

Comment Submission Template for:
General Chapter <797> *Pharmaceutical Compounding—Sterile Preparations*

Revision proposed in *Pharmacopeial Forum* 41(6) Nov/Dec 2015

Send completed template to CompoundingSL@usp.org by January 31, 2016

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General Comments: Please see attached memo dated, January 31, 2016. Additionally, we have included a copy of Massachusetts DRAFT sterile compounding regulation, 247 CMR 17, as we have referenced this document throughout our feedback.

Specific Comments:

Section(s)	Line Number(s)	Existing text: (Provide the proposed text.)	Suggested change: (Provide the revised suggestion to replace the existing text.)	Comment	Rationale / Scientific Evidence
Line 33: Specific Practices	39-48	Proprietary bag and vial systems: Docking and activation of proprietary bag and vial systems (e.g., ADD-Vantage®, Mini Bag Plus®, addEASE®) strictly		<u>Prepared outside ISO 5 conditions</u> We request the committee consider using the term attaching in place of docking. Pharmacy practice does not use the	Agree with respect to reconstitution / dilution for urgent / emergent use for immediate single dose administration.

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		<p>in accordance with the manufacturer's instructions for immediate administration to an individual patient is not considered compounding. However, aseptic technique must be followed when attaching the proprietary bag and vial system. Docking of the proprietary bag and vial systems for future activation and administration is considered compounding and must be performed in accordance with this chapter, with the exception of establishing Beyond-Use Dates and In-Use Times. Beyond use dates (BUDs) for proprietary bag and vial systems must be assigned in accordance with the manufacturer's</p>		<p>term docking.</p> <p>Please add a beyond use date / time for the immediate use. Consider adding time limits to define immediate administration (i.e. hung within 1 hour of attaching). Many things happen in practice and although intended for immediate use-time frames may vary based on practice setting and day-to-day situations.</p> <p><u>Prepared w/i ISO 5 conditions</u> We request that the committee consider defining a time frame for future administration (i.e. one hour, 1 day, 1 week etc.) Or in the alternative as</p>	

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		instructions provided in product labeling.		<p>suggested above, define immediate administration and anything outside that would be future administration.</p> <p>We recommend that the committee consider defining BUD from the time of attaching for both within ISO 5 and outside of ISO 5.</p> <p>We recommend that the committee provide clarity by defining “docking” such as the act of attaching the vial to the iv bag).</p>	
	49-51	<p>Reconstitution or dilution: Reconstituting or diluting a conventionally manufactured sterile product with no intervening steps strictly in accordance</p>		<p>Although we understand the intent of this provision may be to provide clarity regarding requirements for IV admixture in a physician’s office</p>	<p>Reconstitution or dilution of conventionally manufactured sterile product requires aseptic manipulation and should be considered sterile</p>

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		with the manufacturer's labeling for administration to an individual patient is not considered compounding. However, aseptic technique must be followed during preparation, and procedures must be in place to minimize the potential for contact with nonsterile surfaces and introduction of particulate matter or biological fluids.		<p>or nursing care at the bedside, this standard creates an exception that essentially many IV admixtures currently prepared as (low and medium risk CSPs) and would allow such products to be prepared without any of the current safe guards contained in the standard (such as engineering controls and Beyond Use dating). In our opinion, this change is too broad and has the potential to create confusion among pharmacy compounders.</p> <p>If the committee moves forward with this language, we ask that “no intervening steps”</p>	<p>compounding. The proposed standard would allow IV admixtures to be prepared routinely outside of classified space, a practice that should be reserved for urgent / emergent use only.</p>

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				be carefully defined. It is important to understand whether it is the intent of the committee to remove certain products from the current standard altogether. Compounders and Boards of Pharmacy across the country alike need to understand if the committee truly intends to remove many products currently prepared in accordance with the chapter as low or medium risk products from the requirements of the chapter because such products are prepared in accordance with the package insert. We caution the committee to	

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				carefully consider the ramifications (and possible unintended consequences) of this wording.	
Line 62: 1.2 Factors Affecting the Risks Associated with CSPs	66-70	If one or more of the starting components being used to compound is not sterile, the sterility of the compounded preparation must be achieved through a sterilization process, such as terminal sterilization in the final sealed container or sterile filtration, and then maintained through subsequent manipulations of the preparation.		Please clarify whether this language is intended to remove requirement of sterilization of the final patient CSP before dispensing. As worded the language has the potential to remove the requirement for sterilizing the individual dosage form dispensed to the patient if a stock solution or intermediary solution is used during high risk compounding process.	In our opinion, we believe all non-sterile components (including intermediate and stock solutions prepared by the compounder) as well as the final patient preparation (CSP) shall be sterilized prior to dispensing with no subsequent aseptic manipulations being allowed following the sterilization of the final dosage form. Depending on the BUD, stock and intermediate solutions can be stored for some time, we do not believe it is safe to remove the final

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					sterilization process performed on the CSP prepared for the individual patient.
Line 95: 1.3 Risk Categories	96-114	Consistent with this risk-based approach, this chapter distinguishes between two categories of CSPs, Category 1 and Category 2, primarily by the conditions under which they are made and the time within which they will be used. Category 1 CSPs are those assigned a maximum BUD of 12 hours or less at controlled room temperature or 24 hours or less if refrigerated if made in accordance with all of the applicable standards for Category 1 CSPs in this chapter. Category 2 CSPs are those that may be assigned a BUD of	We request that the committee instead consider the following: Low Risk 12 / 24 Low Risk Medium Risk High Risk	We recommend that the committee maintain the current risk categories. While we understand that the committee may be attempting to align facility requirements w/ risk level, we do not agree that rendering a product sterile by using non-sterile ingredients be included in the same category with products compounded using sterile components (Category 2). We urge the USP Committee to separate compounding with non-sterile ingredients into its	Maintaining sterility of conventionally manufactured sterile products is vastly different from creating and subsequently maintaining sterility of non-sterile products. Based on this we highly recommend that the committee consider that high risk compounding remain in a category of its own. This level of compounding requires a level of training and expertise, special equipment as well as facility requirements unique to the risk of this level.

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		<p>greater than 12 hours at room temperature or greater than 24 hours if refrigerated (see 12. Establishing Beyond-Use Dates and In-Use Times) if made in accordance with all of the applicable standards for Category 2 CSPs in this chapter. See Table 1 for a summary comparison of the minimum requirements in this chapter for Category 1 and 2 CSPs. This chapter describes minimum requirements that apply to compounding of all CSPs, and also to repackaging of sterile products. If a compounder does not meet all of the Category 2 requirements, the CSP or repackaged</p>		<p>own category (Category 3) if the category system is maintained.</p> <p>In the alternative if the committee moves forward with the categories as drafted, we request that a reference to the current categories be included. This may eliminate a total redrafting of state regulations that have been promulgated since 2012 incorporating the current USP language.</p> <p>Additionally, we request additional information regarding the rationale / evidence the committee considered when deciding to increase current</p>	<p>Maintaining a separate category for non-sterile to sterile identifies that additional training, competencies and facility design / equipment are required.</p>

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		sterile product will be considered a Category 1, and the shorter BUD applicable to Category 1 CSPs must be assigned. The minimum requirements not specifically described as applicable to Category 1 or Category 2, such as minimum training and competency testing and personal hygiene for personnel, are applicable to compounding of all CSPs and repackaging of sterile products.		BUD.	
Line 197: 2.2 Competency Testing in Garbing and Hand Hygiene	198-208	Gloved fingertip/thumb sampling is important because direct touch contamination is the most likely source of microorganisms. Gloved fingertip sampling evaluates a		We agree that fingertip/thumb sampling is important because direct touch contamination is one of the most likely sources of microorganisms	

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		<p>compounding person's competency in correctly performing hand hygiene and garbing (see Box 2-1). All persons performing compounding must successfully complete an initial competency evaluation, including visual observation and gloved fingertip/thumb sampling [zero colony-forming units (CFUs)] no fewer than three times before being allowed to compound CSPs, to demonstrate that they can perform the procedure consistently. After the initial competency evaluation, compounding personnel must successfully complete gloved fingertip/thumb</p>		<p>and must be a required to evaluate the compounder's competency.</p> <p>We suggest that the committee consider requirements to evaluate the garbing and gloving as well as aseptic technique of the compounder by requiring separate standards that clearly delineates each competency and the requirements.</p> <p>We also recommend that the committee consider higher standards (i.e. to be performed at the time of compounding) for non-sterile to sterile (i.e. high risk) compounding</p>	

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		sampling quarterly (no more than a total of three CFUs). Each fingertip/thumb evaluation must occur after separate, full hand hygiene and garbing procedures.		<p>and / or when the compounder applies a BUD exceeding USP regardless of risk level.</p> <p>We also suggest that the committee consider requiring a fungal specific media be used for pharmacies preparing high risk level CSPs or low / medium risk CSPs with extended (USP) BUDs.</p>	
Line 229: Box 2-2 Media-Fill Testing Procedures	229	When performing these testing procedures, use the most difficult and challenging compounding procedures and processing conditions encountered by the person during a work shift (e.g., the most manipulations, most complex flow of materials, longest		<p>We request that the committee provide clarity regarding the number of media fill units to be completed upon initial qualification and requalification.</p> <p>Also the MA BORP has proposed that a fungal specific media be used in addition to a general growth</p>	

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		<p>time to compound), replacing all the components used in the CSPs with microbial growth medium.</p> <p><input type="checkbox"/> Include all normal processing steps and incorporate worst-case conditions, including sterilizing filtration if used.</p> <p><input type="checkbox"/> Do not interrupt the test once it has begun, unless the normal work day involves interruptions.</p> <p><input type="checkbox"/> If all of the starting components are sterile to begin with, transfer sterile fluid microbial culture medium, such as sterile soybean-casein digest, into the same types of container-closure systems commonly used at the facility to evaluate a person's skill at aseptically</p>		<p>media for high risk level CSPs with extended BUDs, high risk level CSPs prepared in anticipation of a patient specific prescription or order, or high risk level intermediate or stock solutions.</p>	

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		<p>processing CSPs into finished dosage forms.</p> <p><input type="checkbox"/> If some of the starting components are nonsterile to begin with, use a nonsterile commercially available medium, such as soybean-casein digest powder, to make a 3% solution. Prepare the nonsterile culture medium according to the manufacturer's instructions and manipulate it in a manner that reflects nonsterile-to-sterile compounding activities.</p> <p><input type="checkbox"/> Incubate media-filled vials at 20°–35° for a minimum of 14 days. If two temperatures are used for incubation of media-filled samples, incubate the filled containers for at</p>			

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		<p>least 7 days at the lower temperature (20°–25°) followed by 7 days at 30°–35°. Failure is indicated by visible turbidity or other visual manifestations of growth in the medium in one or more container–closure unit(s) on or before 14 days. Investigate media-fill failures to determine possible causes (e.g., sterilizing filter failure). Document and discuss investigational findings with personnel before any re-testing.</p> <p><input type="checkbox"/> If using a purchased pre-prepared microbial growth medium, either verify that the growth medium is growth promoting, or obtain a certificate of analysis (COA) from the supplier of</p>			

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		<p>the growth medium to ensure that it will support the growth of microorganisms.</p> <p><input type="checkbox"/> If using a microbial growth medium prepared in-house, the growth promotion capability of the medium must be demonstrated and documented (see Sterility Tests <71>).</p> <p><input type="checkbox"/> Always store microbial growth media in accordance with manufacturer</p>			
<p>Line 230: 2.4 Reevaluation, Retraining, and Requalification</p>	<p>235-238</p>	<p>Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique; gloved fingertip/thumb sampling; or media-fill tests must pass three successive reevaluations in the deficient area before they can resume compounding of sterile preparations.</p>	<p>247 CMR 17.33(9)</p>	<p>Support. Similar standard included in the DRAFT MA regulations</p>	

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Line 244: TIMING OF REEVALUATION AND REQUALIFICATION	246-262	<input type="checkbox"/> Visual observation— Compounding personnel must be visually observed while performing hand hygiene and garbing procedures initially and then at least quarterly. <input type="checkbox"/> Gloved fingertip sampling— Compounding personnel must perform fingertip/thumb sampling three times initially and then quarterly to confirm their competency and work practices. Fingertip sampling conducted as part of a routine media-fill test can be counted in fulfilling these reevaluation requirements. <input type="checkbox"/> Media-fill testing— After initial qualification, conduct media-fill tests of all personnel engaged		<p>The MA BORP has proposed that gloved fingertip sampling occur at least monthly and more frequently for those who are engaged in high risk compounding and when and for those who are engaged low or medium risk compounding when USP <797> BUD's are extended.</p> <p>The MA BORP has proposed that competency assessments such as cleaning and disinfecting technique occur at least annually unless otherwise stated.</p>	

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		in compounding CSPs at least quarterly to evaluate aseptic technique and requalify them. <input type="checkbox"/> Cleaning and disinfecting—Retrain and requalify personnel in cleaning and disinfecting compounding areas after a change in cleaning and disinfecting procedures.			
Line: 244 TIMING OF REEVALUATION AND REQUALIFICATION	260-262	<input type="checkbox"/> After a pause in compounding— Personnel who have not compounded CSPs in more than 3 months must be requalified in all core competencies before resuming compounding duties.	247 CMR 17.33(6)	Support. Similar standard included in the DRAFT MA regulations.	
Line 293 3.2 Hand Hygiene	297	Hands must be washed with unscented soap and water. Alcohol hand sanitizers alone are not sufficient	247 CMR 17.30(6)(a)	We request that the committee clarify why the requirement for antimicrobial soap was removed.	
Line 312:		CSP	247 CMR 17.30(12)	We recommend	In our experience,

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Table 2. Minimum Garb and Glove Requirements		<p>Category Category 1 PEC type Any Minimum Requirement</p> <p><input type="checkbox"/> Non-cotton, low-lint, disposable gown or coveralls</p> <p><input type="checkbox"/> Low-lint, disposable covers for shoes</p> <p><input type="checkbox"/> Low-lint, disposable covers for head and facial hair that cover the ears and forehead</p> <p><input type="checkbox"/> Sterile gloves and sterile sleeves</p> <p>CSP Category Category 2 PEC type Laminar airflow system (LAFS) and biological safety cabinet (BSC) Minimum Requirement</p> <p><input type="checkbox"/> Non-cotton, low-</p>		<p>that if the committee moves forward with the proposed changes to risk level categories that a reference to current categories (Low, Medium, High) be included.</p> <p>We recommend that the committee consider requiring all CSPs prepared (unless for immediate administration for an emergent / urgent need) be prepared in a classified environment.</p> <p>We have drafted standards for a dedicated compounding room to meet the needs of our institutional registrants who perform on-site</p>	<p>segregated compounding areas / rooms w / a CAI or PEC does not provide the level of protection required for patient safety. The space is often misused (i.e. activities and supplies not essential to compounding) and CAI are often not maintained properly.</p> <p>Additionally, and through our many observations of sterile compounding processes gowns are routinely not worn correctly. Coveralls are a better choice.</p>

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		lint, disposable gowns or coveralls <input type="checkbox"/> Low-lint, disposable covers for shoes <input type="checkbox"/> Low-lint, disposable covers for head and facial hair that cover the ears and forehead <input type="checkbox"/> Mask <input type="checkbox"/> Sterile gloves and sterile sleeves If a sterile gown is used, the use of sterile sleeves is optional <input type="checkbox"/> Eye shield is optional CSP Category Category 2 PEC type RABS (CAI or CACI) or isolator Minimum Requirement <input type="checkbox"/> Non-cotton, low-lint, disposable		<p>administration of the CSPs that they prepare but due to space, budget and design challenges could not comply with a bona fide cleanroom / anteroom design. We believe this middle ground is crucial in order to raise the safety standards for compounding within the practice of pharmacy. We urge the committee to consider similar provisions or in the alternative to ensure that the language committee moves forward with does not prohibit MA from moving in this direction.</p> <p>We recommend that the committee consider requiring the use of coveralls</p>	

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		gowns or coveralls <input type="checkbox"/> Low-lint, disposable covers for shoes and hair <input type="checkbox"/> Sterile gloves		in place of gowns as well as mask for all compounding. We also seek clarity regarding the committee's rationale for allowing the re-use of gowns but not coveralls. We have drafted standards that would allow re-use of coveralls under certain conditions in order to balance patient safety with practicality and the cost to business. See 247 CMR 17.	
Line 320: GOWNS	321-324	Visibly soiled gowns must be changed immediately. Gowns and other garbing items must be segregated and stored before use in an enclosure to prevent contamination (e.g., away from sinks to avoid splashing). Coveralls and sterile		Please see comment above regarding reuse of coveralls.	

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		gowns must not be reused.			
Line 342: EXITING AND REENTERING COMPOUNDING AREAS	342-350	When compounding personnel exit the buffer or segregated compounding area during a work shift, a nonsterile gown can be removed and retained in the ante or segregated compounding area if not visibly soiled, to be re-donned during that same work shift only. Coveralls and sterile gowns may not be reused and must be replaced with new ones. Shoe covers, hair and facial hair covers, face masks, head covering, gloves, and sleeves may not be reused and must be replaced with new ones. Goggles must be either sterilized or disinfected with sterile 70% IPA before each use. Hand hygiene must		Please see comment above regarding reuse of coveralls.	

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		be performed before resuming sterile compounding.			
Line 384: DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY	390-393	<input type="checkbox"/> Ante-areas must meet at least ISO Class 8 standards. Typically, personnel hand hygiene and garbing procedures, staging of components, order entry, CSP handling, and other activities that potentially generate high levels of particulates are performed in this area. Ante-areas are also transition areas to ensure that proper air pressure relationships are maintained between designated areas.		<p>Please provide rationale for considering order entry essential to compounding. We recommend that the committee restrict activities allowed in the anteroom.</p>	<p>In our experience and through our observations of sterile compounding pharmacies, anterooms are often not respected as classified space. It is essential to limit activities allowed in this space to only those essential for compounding (such as hand washing, garbing, product staging)</p>
Line 384: DESIGN REQUIREMENTS TO MAINTAIN AIR QUALITY	399-400	Areas intended for CSP preparation must meet ISO Class 5 standards. ISO Class 5 standards are achieved through use of a PEC, such	247 CMR 17.17(5)	<p>We recommend that the committee consider prohibiting the ISO 5 zone design for compounding. Although this</p>	<p>The “open” clean rooms, i.e. the creation of Primary engineering control(s) with HEPA-filtered air from the ceiling is</p>

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		as a LAFS, BSC, CAI, CACI, or isolator.		design is common in manufacturing, the monitoring requirements for cGMP are much more extensive than compounding.	difficult for pharmacy compounders to sustain and manage proper air flow dynamics. Although HVAC engineers and vendors can achieve, it is difficult to maintain. This design is easier for the compounder to breach the DCA, i.e. critical zone.
Line 403: 4.2 Facility Design and Environmental Controls	401-402	A PEC used for compounding may be placed in an unclassified, segregated compounding area (see below) if only Category 1 CSPs are compounded in the PEC.		As stated above, we recommend CSPs (unless urgent / emergent need) be prepared in a classified environment. A classified environment allows for particulate to be controlled.	
	407-408	The room must be maintained at a		Temperature and humidity are also	

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		temperature of 20° or cooler and a humidity below 60% at all times.		important for environmental control in addition to worker comfort.	
	443-448	Airlocks and interlocking doors can be used to facilitate better control of air balance between a higher classified area and an area of lesser air quality (e.g., between the buffer area and ante-area), or between a classified area and an unclassified area (e.g.,		We recommend the committee requiring that airlocks and interlocking doors be required.	
	452-454	When designing the facility, consider whether all materials used can be easily cleaned. Avoid using door seals and sweeps that are difficult to clean. Hands-free access doors are preferred. Do not use tacky mats in ISO-classified areas.		We recommend that the committee consider requiring hands free doors. Please clarify that tacky mats just outside anteroom / classified prep rooms is not prohibited.	

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Line 455: THE CSP PROCESSING ENVIRONMENT	473-482	The LAFS can consist of either a LAFW or a HEPA filter alone creating an ISO Class 5 zone	247 CMR 17.17(5)	As stated above, we recommend that the committee consider requiring the use of a commercially manufactured PEC.	
	512-519	If ISO Class 5 classification is achieved using an isolator that meets the requirements above, the isolator can be located in an ISO Class 8 area and used to prepare Category 2 CSPs. In addition, when using an isolator, some functions, such as hand washing, can be done in the ISO Class 8 area. Water sources such as sinks and drains must be located at least 1 meter from the isolator. If the isolator does not meet the requirements above, it is considered a RABS	247 CMR 17.18 (3).	In addition to the expert committee's provision for an ISO 8 area for isolators, we request that the committee consider the concept of an ISO 8 classified dedicated compounding room (DCR) for institutional registrants who perform on-site administration of the CSPs in accordance with proposed 247 CMR 17.18 (3).	

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		that must be located within at least an ISO Class 7 area to prepare Category 2 CSPs, or within a segregated compounding area to prepare Category 1 CSPs.			
	520-530	Segregated Compounding Areas: In some situations, a PEC may be located within an unclassified area, without a buffer or ante-area. This type of design is called a segregated compounding area. Category 2 CSPs must never be compounded in segregated compounding areas; only Category 1 CSPs can be compounded in facilities with such designs. It is critical to locate a segregated compounding area away from unsealed		As stated above, we recommend that all sterile compounding (except urgent / emergent need) be prepared within a classified environment.	

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		<p>windows, doors that connect to the outdoors, and significant traffic flow. A segregated compounding area must not be located adjacent to construction sites, warehouses, food preparation areas, or other environmental control challenges. The impact of activities that will be conducted around or adjacent to the segregated compounding area must be considered carefully when designing such an area, and the perimeter of the segregated compounding area must be defined.</p>			
<p>Line 538: AIR-EXCHANGE REQUIREMENTS</p>	<p>546-550</p>	<p>An ISO Class 7 buffer or ante-area supplied with HEPA-filtered air must measure an ACPH of not less</p>		<p>We recommend that the committee consider requiring minimum 30 ACPH independent from the primary</p>	<p>In our experience when the ACPH include the PEC and the PEC requires maintenance and</p>

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		<p>than 30, and the ACPH may need to be higher to maintain the classification, depending on the factors previously described. The ACPH of 30 can include recirculated HEPA-filtered air, but at least half (a minimum of 15 ACPH) must be HEPA-filtered fresh air.</p>		<p>engineering control(s) PEC.</p>	<p>or repair the room is compromised. Requiring the minimum ACPH be independent of the PEC allows for continuity of care during such situations as only the affected PEC will have to be removed from service while the room will remain within minimum certified standards. We have had many compounders have to cease compounding due to a PEC maintenance issue because the minimum ACPH could not be maintained without the affected PEC.</p>
<p>Line 554: ESTABLISHING AND MAINTAINING PRESSURE DIFFERENTIALS</p>	<p>558-559</p>	<p>ISO-classified area. The pressure differential between the ISO Class 7 area and the general pharmacy area must</p>		<p>We request that the committee provide clarity. We do not believe the language as written accounts for the</p>	

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		not be less than 0.02-inch water column.		ISO 7/8 ante room and the pressure that it creates. Differential pressure is 0.02 between buffer and ante AND 0.02 between ante and general pharmacy area.	
	560-563	A pressure gauge or velocity meter must be used to monitor the pressure differential or airflow between the ante-area and buffer area and between the ante-area and the general environment outside the classified areas. The results must be reviewed and documented on a log at least daily or by a continuous recording device.	247 CMR 17.15(5)	Please consider adding language to require CAPA in response to out of spec results.	
Line 564: 4.3 Constructing Areas to Achieve Easily Cleanable Conditions	576-577	Classified areas and segregated compounding areas must not contain dust-collecting overhangs, such as		While we agree with the committee, we request that the committee consider provision to allow older	

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		utility pipes, or ledges, such as windowsills.		footprints to come into compliance over x period of time (such as requiring upon new construction and or renovations)	
	579-581	Any other penetrations through the ceiling or walls must be sealed. The buffer area or area inside the perimeter of a segregated compounding area cannot contain water sources (e.g., sinks) or floor drains.		<p>As stated above, we recommend the committee consider requiring sterile compounding (except urgent / emergent need) in a classified environment.</p> <p>In the alternative, if the committee moves forward with the language as drafted, we request that the committee clarify “area inside the area of SCA” and address provisions for proper hand hygiene if a sink is not allowed in the area</p> <p>Additionally, we</p>	

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				request that the committee consider providing clarity regarding the language that allows an Isolator in an ISO 8, i.e. is that considered a buffer area because a sink is allowed.	
Line 584: 4.4 Placement and Movement of Materials		Only furniture, storage shelving, counters, cabinets, supplies, and other materials necessary for performing compounding activities are permitted in buffer or segregated compounding areas. Any objects located in buffer or segregated compounding areas must be smooth, impervious, free from cracks and crevices, non-shedding, and easily cleaned and disinfected.		We recommend removal of the word cabinets. Cabinets collect dust and do not promote easy cleaning. Cabinets are often made of shedding materials that do not stand up to degradation of cleaning chemicals.	There is no need for a cabinet in a buffer room.

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	596-600	Certain devices (e.g., computers) and objects (e.g., carts and cabinets) essential to compounding can be located in the segregated compounding area, but must be located at an appropriate distance from the PEC so that they have no detrimental effects on the air quality inside the PEC. The appropriate distance must be determined by considering the surrounding environment and the activities conducted in it.		As stated above, we recommend the committee consider requiring sterile compounding (except urgent / emergent need) be prepared in a classified environment. With that said we do agree that carts and other equipment should not have detrimental effects on classified spaces.	
Line 607 4.5: Certification and Recertification of Facilities	608-610	Before a facility is used to compound either Category 1 or Category 2 CSPs, it must be certified by an independent, qualified individual as meeting its design and air quality		Agree an independent, qualified individual must certify that a facility meets its design and air quality specifications	

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		specifications (see Table 3).			
	622-623	Total Particle Counts Testing under typical operating conditions by qualified operators using current, state-of-the-art electronic equipment.		We recommend clarifying the language to require an independent qualified individual during certification and recertification.	Agree can be done by trained internal personnel for routine monitoring.
	627	Certification of other ISO-classified areas must include:	All requirements for PEC to be included in other classified areas (615-626).	We recommend considering requirement for smoke studies of the rooms. Additionally, please consider adding all the elements included under PEC certification (lines 615-626).	
	697-701	The sampling program must contain a listing of the sample locations, procedures for collecting samples, frequency of sampling, size of sample (e.g., surface area, volume of air),		The MA BORP requests that the committee add a provision that the sampling program must be developed in conjunction with a qualified professional such as a	

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		time of day sampled in relation to activities in the compounding area, and levels that will trigger corrective action. Sampling timing and locations should be carefully selected based on their relationship to the operation performed in the area.		microbiologist, infection control professional or industrial hygienist.	
Line 714: 5.2 Monitoring Air Quality for Nonviable Airborne Particles Line 722: AIR SAMPLING TIMING AND LOCATIONS	729-730	Total particle counts of all ISO-classified areas must be conducted during typical operations every 6 months.	More frequently in certain circumstances 247 CMR	We recommend that the committee consider aligning the non-viable particulate and viable particulate testing.	Non-viable counts should be performed as frequently as viable counts as particulate is an indicator of environmental control.
Line 746: 5.3 Monitoring Air Quality for Viable Airborne Particles Line 752: AIR SAMPLING TIMING AND LOCATIONS	755-756	Active air sampling of all ISO-classified areas must be conducted during typical operating conditions at least monthly.		Agree. MA has proposed similar standard	
	758-761	A general microbiological		We recommend that the committee	A two plate method eliminates the need

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		<p>growth medium that supports the growth of bacteria and fungi, 759 such as trypticase soy agar (TSA) or soybean-casein digest medium, must be used.</p> <p>Samples must be incubated at 20°–25° for 5–7 days and then at 30°–35° for 2–3 additional days.</p>		<p>consider requiring a two-plate (general growth and fungal specific) sampling method.</p>	<p>to transfer plates between 2 temperatures at required timing intervals, speeds up the results as both plates can be incubated concurrently. Additionally, in the event of a breach and total loss of control, 2 plates reduce the chances of a “too many to count / identify”) and allow the microbiologist a better chance of identifying the various microorganisms which in turn facilitates CAPA.</p>
<p>Line 765: Box 5-1 Active Air Sampling Procedures for Viable Airborne Monitoring</p>	<p>765</p>	<p>Using an active air sampling device, test at least 1 cubic meter or 1,000 liters of air from each area sampled.</p> <p>Invert the media plates and incubate</p>		<p>We agree with requiring the 1000 liters</p> <p>We agree with the incubation procedures; however, we ask the committee to</p>	<p>In our experience and through our observations of sterile compounding pharmacy oversight, we have seen instances in which the results</p>

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		the medium at 20°–25° for 5–7 days and then at 30°–35° for 2–3 additional days.		consider requiring two-plate testing method as described above and editing the language to align with a two-plate process. In the alternative, if the committee moves forward with language for 1-plate testing, we ask that the committee consider clarifying the language here (line 765), so two-plate and concurrent incubation is not prohibited.	have not been calculated correctly (i.e. the corrective measure was not taken into consideration during testing in which less air was collected).
Line 766: DATA EVALUATION AND ACTION LEVELS	772-778	Highly pathogenic microorganisms (e.g., gram-negative rods, coagulase positive staphylococcus, molds and yeasts) are potentially fatal to patients receiving CSPs and must be immediately		Agree. We recommend that the committee consider adding a requirement that a coagulase test in addition to identity to the genus level be performed for all identified	Coagulase positive Staphylococcus requires immediate remediation regardless of CFU count; therefore, identity to the genus level for this microorganism requires additional test to ensure the

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		<p>remedied through cleaning and disinfection, regardless of CFU count. If levels measured during viable air sampling exceed the levels in Table 4, the genus must be identified, and when possible, identify the species of any microorganism recovered, with the assistance of a credentialed microbiology laboratory.</p>		<p>Staphylococcus organisms.</p> <p>Additionally, we recommend that the committee consider adding clarity that identity of microorganism regardless of CFU count (i.e. even if within action levels)</p>	<p>coagulase status (i.e. positive or negative).</p> <p>Identity is required regardless of risk count so the compounder knows whether or not an organism of concern is present. In our experience and through our observations of sterile compounding pharmacy practice, many compounders misinterpret that actionable level chart. For instance, we have seen compounders not send plates for identification unless and until the count on the plate exceeds the USP action level. This has caused issues with respect to properly</p>

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					<p>identifying and remediating microorganisms listed by USP as highly pathogenic and requiring immediate remediation regardless of CFU count.</p>
<p>Line 779: Table 4. Action</p>	<p>779</p>	<p>Table 4. Action Levels for Viable Airborne Particle Air Sampling</p>		<p>We recommend that the committee consider adding language to the chart that includes highly pathogenic organisms action level (i.e. adding reference in table that even 1 CFU HPO is actionable)</p>	<p>In our opinion, having this information in the chart will help clarify that this result meets actionable levels. We have seen this information misinterpreted or missed by the compounder who is referring to the chart to determine whether the results are actionable.</p>
<p>Line 790: SAMPLING TIMING AND LOCATIONS</p>	<p>795-796</p>	<p>Multiple locations must be sampled at least monthly within each ISO-classified area, including the following (see</p>		<p>Agree. As stated above, MA has drafted regulatory language that will increase monitoring and has</p>	

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		<1116>:		aligned the monitoring with the levels of compounding based on the potential of risk. Additionally, MA has drafted standards that will require additional monitoring of both personnel and the environment when the compounder prepares high risk compounds (including intermediate / stock solutions) or assigns a BUD exceeding USP <797>.	
Line 801: SAMPLING PROCEDURES	802-805	Contact sampling devices (e.g., plates, paddles, or slides) containing microbial growth media must be used for sampling flat surfaces. Sterile swabs wetted with sterile water can be used when sampling irregular surfaces		We recommend that the committee consider, restricted the use of swabs for testing to independent qualified individual. Many pharmacies perform testing with internal staff. Pharmacists are	

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		and difficult-to-reach locations in classified areas, such as crevices, corners, and spaces between surfaces.		<p>not qualified to conduct sampling/ analysis of swabs. To our knowledge a training course is not available.</p> <p>We recommend that the committee consider requiring plates for routine sampling and allow testing of irregular surfaces during certification and recertification conducted by independent qualified individual. In the alternative, we seek clarity regarding the requirements for training and competency assessment for sampling and analyzing with sterile swabs.</p>	
	806-807	Surface sampling devices must contain general microbial growth media (e.g.,		<p>Agree. We also seek clarity and the expert guidance of</p>	<p>MA has had multiple conversations regarding the</p>

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		soybean casein digest media) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80).		the committee regarding the appropriate agent to neutralize sporicidal agents.	effectiveness of plates and requirements for neutralizing agents with respect to sporicidal cleaning agents. Guidance is needed in this area.
	808-809	Use a surface sampling device (e.g., plates, paddles, or slides) in the size range of 24- to 36-cm ² . Contact sampling devices must be certified by the manufacturer to meet growth promotion tests in Microbial Enumeration Tests <61>.		We request that the committee please provide guidance regarding the size of sampling plates.	In our experience, sampling vendors report use of 60MM plates but not all 60MM plates meet the minimum surface area 24cm². Expert guidance is needed in this area.
Line 815: Box 5-2 Using Devices for Flat Surface Sampling	815	Invert the plates and incubate the contact sampling devices at 20°–25° for 5–7 days and then at 30°–35° for 2–3 additional days.		As stated above, we recommend that the committee consider requiring two plate (general growth media and fungal specific media) testing. We recommend	

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				<p>that the committee consider adding language requiring identification of organisms for any and all growth (regardless of CFU). We also recommend that the committee consider adding language requiring the compounder to perform coagulase testing on all identified staphylococcus organism (as stated above)</p>	
<p>Line 828: Table 5. Action Levels for Surface Sampling</p>	<p>828</p>	<p>Table 5. Action Levels for Surface Sampling</p>		<p>We recommend that the committee consider requiring action levels greater than or equal to (similar to the drafted language for air sampling). We also recommend that the committee</p>	<p>Every surface has the potential for transfer contamination to personnel or products used in compounding. As written the language is too confusing and will be difficult to enforce.</p>

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				<p>consider not bifurcating action levels based on whether work surface or non-work surface. In the alternative, please provide definitions for what is a work surface and what is not. We recommend that the committee consider using the language for work surface for all ISO 7 and ISO 8 areas and strike the requirements for non-work surfaces.</p> <p>Also we request the committee add greater than or equal to for the action levels (>).</p>	
<p>Line 1211: 9.2 Creating Master Formulation Records</p>	<p>1212-1213</p>	<p>A Master Formulation Record must be created for CSPs prepared in a batch for multiple patients or for CSPs prepared</p>		<p>We request that the committee consider adding:</p> <ul style="list-style-type: none"> • low / medium risk CSPs with extended 	

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		from nonsterile ingredients		BUDs <ul style="list-style-type: none"> • allergen extracts • media fill challenge testing 	
Line 1218: 9.3 Creating Compounding Records	1219-1221	A Compounding Record must be created by the compounder preparing the CSP to document the compounding process. The Compounding Record or inventory control system must permit traceability of all ingredients.		Agree.	
Line 1247: 10.1 Physical Inspection of CSP	1252-1253	Some CSPs also must be visually checked for certain characteristics (e.g., emulsions must be checked for phase separation).		We recommend that the committee consider prohibiting the preparation of emulsions and other demonstrably difficult preparations as discussed above. We recommend	

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				<p>that the committee only allow compounding using components that are conventionally manufactured sterile product (i.e. not created through a high risk compounding process).</p> <p>We recommend that the committee consider the FDA definition of demonstrably difficult in its decision to decide whether preparation of suspensions, emulsions, pellets, metered dose inhalers is manufacturing vs. high risk compounding.</p> <p>If the committee moves with the following language</p>	

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				and allows such agents to be compounded, we recommend that the committee consider drafting additional safety standards and requirements for such processes.	
Line 1264: 10.2 Sterility Testing	1266-1268	If a Category 2 CSP is assigned a BUD that requires sterility testing (see Table 8), the testing must be performed in a manner consistent with <71>, with the exception, in some cases, of the batch sizes specified in Sterility Tests <71>.		The MA BORP has proposed sterility testing requirements for specific types of CSP's and makes no exemption for batch size.	
	1279-1286	If sterility testing will be conducted, ideally the results should be obtained before dispensing to patient(s). If it is anticipated that there will be situations in which there may be an urgent need to dispense a CSP	A compounder may not dispense a CSPs that required sterility testing until the sterility testing results have been received and confirmed to be negative. See 247 CMR	We recommend that the committee consider removing language allowing dispensing at risk. In the alternative if the committee moves forward with the language as drafted, we	CSPs meeting the USP requirements for sterility and or bacterial endotoxin testing should not be dispensed unless and until results are received. The compounder can always provide

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		before the results of the sterility testing are known, a written procedure (SOP) must be developed and followed; this SOP must describe how these situations will be handled. In addition, this SOP must require frequent observation of the incubating test specimen and must require immediate recall of the dispensed CSP (if possible) or immediate notification of the patient's prescriber, if any evidence of microbial growth is found during the test.	17.40(2)	request that the committee define required action steps to be taken by the compounder and the patient's prescriber in addition to the notification requirements. Also please provide guidance regarding patient notification and proper steps for adverse event monitoring for patients who have received such products.	medication to the patient by preparing CSP for the individual patient at the time it is needed and applying a USP BUD. Recall of the CSP is often not possible as it is likely that the CSP will have administered prior to the results being received.
	1287-1293	Positive sterility test results must prompt a rapid and systematic investigation into the causes of the sterility failure, including identification of the contaminating	247 CMR 17.40 (10) 247 CMR 17.40(5)	Agree. MA has drafted similar standards. We recommend that the committee consider adding	

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		organism (at least to the genus level) and any aspects of the facility, process, or personnel that may have contributed to the sterility failure. The source of the contamination, if identified, must be corrected, and the facility should determine whether the conditions causing the sterility failure affect other CSPs. The investigation and resulting corrective actions must be documented.		requirement o perform coagulase testing on all identified staphylococcus organisms (as stated above).	
Line 1439: METHOD OF ACHIEVING STERILITY	1451-1465	WHETHER THE CSP WILL BE STERILITY TESTED AND THE RESULTS KNOWN BEFORE THE DRUG IS RELEASED OR DISPENSED		As stated above, we request the committee remove language referring to dispensing at risk.	
	1494-1498	It must be recognized that CSPs may be stored under different	247 CMR 17.41(7)	Agree. MA has drafted similar standards.	

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		storage conditions before they are used (e.g., they may first be frozen, and then thawed in the refrigerator, and finally kept at controlled room temperature before administration). The storage time of a CSP must not exceed the original BUD placed on the CSP for its labeled storage conditions, and BUDs are not additive			
	1504	Table 8. BUDs for Category 2 CSPs	247 CMR 17.41 (5) and (6)	We agree with the 45 day maximum BUD for high risk. We recommend the committee consider allowing a 90 day maximum for low and medium risk CSPs. Allowing for a maximum 90 day BUD for low and medium risk CSPs will allow for continuity of care	

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				<p>for patient's receiving CSPs through an implantable infusion pump for which the CSP is made from conventionally manufactured sterile products. Although high risk CSPs for use in implantable pumps are also dispensed to patients, the risk of non-sterile to sterile compounding dictates the need to restrict the BUD to no more than 45 days.</p> <p>MA has drafted similar standards.</p> <p>We request that the committee add reference to current risk levels (as stated above) consider updating table to provide</p>	

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				clarity.	
	1516-1518	Table 9. In-Use Times for Conventionally Manufactured Products and CSPs Opened, Stored, and Used for Sterile Compounding in ISO Class 5 or Better Air Quality		We request that the committee provide clarity, chart and definitions are difficult to understand.	
	1519-1520	Table 10. In-Use Times for Conventionally Manufactured Products and CSPs Opened and/or Stored in Worse than ISO Class 5 Air		We request that the committee provide clarity, chart and definitions are difficult to understand.	
Line 1522: 13. QUALITY ASSURANCE AND QUALITY CONTROL	1522-1588			Agree. MA has drafted similar standards. See 247 CMR 17.49	
Line 1595: 14.1 Storing CSPs within the Compounding Facility	1606-1608	When it is known that a CSP has been exposed to temperatures that exceed storage temperature limits, (i.e., temperatures warmer than the	Storage locations that do not maintain the required temp for their location all CSPs should be evaluated using scientific peer	We request that the committee provide clarity regarding the temperature units. Similarly, please provide clarity with respect to the 'exceeding	Stability of medications at different temperatures vary dependent on temperature and may be shorter than 4 hours.

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		warmest labeled limit or temperatures exceeding 40° for more than 4 hours), the CSP should be discarded.	reviewed references to determine whether to discard.	40 degrees'. If the committee intended for the units to be F, 40 degrees F is still within refrigerator temperature range. Difficult to ascertain the committee's intent. Does the committee intend to set a limit with respect to exceeding controlled room temperature for greater than 4 hours? We recommend the committee clarify this standard and in doing so also consider that stability differs for medications and may actually be shorter than 4 hours at room temperature.	
Line 1704: 17. RADIOPHARMACEUTICALS	1704-1767	... Unless done in strict conformance with the		As stated above, we recommend that the committee	

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AS CSPA		manufacturer's package insert		evaluate the possible unintended consequences of this very broad definition.	
Line1768: GLOSSARY	1861-1863	Laminar airflow system (LAFS): A device or zone within a buffer area that provides an ISO Class 5 or better environment for sterile compounding. The system provides a unidirectional HEPA-filtered airflow.	247 CMR 17.17(5)	We recommend that the committee consider prohibiting this design for compounding. Although this design is common in manufacturing, the monitoring requirements for cGMP are much more extensive than compounding.	The "open" clean rooms, i.e. the creation of Primary engineering control(s) with HEPA-filtered air from the ceiling is difficult for pharmacy compounders to sustain and manage proper air flow dynamics. Although HVAC engineers and vendors can achieve, it is difficult to maintain. This design is easier for the compounder to breach the DCA, i.e. critical zone.

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	1783	Batch: More than one unit of CSP prepared in a single process and intended to have uniform characteristics and quality, within specified limits.		<p>We request that the committee provide clarity regarding the definition of batch. Does the committee intend for this definition to cover multiple single dosage units for the same patient?</p> <p>MA has drafted language regarding batching which considers multiple products made in anticipation of patient prescriptions but excludes multiple dosage units for the same prescription.</p>	<p>We recommend that batching cover multi-patient distribution and not multiple CSPs for 1 patient per 1 prescription.</p>
Other Observations / Considerations:					
Above Action Level environmental Monitoring / Adverse Trending			247 CMR 17.28	We recommend that the committee consider adding guidance for response to above action level Environmental	MA continues to develop guidance for appropriate response to Environmental Monitoring which is much needed.

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				<p>Monitoring Results / Adverse trending</p> <p>We recommend that the committee also consider adding definition of proper remediation (i.e. CAPA and repeat EM to demonstrate levels within USP action levels)</p> <p>See 247 CMR 17.37</p>	<p>We recommend that the committee consider providing an expert opinion regarding this area.</p>
Robotics				<p>We recommend that the committee consider adding standards specific to the use of sterile compounding robotics.</p>	
Allergen Extracts			<p>See 247 CMR 17.10</p>	<p>Please clarify why all references to allergen extracts has been removed</p> <p>We recommend the committee consider adding standards for CSPs prepared from allergen extracts.</p>	
Line of Demarcation				<p>The reference to</p>	

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				line of demarcation has been removed. Was this intentional? We recommend that the committee consider including standard for line of demarcation.	

(Add additional lines to the table as necessary.)