enhancements through Successful Implementation of United States Pharmacopeia Chapter 797 Standards (USP 797) in a Physician Infusion Center Pharmacy

John S. Adams, MD[1], K. Dale Hooker, PharmD[2],

[1]Knoxville Infectious Disease Consultants (KIDC), Knoxville, TN, [2]Healix Infusion Therapy, Inc., Sugar Land, TX

John S. Adams, MD
Knoxville Infectious Disease Consultants
2210 Sutherland Avenue, Suite 110
Knoxville, TN 37919
(865) 525-4333
jsa4id@pol.net

Abstract

Background: In 6/08, the USP 797 published significant changes in the compounding of sterile products (CSPs). Intended to improve infection control (IC) practices in preparation of CSPs, they are recognized as official standards (stds) by the FDA, with adoption as law by a majority of state and federal agencies, including boards of pharmacy. Knoxville ID Consultants opened a pharmacy and infusion center in 7/05 with a small clean room for compounding of intravenous antimicrobials (IVAB), where patients may receive IVAB for storage up to 7 days at home. Implementation of the new stds was deemed important to ensure effective IC practices and sterile CSPs for patient use. **Methods**: A gap analysis was performed, evaluating and comparing current policies and procedures, processes, and the facility with those of USP 797. A resultant plan was made to update the pharmacy and infusion center accordingly. The plan was implemented and evaluated for adherence to the new stds, along with cost impact. Before and after procedures, data and facility pictorials were compared. **Results**: Gap analysis identified 18 major areas, of which 13 were applicable to the pharmacy and infusion center. Five (38%) were compliant, primarily in compounding, patient training, and monitoring. The other 8 areas required changes, with the methods of achieving compliance noted below. Environmental Quality & Control (EQC) contained 28 subsections, of which 22 (79%) required changes, including physical plant modifications. Clean room construction added positive-pressure, HEPA filtered rooms, resulting in the greatest cost impact. The project was completed in six months. A subsequent audit, clean room certification, and microbial sampling indicated successful implementation.

Methods to Achieve Complicance	Microbial Risk	Personnel Training	Immediate Use	Drug Storage	Hazardous Drugs	EQC	SOPs	Drug Dating
Policy/Procedure Change	√		√	√	√	√	√	√
Process Change		√	√	√		√		
Competency/Training		√				√		
Physical Plant Modifications						√		
Outsourcing					√	√		

Conclusions: The initial evaluation and gap analysis indicated a low adherence, but compliance was achieved in all areas in 6 months. Compounding in accordance with USP 797 can be successfully implemented into a physician infusion center pharmacy.

Introduction

Preparation of compounded sterile products has been an area fraught with inconsistencies and lacking in oversight for several decades. As reports of contamination in sterile products continued to grow,[1,2] the FDA urged additional controls be taken. The United States Pharmacopeia first published standards in 2004 (USP Chapter 797), with revised official and enforceable standards effective June 1, 2008.[3] The USP standards, created to ensure that compounded sterile preparations (CSPs) are of the highest quality, are applicable to all practice settings. This has been difficult for many to comply with due to complexity and increased cost. Knoxville Infectious Disease Consultants (KIDC) opened an infusion center and pharmacy in 2005 to serve the needs of patients requiring intravenous antimicrobials (IVAB), both in the office and at home. Patients often receive IVAB dispensed from the pharmacy to take home and store in the refrigerator for self administration. The previous pharmacy consisted of a small clean room and was compliant with published standards at that time.[4] KIDC determined that implementation of the new standards was important, especially for an Infectious Disease Practice, to ensure effective infection control practices and sterile CSPs for patient use. With a move to new space planned, compliance and facility modifications were incorporated into this in accordance with the new standards.

Methods

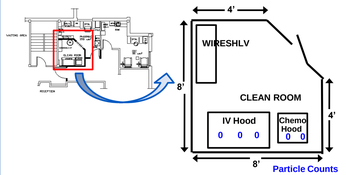
A gap analysis was performed, evaluating and comparing current policies and procedures, processes, and the facility with those of USP 797. Each applicable category was thoroughly reviewed and analyzed against current policy, process, and the current facility design. Each standard was noted as either being in compliance or not. Those standards that were not in compliance were recorded. Once all non-compliant categories were identified, a plan was created to update the pharmacy, create new policies and procedures, and develop training programs with competencies. The plan included a detailed facility and environmental design, along with materials and build-out instructions. Costs were also included in the plan.

The plan was completed and approved by the practice in 2008. Implementation of the plan began in January, 2009. Facility modifications required six months; policy and procedure and training program development occurred incrementally over this timeframe. Facility modifications were identified in the plan as the most costly with the greatest requirements for change.

Changes were completed in all areas in June, 2009. Once completed, the facility was analyzed by a certifier in accordance with testing and certification procedures outlined in the Controlled Environment Testing Association (CETA). Facility clean room analysis included particle counts, temperature, humidity, air flow, pressure differentials, and viable air sampling. These results were analyzed and compared to data available in the previous environment. Personnel training and competency assessment was completed and production in the new sterile environment began.

Results

Floor Plan before USP 797 Compliance



Floor Plan after USP 797 Compliance

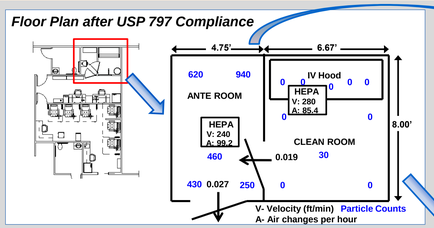


Table 1. Gap Analysis Results (5/13—38% Compliant)

CATEGORY	COMPLIANCE (Y/N)
Microbial Risk	N
Personnel Training	N
Immediate Use	N
Drug Storage	N
Hazardous Drugs	N
Compounding Accuracy	Y
Environmental Quality and Control	N
SOPs	N
Final Product Check	Y
Drug Dating	N
CSPs Quality Maintenance	Y
Patient Training	Y
Patient Monitoring	Y

METHODS TO ACHIEVE COMPLIANCE IN FAILED CATEGORIES

Microbial Risk
- Policy/Procedure Change
  - No high-risk level CSPs (See Table 2) allowed to be prepared at KIDC

Personnel Training
- Process Change
- Competency/Training
  - Evaluation of skills by "Qualified Observer"

Immediate Use
- Policy/Procedure Change (See Table 2)
- Process Change

Drug Storage
- Policy/Procedure Change
- Process Change and Expiration Dating
  - Multiple-dose containers (28 days)
    Single-dose containers (6 hours)
    Containers opened outside hood (1 hour)

Hazardous Drugs
- Policy/Procedure Change
- Outsourcing of Hazardous Drugs to Facility with NEGATIVE Pressure Room

SOPs
- Policy/Procedure Changes

Drug Dating
- Policy/Procedure Change (See Table 2)

Environmental Quality and Control
- Policy/Procedure Change
- Process Change
- Competency/Training
- Physical Plant Modifications (See Table 3)

Table 2. New Requirements for Drug Expiration Dating

*Immediate Use**	*Low Risk†*	*Medium Risk‡*	*High Risk§*
Use within 1 hours	14 days (refrigerated)	9 days (refrigerated)	3 days (refrigerated)
• First dose IVAB mixed in Infusion Center	• Single dose IVAB, eg. Vancomycin reconstitution • Several simple preparations in elastomeric devices or piggybacks	• Ambulatory bags with multiple doses of IVAB • Large batches • Parenteral Nutrition	• Morphine injection made from morphine powder

* Preparing outside hood.
†Measuring and mixing with ≤ 3 ingredients.
‡Complex manipulations requiring multiple ingredients or long duration.
§Compounded from nonsterile ingredients, equipment before terminal sterilization.

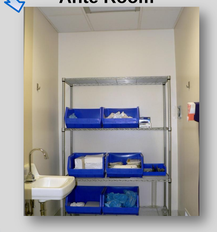
Infusion Center

Pharmacy

Table 3. Methods to Achieve Compliance for Environmental Quality & Control

Physical Plant Modifications	
Rooms/Air	New clean room and ante room constructed with increased air changes
Positive Pressure	A/C added and gauges to monitor
Facility Design	New HEPA filtered ante room/clean room Temperature & Humidity control
Process Change	
Viable Particle Sampling	Perform semi-annually by CETA certifier
Growth Media	Provided by CETA certifier
Viable Air Sampling	Perform semi-annually by CETA certifier with 3-4 samples collected: 1 from hood, 1 from cleanroom, 1 from ante room and 1 control
Sampling Devices	Provided by CETA certifier
Incubation Period	Performed by CETA certifier and laboratory
Incubation Period (2)	Temperature and time period needed
Competency/Training	
Personal Training/evaluation	Training, Competency Testing, Observation
Competency Evaluation	Evaluated initially and annually
Policy/Procedure Change + Process Change	
Environmental Sampling Program	New P/P adopted Performed by CETA certifier
Sampling Process	Performed semi-annually by CETA certifier
Action/Evaluation	New p/p and process adopted
Surface Collection	Performed on-site and reported as cfu per unit of surface area
Action/Documentation	Exceeding action level requires re-evaluation
Process Change + Competency/Training	
Gloved Fingertip Sampling	Performed under supervision by a Qualified Observer
Policy/Procedure + Process Change + Competency/Training	
Primary Engineering Control (Hood)	Sterile gloves required All supplies must be wiped down with a disinfectant
Hood Cleaning	Sterile gloves, disinfectant, cleaning schedule Work surfaces, floors cleaned daily Walls, ceilings cleaned monthly All materials shall be nonshedding
Personnel Cleansing	Non cosmetics, no artificial nails Routinely disinfect gloves
Evaluation via Glove Fingertip Sampling	No disinfection immediately prior to sampling
Garbing Evaluation	Performed under Observation

Ante Room



Clean Room (at rest)

Clean Room (working)

Practice Area

Table 4. Statistics of Clean Room Prior to and After USP 797 Compliance

	PRE	Compliance (Y/N)	POST	Compliance (Meet/Exceed)
Temperature(°F)	66	Y	71.6	Meet
Humidity	Not tested	-	48%	Meet
Pressure	Not tested	N	+	Meet
ISO Class* of Hood	5	Y	5	Meet
ISO class of Ante Room (Require ISO Class 8)	N/A	-	6	Exceed
ISO class of Clean Room (Require ISO Class 7)	Not tested	-	6	Exceed
Clean Room Air Changes/Hr. (ACPH)†	Not tested	-	85.4	Exceed

*ISO Class 5 (equivalent to Class 100) requires ≤ 3,520 particles of 0.5µm or larger per m³.
ISO Class 6 (equivalent to Class 1,000) requires ≤ 35,200 particles of 0.5µm or larger per m³.
ISO Class 7 (equivalent to Class 10,000) requires ≤ 352,000 particles of 0.5µm or larger per m³.
ISO Class 8 (equivalent to Class 100,000) requires ≤ 3,520,000 of 0.5µm or larger per m³.
†ACPH: HEPA filter should provide not less than 30 air changes per hour.

Table 5. Infection Control Air Sampling Data

Location	Total Counts	Total Air Vol (L)	Bacterial Air Strip (CFU/m³)	Bacterial Species	Compliance (Y/N)
Results in Original Facility					
IV Hood	0	400	<2	N/A	Y
IV Room	0	400	<2	N/A	Y
Results in New Facility post Construction prior to full USP 797 Implementation					
Hood*	12	400	30	(12) Bacillus sp.	N
Clean Room†	14	400	34	(13) Bacillus sp. (1) Coag-Neg Staphylococcus sp.	N
Ante Room‡	35	400	88	(35) Bacillus sp.	N
Results in New Facility after full USP 797 Implementation					
Hood	0	500	<2	N/A	Y
Clean Room	1	500	2	Micrococcus sp.	Y
Ante Room	0	500	<2	N/A	Y

* Hood (ISO Class 5) requires ≤ 1 CFU/m³.
†Clean Room (ISO Class 7) requires ≤ 10 CFU/m³.
‡Ante room (ISO Class 8 requires ≤ 100 CFU/m³.

COST INFORMATION

- Pharmacy and Clean Room Build-Out:

  Clean Room Basic Build-out: 92 sq ft X $19 = $1,748
  Pharmacy Basic Build-out: 208 sq ft X $19 = $3,952
  HEPA Filters = $550 Each X 2 = $1,100
  Flooring, Ceiling, Plumbing = $2,000 est. (Included in Relocation)
  Additional AC = $2,000 est. (Included in Total Space Build-out)
  Total Pharmacy Build-out = $10,800
  (Total Infusion Center Build-out = $5,000)

  Versus:

  Barrier Isolator instead of Clean Room

  4 foot Isolator = $20,000 Purchase Price
  - Considered 80% Less Efficient than a Clean Room

- Additional Monthly Expenses (Similar for Each)

  $750 (Sterile Gloves, Sterile Alcohol, Clean Room Maintenance)

Discussion

- Evaluation of the USP 797 and standards was initially perceived to be complicated and difficult to achieve.
- The gap analysis provided a step-by-step evaluation of compliance issues. It was important to analyze each area carefully as many were achievable with a small change in policy and procedure.
- The gap analysis identified 18 major areas, of which 13 were applicable to the pharmacy and infusion center.
- Five (38%) were compliant, primarily in compounding, patient training, and monitoring.
- Eight (61%) areas mandated change – the greatest time challenges being in the areas of staff training/education and EQC.
- Facility modifications required the most discussion and expert assistance. Both a clean room and barrier isolator were evaluated for methods to achieve compliance; KIDC chose a clean room due to increased compounding efficiency and lower cost, combining the build-out with a practice relocation.

Conclusions

- The initial evaluation and gap analysis indicated a low adherence, but compliance was achieved in all areas in 6 months.
- Although the task of compliance with the requirements of USP 797 may initially appear overwhelmingly complex and not easily attainable, we have demonstrated that efficient and affordable implementation of USP 797 standards can be successfully achieved in a physician infusion center pharmacy.
- Implementation of the standards provided a proven pathogen-free environment for compounding of sterile products, which should equate to even greater sterility of CSPs.
- Costs related to USP 797 compliance can vary greatly dependent upon expertise of pharmacists, consultants, and contractors, and require extensive oversight, particularly with facility modifications.

References

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3. The USP 27th rev, National Formulary 22nd ed. Chap.<797>. The United State Pharmacopeial Convention; 2003; Rockville, MD.
4. ASHP Technical Assistance Bulletin. Am J Hosp Pharm. 1993; 50:2386-2398.