AGENDA

FLORIDA DEPARTMENT OF HEALTH

BOARD OF PHARMACY AND

BUREAU OF ENFORCEMENT

USP 797 INSPECTION REVIEW WORKSHOP

October 9, 2014

Embassy Suites
4955 Kyngs Heath Road
Kissimmee, FL 34746
(407) 597-4000

Board Members:
Jeff Mesaros, PharmD, Chair, Orlando
Michele Weizer, PharmD, Vice-Chair, Boca Raton
Mark Mikhael, PharmD, Orlando
Leo "Lee" Fallon, BPharm, PhD, The Villages

Board Staff:
Patrick Kennedy, Executive Director

Board Counsel:
David Flynn, Assistant Attorney General

Bureau of Enforcement:
Mark Whitten, Bureau Chief

Investigative Services Unit Staff:
Christopher Ferguson, Chief
Michelle Miller, Field Operations Manager
Robert DiFiore, BPharm, Senior Pharmacist,
Mary Crane, BPharm, R. Ph., Senior Pharmacist
James Shepherd, BPharm, R. Ph., Senior Pharmacist
Richard Wachle, M.S., R. Ph., C Ph., Senior Pharmacist
John D. Taylor, B.S., R. Ph., Senior Pharmacist
Lisa Nickerson, Senior Management Analyst II
Rhonda Myers, Government Analyst I

Participants in this public meeting should be aware that these proceedings are being recorded.

Thursday, October 9, 2014 – 9:00 a.m.

1. Review and discussion of Proposed ISU Sterile Compounding Inspection Form
    - Low Risk
    - Medium Risk
    - High Risk
    - Immediate Use Compounding
    - Single/Multiple Dose Container Bud
    - Hazardous Drugs
    - Radiopharmaceuticals
    - Facility Design and Certification
    - Quality and Control
    - Personnel Cleansing, Garbing & Competency Evaluation
    - Verification
    - Dispensing/Distribution
    - USP 71 Sterility Testing
    - Miscellaneous
2. Wrap Up

	INSPECTION QUESTION
	LOW RISK
1	Low risk CSP's are properly identified: Aseptic manipulations within an ISO Class 5 environment using three or fewer sterile products and no more than two entries into any container.
2	Low Risk CSP's, in absence of passing sterility test, stored not more than 48 hours at controlled room temperature, 14 days at cold temperature, or 45 days in solid frozen state at -25° to -10° or colder.
3	Low Risk media-fill tests are completed at least annually by compounding personnel. Media-filled vials are appropriately incubated for 14 days.
4	Low Risk CSP's with 12 hour BUD are properly identified and comply with all four specific criteria. 1. PEC in Segregated Compounding area 2. Away from windows, doors , high traffic areas 3. Hygiene & garbing required, sinks not adjacent to PEC. 4. Cleaning & Disinfecting, Personnel training, Competency evaluation, Garbing, Aseptic work practices, Viable and non-viable environmental sampling apply.
	MEDIUM RISK
5	Medium Risk CSP's are properly identified: Aseptic manipulations within an ISO Class 5 environment using prolonged and complex mixing and transfer, more than three sterile products and entries into any container, and pooling ingredients from multiple sterile products to prepare multiple CSPs.
6	Medium Risk CSP's, In absence of passing sterility test, stored not more than 30 hours at controlled room temperature, 9 days at cold temperature, or 45 days in solid frozen state at -25° to -10° or colder.
7	Medium Risk media-fill tests are completed at least annually by compounding personnel. Media-filled vials are appropriately incubated for 14 days.
	HIGH RISK
8	High Risk CSP's are properly identified: Confirmed presence of nonsterile ingredients and devices, or confirmed or suspected exposure of sterile ingredients for more than one hour to air quality inferior to ISO Class 5 before final sterilization.
9	High Risk CSP's, in absence of passing sterility test are not stored more than 24 hours at controlled room temperature, 3 days at cold temperature, or 45 days in solid frozen state at -25° to -10° or colder.
10	High Risk Media-fill tests have been completed at least semiannually by compounding personnel. Media-filled vials are appropriately incubated for 14 days.
11	A 0.2-µm certified sterilizing membrane filter is used that is chemically and physically compatible with the CSP. Filtration is completed rapidly without filter replacement. Sterilization method is verified to achieve sterility for the quantity and type of containers.
12	Outsourced endotoxin testing results indicate that it is compliant with USP<85>.
13	Is a USP<85> Endotoxin testing done on site?
14	Endotoxin testing method is compliant? Indicate: Gel clot, chromogenic or turbidimetric?

15	High Risk CSP's are within allowable limits for bacterial endotoxins.
16	Sterilization method used has documentation that acceptable strength and purity of ingredients and integrity of containers is maintained.
17	The manufacturer recommended filter integrity (e.g., bubble point) test is performed and documented for all sterilizing filters after filtering CSPs.
18	Autoclave cycle has been verified using appropriate biological indicators. Solutions are passed through a 1.2-µm or smaller filter into final containers to remove particulates before sterilization.
19	Dry heat ovens used for sterilization have HEPA filtered forced air. Only those items that will be damaged by steam are sterilized by dry heat.
20	The description of dry heat sterilization conditions and duration for specific CSPs is included in written documentation in the compounding facility. The effectiveness of dry heat sterilization is verified using appropriate biological indicators and other confirmation.
21	Dry heat depyrogenation is used to render glassware or containers, such as vials free from pyrogens as well as viable microbes. The description of the dry heat depyrogenation cycle and duration for specific load items is included in written documentation in the compounding facility. The effectiveness of the dry heat depyrogenation cycle is verified using endotoxin challenge vials (ECVs).
22	Presterilization procedures for high-risk level CSPs, such as weighing and mixing, are completed in no worse than an ISO Class 8 environment.
23	Sterility testing is completed for all High-risk level CSPs prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8°, and 6 hours at warmer than 8° before being sterilized.
24	Endotoxin testing is conducted for High-risk level CSP's that are prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8°, and 6 hours at warmer than 8°, before being sterilized or in multidose containers for administration to multiple patients. (excluding those for inhalation and ophthalmic administration)
	IMMEDIATE USE COMPOUNDING

25	Immediate-use compounding complies with all six specified criteria. 1. Low-risk sterile nonhazardous products or diagnostic radiopharmaceutical products from the manufacturers' original containers. Anti-neoplastics shall not be prepared as immediate-use CSPs because they are hazardous drugs. 2. Unless required for the preparation, the compounding procedure is a continuous process not to exceed 1 hour. 3. During preparation, aseptic technique is followed and, if not immediately administered, the finished CSP is under continuous supervision to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, mix-ups with other CSPs, and direct contact of outside surfaces. 4. Administration begins not later than 1 hour following the start of the preparation of the CSP. 5. Unless immediately and completely administered by the person who prepared it or immediate and complete administration is witnessed by the preparer, the CSP shall bear a label listing patient identification information, the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour BUD and time. 6. If administration has not begun within 1 hour following the start of preparing the CSP, the CSP shall be promptly, properly, and safely discarded.
	SINGLE/MULTIPLE DOSE CONTAINER BUD
26	Beyond-use date does not exceed 28 days for multiple-dose containers after initial opening or entry, unless specified otherwise by the manufacturer.
27	Beyond-use time does not exceed 6 hours for closure sealed single-dose containers in ISO Class 5 or cleaner air after initial opening or entry, unless specified otherwise by the manufacturer.
28	Beyond-use time does not exceed 1 hour for closure sealed single-dose containers after being opened or entered in worse than ISO Class 5 air.
29	Single-dose ampules are discarded immediately after use.
	HAZARDOUS DRUGS
30	Hazardous drug buffer room is at least 0.01 inch water column negative pressure with 30 ACPH of HEPA filtered air.
31	Personnel compounding hazardous drugs wear appropriate personal protective equipment.
32	Appropriate primary engineering controls (BSCs and CACIs) are used for concurrent personnel protection and exposure of critical sites.
33	Hazardous drugs are stored separately from other inventory in a manner to prevent contamination and personnel exposure.
34	At least 0.01 inch water column negative pressure and 12 air changes per hour in non-cleanrooms in which CACIs are located. FAC: USP Chapter 797 requires that: "When closed-system vial-transfer devices (CSTDs) (i.e., vial-transfer systems that allow no venting or exposure of hazardous substance to the environment) are used, they shall be used within an ISO Class 5 environment of a BSC or CACI. The use of the CSTD is preferred because of their inherent closed system process. In facilities that prepare a low volume of hazardous drugs, the use of two tiers of containment (e.g., CSTD within a BSC or CACI that is located in a non-negative pressure room) is acceptable." For purpose of said provision, a "low volume of hazardous drugs" is defined as less than 40 doses per month.

35	Hazardous drugs are handled with caution at all times using appropriate chemotherapy gloves during receiving, distribution, stocking, inventorying, preparing for administration, and disposal. Spill kits are available.
36	Hazardous drugs are prepared in an ISO Class 5 environment with protective engineering controls in place, following aseptic practices specified for the appropriate contamination risk levels.
37	Access to hazardous drug preparation areas is limited to authorized compounding personnel.
38	A pressure indicator is installed and differential pressures are monitored and documented daily for hazardous buffer room.
39	Annual documentation of hazardous drug training of personnel regarding storage, handling, containment techniques and disposal of hazardous drugs is available.
40	Compounding personnel of reproductive capability have confirmed in writing that they understand the risks of handling hazardous drugs.
41	Facility maintains appropriate disposal containers for all hazardous waste.
	RADIOPHARMACEUTICALS
42	Facility has appropriate primary engineering controls and radioactivity containment and shielding. Location of primary engineering controls permitted in ISO Class 8 controlled environment.
43	Radiopharmaceuticals prepared as low-risk level CSPs with 12-hour or less BUD are prepared in a segregated compounding area. Segregated compounding area is designated with a line of demarcation.
44	Technetium-99m/Molybdenum-99 generators are eluted in ISO Class 8 conditions.
45	When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or a donor's white blood cells), the manipulations are clearly separated from routine material-handling procedures and equipment used in CSP preparation activities, and they are controlled by specific standard operating procedures in order to avoid any cross-contamination.
	FACILITY DESIGN AND CERTIFICATION
46	Certification and testing of primary (LAFWs, BSCs, CAIs and CACIs) and secondary engineering controls (buffer and ante areas) have been performed by a qualified individual no less than every six months and whenever the device or room is relocated, altered, or major service to the facility is performed. Corrective action for deficiencies are documented. Certification procedures such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2006) are conducted under dynamic conditions.
47	Facility has pressure gauges or velocity meters to monitor the pressure differential or airflow between the buffer area and ante-area, and the ante-area and the general environment outside the compounding area. The results are reviewed and documented on a log at least daily or by a continuous recording device. The pressures differentials meet or exceed 5 Pa (0.02 inch water column (w.c.)). Alternatively, in facilities where low- and medium-risk level CSPs are prepared, differential airflow is maintained at a minimum velocity of 0.2 meter/second (40 fpm) across a line of demarcation between buffer area and ante-area.
48	Primary engineering controls provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites.

49	Air pattern analysis via smoke studies are conducted at the critical site to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.
50	Clean rooms for nonhazardous and nonradioactive CSPs are supplied with HEPA filtered air that enters from ceilings with return vents low on walls, and that provides not less than 30 air changes per hour.
51	The primary engineering controls are placed within a buffer area in such a manner as to avoid conditions that could adversely affect their operation. The PEC is placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross drafts.
52	Primary engineering controls for nonhazardous and nonradioactive CSPs are located in buffer areas, except for CAIs that are proven to maintain ISO Class 5 air when particle counts are sampled 6 to 12 inches upstream of critical site exposure areas during performance of normal inward and outward transfer of materials, and compounding manipulations when such CAIs are located in air quality worse than ISO Class 7.
53	Adequate recovery time for isolators to achieve ISO Class 5 air quality is allowed after material transfer before and during compounding operations.
54	All HEPA filters are leak tested after installation and every six months thereafter.
55	Activities and tasks carried out within the buffer area are limited to only those necessary when working within a controlled environment.
56	Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed are brought into the buffer room.
57	Surfaces and essential furniture in buffer rooms or zones and clean rooms are nonporous, smooth, non-shedding, impermeable, cleanable, and resistant to disinfectants.
58	The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area are smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability, and minimizing spaces in which microorganisms and other contaminants may accumulate.
59	Ceiling tiles are caulked around each perimeter and to walls to seal them to the support frame. The exterior lens surface of ceiling lighting fixtures is smooth, mounted flush, and sealed. All other penetrations through the ceiling or walls are sealed.
60	The buffer area does not contain sources of water (sinks) or floor drains. Work surfaces are constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected.
61	Carts are made of stainless steel wire, or nonporous plastic, or sheet metal construction with good quality, cleanable casters.
62	Storage shelving, counters, and cabinets in the buffer area are smooth, impervious, free from cracks and crevices, non-shedding, cleanable, and disinfectable.
63	When devices (e.g., computers and printers) and objects (e.g., carts and cabinets) are placed in buffer areas, air quality is verified by particle counts on certification.
	QUALITY AND CONTROL

64	An appropriate environmental sampling plan has been developed for airborne viable particles based on a risk assessment of compounding activities performed. Volumetric air sampling is conducted every six months and sites include locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas, and the areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 environment, counters near doors, pass-through boxes). The plan includes sample locations, method of collection, frequency of sampling, volume of air sampled, and time of day as related to activity in the compounding area and action levels.
65	Surface sampling is accomplished in all ISO classified areas on a periodic basis using TSA contact plates with lecithin and polysorbate 80 and/or swabs and is done at the conclusion of compounding.
66	Evaluation of airborne microorganisms using volumetric collection methods in the controlled air environments is performed by properly trained individuals for all compounding risk levels.
67	Volumetric air sampling using malt extract agar (MEA) or some other media that supports the growth of fungi is used in high-risk level compounding environments.
68	For low-risk level CSPs with 12-hour or less BUD, air sampling is performed at locations inside the ISO Class 5 environment and other areas that are in close proximity to the ISO class 5 environment.
69	The number of discrete colonies of microorganisms is counted and reported as colony-forming units (cfu) and documented on an environmental monitoring form. Counts from air monitoring are transformed into cfu/cubic meter of air and evaluated for adverse trends.
70	Sampling data is collected and reviewed on a periodic basis as a means of evaluating the overall state of control of the compounding environment.
71	Competent microbiology personnel are consulted if an environmental sampling consistently shows elevated levels of microbial growth. If any mold, yeast, coagulase positive staphylococcus, or gram negative rods are detected immediate remediation and investigation into the cause and source was conducted.
72	Written procedures detail cleaning and disinfecting the sterile compounding areas including cleansers, disinfectants, and non-shedding wipe and mop materials.
73	Surfaces in the LAFWs, BSCs, CAIs, and CACIs are cleaned and disinfected frequently, including at the beginning of each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual CSPs, when there are spills, and when surface contamination is known or suspected from procedural breaches.
74	A written procedure is in place for cleaning and disinfecting the Direct Compounding Areas.
75	Cleaning and disinfecting occurs before compounding is performed. Items are removed from all areas to be cleaned, and surfaces are cleaned by removing loose material and residue from spills, e.g., water-soluble solid residues are removed with Sterile Water and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent, such as sterile 70% IPA, which is allowed to dry before compounding begins.
76	Work surfaces in ISO Class 7 and 8 areas and segregated compounding areas are cleaned at least daily. IPA (70% isopropyl alcohol) remains on surfaces to be disinfected for at least 30 seconds before such surfaces are used to prepare CSPs.
77	Floors in ISO Class 7 and 8 areas are mopped daily by trained personnel at a time when no aseptic operations are in progress using approved agents and procedures described in written SOP's.

78	Shelving, walls, and ceilings in ante-areas are cleaned and disinfected at least monthly.
79	Cleaning and disinfecting agents and methods of application are in accordance with written SOPs and followed by custodial and/or compounding personnel.
80	Cleaning materials, such as wipes, sponges, and mops, are non-shedding, preferably composed of synthetic micro fibers, and dedicated to use in the buffer area, ante-area, and segregated compounding areas and are not removed from these areas except for disposal. If cleaning materials are reused (e.g., mops), there are procedures based on manufacturer recommendations that ensure that the effectiveness of the cleaning device is maintained and repeated use does not add to the bioburden of the area being cleaned.
81	Supplies and equipment removed from shipping cartons are wiped with a suitable disinfecting agent (e.g., sterile 70% IPA).
82	Disinfectant sprayed or wiped on a surface to be disinfected is allowed to dry, and during this time the item is not be used for compounding purposes.
83	Sterile 70% IPA pads are used to disinfect the sterile entry points of packages and devices. Wetted gauze pads or other particle-generating material are not appropriate.
	PERSONNEL CLEANSING, GARBING & COMPETENCY EVALUATION
84	Personnel preparing CSP's are free from rashes, sunburn, weeping sores, conjunctivitis, and active respiratory infections.
85	Compounding personnel remove personal outer garments; cosmetics; artificial nails; hand, wrist, and body jewelry that can interfere with the fit of gowns and gloves; and visible body piercing above the neck.
86	Facility has adequate supplies to meet PPE requirements of USP<797>.
87	Garbing and hand hygiene are accomplished in the ante-area in order of dirtiest to cleanest: shoes or shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; non-shedding gown.
88	Sterile gloves are donned in the buffer room after hand cleansing with an alcohol-based product with persistent activity and hands are allowed to dry.
89	Gloves are routinely disinfected with sterile 70% IPA after contacting nonsterile objects.
90	Personnel repeat garbing and hand hygiene after they are exposed to direct contact contamination or worse than ISO Class 8 air. Gowns may be hung in the anteroom and reused during the same workshift.
91	Personnel garbing requirements are followed for CAIs unless manufacturer provides written documentation based on validated testing that any components of PPE are not required to maintain sterility of CSPs.
92	Documentation indicates compounding personnel have successfully completed didactic training, passed written competency assessments, undergone skill assessment using observational audit tools, and media-fill testing before any compounding personnel begin to prepare CSPs.

93	Compounding personnel who fail written tests, observational audits, or whose media-fill test vials have one or more units showing visible microbial contamination, are reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic work practice deficiencies. Compounding personnel pass all evaluations prior to resuming compounding of sterile preparations.
94	Corrective action is documented for compounding personnel who fail written tests or media-fill test.
95	Other cleaning personnel performing cleaning and disinfecting procedures (e.g. environmental) are thoroughly trained in proper hand hygiene, and garbing, cleaning, and disinfection procedures by a qualified aseptic compounding expert.
96	Compounding personnel and other personnel responsible for cleaning routinely undergo performance evaluation of proper hand hygiene, garbing, and all applicable cleaning and disinfecting procedures conducted by a qualified aseptic compounding expert. Visual observation of hand hygiene, garbing and cleaning is documented and maintained to provide a permanent record and long-term assessment of personnel competency.
97	Compounding personnel are visually observed annually or semiannually (high risk) during the process of performing hand hygiene, garbing procedures and aseptic technique. The visual observation is documented on a form for Assessing Hand Hygiene, Garbing and Aseptic Technique and maintained to provide a permanent record.
98	Immediately after the compounder completes the hand hygiene and garbing procedure, the evaluator collects a gloved fingertip and thumb sample from both hands of the compounder onto appropriate agar plates. The plates are incubated at 30-35° for 2–3 days. All compounding personnel have successfully completed an initial competency evaluation and gloved fingertip/thumb sampling procedure (0 cfu) no less than three times before initially being allowed to compound CSPs for human use.
99	Re-evaluation of glove fingertip testing onto appropriate agar plates (Trypticase soy agar (TSA) with lecithin and polysorbate 80) for all compounding personnel occurs at least annually for low- and medium-risk level CSPs and semiannually for high-risk level CSPs before being allowed to continue compounding CSPs. Gloves shall not be disinfected with sterile 70% IPA prior to testing. The cfu action level is based on the total number of cfu on both gloves and not per hand.
	VERIFICATION
100	Facility has written procedures to verify correct identity, quality, amounts, and purities of ingredients used in CSPs.
101	Labels of CSPs contain name and address of pharmacy, correct names and amounts or concentrations of ingredients, total volumes, beyond-use dates, storage conditions, and route(s) of administration.

102	Facility has documentation that procedures have been followed to ensure sterility, purity, correct identities and amounts of ingredients, and stability.
103	CSP's are visually inspected for abnormal particulate matter and color, and intact containers and seals.
104	Beyond Use Dates are assigned using direct stability-indicating assays or authoritative literature that supports the assigned BUD.
105	Storage time of assembled bag and vial systems are according to the manufacturer recommendations. (eg Minibag plus, Addvantage, Add-ease)
106	Facility has written procedures for proper packaging, storage, and transportation conditions to maintain sterility, quality, purity, and strength of CSPs.
107	Policies address packaging to maintain physical integrity, sterility, stability, and purity of CSPs.
	DISPENSING/DISTRIBUTION
108	Modes of transport are used that maintain appropriate temperatures and prevent damage to CSPs.
109	Facility provides a multiple component formal training program to ensure patients and caregivers understand the proper storage, handling, use, and disposal of CSPs.
110	Written standard procedures describe means for patients to ask questions and report concerns and adverse events with CSPs, and for compounding pharmacists to correct and prevent future problems.
	USP <71> STERILITY TESTING
111	Outsourced sterility testing results indicate that it is compliant with USP<71>.
112	Outsourced: The number of articles tested are appropriate according to USP<71>.
113	Outsourced: The volume/quantity tested is according to USP<71>.
114	On site: Membrane filtration is used if appropriate. (The technique of membrane filtration is used whenever the nature of the product permits; that is, for filterable aqueous preparations, for alcoholic or oily preparations, and for preparations miscible with, or soluble in, aqueous or oily solvents, provided these solvents do not have an antimicrobial effect in the conditions of the test.) Filters are rinsed according to USP<71>.
115	On site: Direct inoculation is done only when membrane filtration cannot be carried out. Volume to be inoculated does not exceed 10% of the culture media volume.
116	On site: The number of articles tested are appropriate according to USP<71>.
117	On site: The volume/quantity tested is according to USP<71>.
118	On site: A growth promotion test has been done on the media with the 5 specified organisms (not more than 100 CFU) according to USP<71>.

119	On site: A USP<71> method suitability test has been done with appropriate inoculum, additives and rinses.
120	On site: TSB or SCD is incubated at 20-25 C for 14 days (2 incubators present).
121	On site: FTM is incubated at 30-35 C for 14 days (2 incubators present).
122	On site: Sterility testing is documented including lot numbers and expiration dates of media.
123	Sterility testing reports are reviewed and appropriate actions taken and documented.
	MISCELLANEOUS
124	Facility engaged in office use sterile compounding for human use is registered with FDA as an outsourcing facility.
125	Compounding records are properly maintained.